afssa
AGENCE FRANÇAISE DE SECURITE SANITAIRE DES ALIMENTS

Sel et santé

Actes du colloque international (11-12 janvier 2002, Paris)

Salt and health

Proceedings of the international conference (January 11th-12th 2002, Paris)

- Février 2003 -

Colloque International « Sel et Santé »

11-12 janvier 2002

Ministère de la Santé – Paris, France

International Conference « Salt and Health »

January 11th-12th 2002

Ministry of Health – Paris, France

Comité scientifique d'organisation du colloque / Scientific organising committee of the conference

Jean-Louis Berta (Afssa)

Pierre Ducimetière (Inserm)

Joël Ménard (Chaire de Santé Publique, Paris VI)

Pierre Méneton (Inserm)

Elio Riboli (CIRC Nutrition et Cancer)

Marie-Christine de Vernejoul (Inserm)

Comité de coordination éditoriale / *Editorial board*

Raphaëlle Ancellin (Afssa)

Juliette Chevalier (Afssa)

Céline Dumas (Afssa)

Carole Thomann (Afssa)

■ **Introduction** / ***Introduction*** 7

Martin Hirsch 9
Bernard Kouchner 11

La place des études internationales en épidémiologie cardiovasculaire
Pierre Ducimetière 15

■ **Gènes, hypertension et sensibilité au sel** / ***Genes, hypertension and salt sensitivity*** 19
Président de séance : Pierre Méneton / *Chairman : Pierre Méneton*

Gènes influençant le métabolisme du sel et la pression artérielle
Xavier Jeunemaître 23
The alpha-adducin gene's history
Giuseppe Bianchi 31

Discussion 39

Altered renal sodium handling and blood pressure : genetic and metabolic influences
Pasquale Strazzullo 41

Discussion 53

The desire for salt
Gary K. Beauchamp 55

Discussion 65

■ **Apport en sel et hypertension : les études d'observation et d'intervention** / ***Salt intake and hypertension : observational and intervention studies*** 67
Présidents de séance : Alberto Zanchetti et Theodore A. Kotchen / *Chairmen : Alberto Zanchetti and Theodore A. Kotchen*

INTERSALT and INTERMAP studies
Paul Elliot 71
Salt and cardiovascular disease
Graham A. MacGregor 73
Relationship between salt sensitivity and diseases and its correction by dietary interventions
Alexander G. Logan 95

Discussion 99

The DASH-sodium trial results : the effects on blood pressure of dietary sodium and the DASH dietary pattern
Eva Obarzanek 103

Discussion 109

Salt intake early in life : does it increase the risk of hypertension ?
Johanna M. Geleijnse 111

Discussion 117

■ **Apport en sel et maladies cardiovasculaires /** ***Salt intake and cardiovascular diseases*** 119
Présidents de séance : Jean-Louis Imbs et Marie-Christine de Vernejoul /
Chairmen : Jean-Louis Imbs and Marie-Christine de Vernejoul

Salt, blood pressure, cardiovascular disease and taste
Malcolm R. Law 123
Population based studies of sodium and blood pressure in the United States and China : experience in the Yi Migrant Study, TONE, TOHP and Nhanes I Study
Paul K. Whelton 125
High sodium intake is associated with increased mortality and the risk of cardiovascular disease
Jaakko Tuomilehto 135

Discussion 137

Salt, hypertension and human health
Michael H. Alderman 139
Une réduction modérée des apports sodés est-elle dangereuse ?
Hugh E. de Wardener 147
Sel et traitement anti-hypertenseurs
Albert Mimran 153

Discussion 155

Salt intake and the risk of CHD and stroke
Ivan J. Perry 159
Does salt have a detrimental effect on the cardiovascular system that is not mediated by blood pressure ?
Franz H. Messerli 169
Salt and left ventricular hypertrophy
Roland E. Schmieder 171

Discussion 173

■ **Sel et ostéoporose /** ***Salt and osteoporosis*** 175

Salt intake, calcium metabolism and osteoporosis
Francesco P. Cappuccio 177

Discussion 183

■ **Sel et politique de santé publique /** ***Salt and public health policies*** 185
Président de séance : Joël Ménard / *Chairman : Joël Ménard*

Salt intake and publi health in Belgium
Jozef V. Joossens 189
Regulations and health Policies on Salt in Finland
Heikki Karppanen 197
The experience of the UK in salt reduction
Lisa Jackson 203
Salt and Public Health policies : regulations and policies on salt in the US
Martha Hill 209

Une politique de santé publique pour réduire les apports de sel en France
Serge Hercberg 211
La consommation de sel, ses déterminants et ses possibles évolutions en France
Jean-Luc Volatier 217
Discussion 219

■ **Conclusion /** ***Conclusion*** 223

Martin Hirsch 225

■ **Glossaire /** ***Glossary*** 227

Avertissement :
Tous les textes ont été revus par les auteurs, à l'exception des discussions et des introductions de sessions. Celles-ci n'engagent pas la responsabilité des intervenants. Les discussions et les introductions de sessions menées en anglais ont fait l'objet d'une traduction en Français (VF).

En l'absence de validation des textes par les intervenants, ce sont les résumés fournis lors du colloque qui sont publiés.

Warning:
All texts have been reviewed by the authors, with exception of the discussions and the introductions of the sessions, for which the speakers are not liable. The discussions and the introductions of the sessions in English have been translated in French (VF).

In the absence of reviewed contributions, the conference abstracts are published in the proceedings.

Introduction

Introduction

Martin HIRSCH

Directeur général
Agence française de sécurité sanitaire des aliments (Afssa), Maisons-Alfort, France

Nous sommes très heureux de vous accueillir dans le cadre de ce colloque.

Les scientifiques et les organismes sanitaires ne sont pas les seuls à s'intéresser au sel, lequel suscitait déjà l'intérêt de certains mouvements surréalistes il y a un siècle. La revue Dada a ainsi publié à l'époque une publicité, conçue à la fin du XIXe siècle par Marcel Duchamp à partir d'une comptine, et qui prenait la forme du slogan suivant : « Marcel Duchamp, marchand du sel, se prend pour un grand et met son petit grain de sel ». L'artiste montrait ainsi comment il était possible d'attraper les oiseaux avec un peu de sel. En outre, cette réclame fait naître la question de savoir si, face au problème du sel, il vaut mieux choisir une tactique ou une stratégie, sachant que la première consiste à « savoir quoi faire quand il n'y a rien à faire », et la seconde à « savoir quoi faire quand il y a quelque chose à faire ». Nous verrons si les recommandations formulées dans le cadre de ce colloque peuvent s'inscrire dans ces approches.

Nous accueillons maintenant le Ministre de la Santé.

Le contexte de l'organisation du colloque

Monsieur le Ministre, il y a près d'un an, le volumineux ouvrage intitulé "*Les apports nutritionnels conseillés pour la population française"* vous était présenté et actait une double exception concernant le sel. D'une part, il indiquait que s'il n'y a aucun argument en faveur d'apports excessifs en aucun nutriment, il est difficile de trouver des arguments scientifiques à cette exception flagrante du sel. De fait, si les scientifiques s'accordent sur un besoin minimal physiologique de 2 g/j pour le sel, il est légitime de s'interroger sur les conséquences d'un apport moyen quatre à dix fois supérieur et certainement sous-estimé. D'autre part, il était prévu que la question du sel ferait l'objet d'approfondissements ultérieurs avant qu'un avis définitif ne soit rendu en la matière, parce que les enjeux de la consommation de sel justifient une réflexion scientifique et pluridisciplinaire, d'autant que la France n'a pas entrepris de réduire la consommation de sel de la population.

Ces constats ont conduit :

- à l'organisation de ce colloque scientifique en vue de répondre aux enjeux de santé publique posés par la consommation de sel ;
- à la création d'un groupe de travail visant à proposer des actions de diminution des apports sodés et dont les conclusions vous ont été remises.

L'information scientifique actualisée sur le sel n'est pas aisément disponible. En outre, la question du lien entre sel et santé n'a fait l'objet d'aucun débat en France ces dernières années. Le dernier colloque international s'est tenu aux Etats-Unis il y a deux ans. Pourtant l'importance du sujet n'est pas contestée, la discussion scientifique est loin d'être épuisée et les connaissances évoluent, notamment sous l'effet des recherches génétiques, des études épidémiologiques diverses et de consommations alimentaires. Certaines questions restent sans réponse et controversées.

Nous avons donc organisé, avec la collaboration de l'INSERM, une présentation et une discussion des travaux scientifiques les plus récents sur la question du sel.

Les spécificités du colloque

Ce colloque scientifique présente plusieurs particularités : il est ouvert au public, multidisciplinaire et international ; il accueille des intervenants d'une qualité exceptionnelle et n'a pas été conçu selon les clivages traditionnels qui traversent le milieu médical français, que vous dénoncez régulièrement et qui ne laissent pas place à la question du sel. Le financement intégralement public du colloque garantit son indépendance sur un sujet aux enjeux sensibles ou stratégiques pour les industries pharmaceutique et agroalimentaire.

Enfin, ce colloque aborde les questions de santé publique et les stratégies d'action et de prévention mises en œuvre dans différents pays. En France, il doit permettre aux chercheurs de présenter un travail considérable et original mené durant les derniers mois et débouchant sur des propositions d'actions solides et éprouvées faites aux Ministres respectivement chargés de la Santé, de l'Agriculture et de la Consommation en vue de réduire les apports sodés. A cet égard, un rapport a été récemment transmis aux personnes intéressées et sera présenté dans le cadre de cette conférence par un groupe de travail investi de plusieurs missions :

- proposer des mesures pour respecter une distribution de sel de 5 à 12 g/j ;
- identifier les aliments vecteurs de l'essentiel de l'apport sodé alimentaire;
- proposer des recommandations effectives d'abaissement de la teneur en sel de certains aliments vecteurs tout en respectant l'approche organoleptique, sécuritaire et technologique ;
- effectuer des simulations de l'apport sodé de la population française ;
- réfléchir sur les moyens de communication devant accompagner les mesures d'abaissement de la consommation de sel.

Ce mandat a été accompli en neuf mois environ, bien que le groupe de travail ait réuni à la fois des scientifiques, des représentants de consommateurs ou d'organismes professionnels et alors que le contexte de la création de ce groupe n'incitait pas particulièrement ces acteurs à la coopération. Une discussion constructive et volontariste, notamment du point de vue de la branche professionnelle alimentaire, a toutefois permis à ces derniers de proposer ensemble des voies concrètes pour atteindre des objectifs de santé publique à partir de logiques et de contraintes diverses et parfois contradictoires.

Le président du groupe de travail, le Dr. Serge Hercberg, a largement contribué à cette réussite. Egalement vice-président du Comité stratégique du Programme National Nutrition - Santé (PNNS), il garantit la cohérence des actions conduites dans ce cadre. De même, le Pr. Joël Ménard, qui coordonne le Plan cardiovasculaire, a été membre du groupe de travail et du Comité d'organisation du colloque.

L'Afssa a donc le sentiment d'avoir mobilisé les différentes compétences professionnelles et scientifiques qu'elle réunit et d'avoir joué son rôle. Partant de l'évaluation scientifique, elle recommande ainsi diverses actions susceptibles de s'intégrer dans la politique ministérielle de santé publique.

Bernard KOUCHNER

Ministre délégué à la Santé
Paris, France

Monsieur le Directeur Général, Monsieur le Professeur, je vous remercie d'avoir précisé que l'ensemble des considérations concernant le sel s'intègre dans une problématique de santé publique, dont relèvent diverses agences telles que l'Afssa. Traversé d'interrogations, voire d'inquiétudes, ce champ connaît néanmoins une progression manifeste et rend ainsi possible aujourd'hui un tel congrès. Dans cette perspective, le présent colloque doit permettre d'approfondir les aspects scientifiques de la relation entre sel et santé. Cette tâche se révèle relativement lourde au regard des débats animant la nutrition française mais essentielle en tant que thématique nutritionnelle.

Les enjeux de santé publique liés à la consommation du sel

Les conséquences à long terme d'une alimentation insatisfaisante sont évidentes. Aujourd'hui, les pathologies majeures les plus fréquentes en France, qui sont souvent invalidantes et mortelles, nuisent à la qualité de la vie et coûtent à la société, sont largement générées par la nutrition. C'est le cas de multiples cancers, des maladies cardiovasculaires, du diabète ou de l'ostéoporose. Le Programme National Nutrition - Santé (PNNS), lancé par le gouvernement il y a un an, coordonné par la Direction Générale de la Santé et devant être mis en œuvre jusqu'en 2005, vise des objectifs quantifiés, préconise des stratégies et des actions, fournit des moyens et affirme la cohérence indispensable de l'action publique et privée dans le domaine de la nutrition.

L'impact de la consommation du sodium constitue une grave et ancienne préoccupation médicale. Le régime sans sel individuel fait partie de l'arsenal thérapeutique mais sa mise en œuvre se révèle souvent extrêmement complexe dans la vie quotidienne des patients qui manifestent parfois une résistance à le suivre. L'incidence de la consommation de sel par la population générale sur le développement de pathologies chroniques n'a certainement pas été suffisamment prise en compte. En France, cette consommation est aujourd'hui estimée à 9 ou 10 g de sel par jour et par habitant en moyenne. Mais 20 % de la population consomme plus de 12 g, cette quantité s'avérant inacceptable. De fait, le fait de saler un plat avant de le goûter constitue une pratique spécifiquement française qui choque les étrangers.

La consommation de sel évolue en réalité avec la transformation des modes alimentaires et la diversification de l'offre. Alors que la longévité progresse, les conséquences, pour les générations futures, de cette pratique nutritionnelle doivent dès aujourd'hui faire l'objet de mesures préventives de santé publique prises sur la base de connaissances scientifiques. Votre contribution doit d'ailleurs s'inscrire dans cette perspective. Quoi qu'il en soit, vous devez prendre en compte les diverses dimensions de l'alimentation, et notamment celles du plaisir, du partage et de la convivialité qui caractérisent les repas accompagnant en France la plupart des événements marquants de l'existence.

De fait, alimentation équilibrée n'est pas synonyme de tristesse. Au contraire, l'alimentation s'enracine profondément dans nos cultures et se charge dans certains cas d'émotions, de symboles, de rêves et plus généralement d'humanité. Or une représentation élargie de la santé - et de vos travaux - impliquent respect et valorisation de cette dimension.

La relation entre sel et santé s'inscrit dans une perspective historique. Essentiel à la vie, le sel a tout d'abord fait l'objet d'une quête incessante de la part des populations qui en étaient privées, comme le montre encore le spectacle extraordinaire de la caravane du sel qui traverse les déserts du Mali ou la Cordillère des Andes pour rejoindre les oasis ou les montagnes isolées. Ensuite, le sel a toujours joué un rôle commercial essentiel. Au XIVe siècle, il fonde, en France, la perception de la gabelle destinée à financer la guerre. Par ailleurs, il représente, avec le pain, un symbole fort d'hospitalité pour des peuples enclavés, par exemple dans les Balkans. Enfin, avant que les chaînes de froid ne soient maîtrisées, le sel a constitué un moyen de conservation historique des aliments, encore utilisé dans certains cas. Il garantit aujourd'hui la sapidité de nombreux produits. « Sans sel, la vie n'aurait certainement pas de sel – le sel de la vie et le sel de la terre ».

Consommation de sel et politiques de santé publique

Le goût du sel s'apprend dès l'enfance. La réglementation sur les produits diététiques de la petite enfance fixe une limite maximale mais les consommateurs aiment les saveurs vives incitant ainsi à augmenter la teneur en sel des aliments commercialisés. L'excès de sel dans l'alimentation résulte certainement de la conjugaison de plusieurs facteurs : demande des consommateurs, absence d'autres agents de saveur, accoutumance au goût salé affadissant toute nourriture brutalement moins salée. Plus de 70 % du sel consommé provient aujourd'hui de produits achetés plutôt que de la salière.

Dès 1999, l'Afssa a réalisé un important travail de compilation et d'analyse scientifique, qui l'a conduite à présenter il y a un an le rapport sur les apports nutritionnels conseillés pour la population française. Concernant le sel, un avis provisoire avait alors été publié, les scientifiques ne parvenant pas à une lecture claire et univoque des données disponibles. En outre, le PNNS ne mentionne pas d'objectif dans ce domaine mais vise à réduire en cinq ans de 10 mm Hg la pression artérielle systolique des adultes. Le présent colloque doit permettre de débattre de cette question sur les plans épidémiologique, métabolique et génétique. Le PNNS tend plus globalement à l'amélioration de l'état de santé de la population par la nutrition, à travers l'évolution des comportements consuméristes et de l'offre alimentaire. Les risques de pathologies liées à la nutrition devraient en sortir réduits.

Je souhaite la bienvenue au Pr. Joël Ménard, ancien Directeur Général de la Santé et qui se trouve à l'origine du regain d'intérêt du Ministère de la Santé pour la nutrition. Il présidera la table ronde sur les politiques de santé publique relatives au sel menées dans divers pays. Ses expériences essentielles contribueront à orienter les décisions nécessaires dans notre pays.

En mars 2001, l'Afssa a formulé des propositions visant à faire évoluer la consommation de sel en France. Je remercie à ce titre le Dr. Serge Hercberg qui a piloté le groupe de travail "Sel" dont la méthode exemplaire était fondée sur le dialogue et la pluri-sectorialité mise en avant dans le PNNS. Cette initiative a réuni des scientifiques de compétence reconnue, des représentants des diverses filières industrielles et artisanales, de la distribution alimentaire et de la restauration collective, des consommateurs, des professionnels de la communication et des agents publics.

Comme je le disais aux assureurs à propos de la loi sur le droit des malades et l'amélioration de la qualité, les questions de santé excluent la complaisance et ne doivent pas laisser s'éterniser le dialogue. De ce point de vue, la création de l'Afssa représente un progrès considérable. Une discussion constructive permet en effet de faire émerger des propositions claires.

Le groupe de l'Afssa a ainsi construit des recommandations précieuses sur la base d'une analyse approfondie de la situation française. Ses conclusions vous seront communiquées au cours de ce colloque. En se fixant l'objectif réaliste d'une réduction d'environ 4 % par an sur cinq ans de l'apport sodé et en suggérant à cette fin des stratégies, le groupe de travail répond à un besoin de ma politique nutritionnelle de santé publique. Je porterai la plus grande attention à ces recommandations afin de mettre en œuvre le plus rapidement possible toutes actions utiles dans ce cadre. Je les attends d'ailleurs impatiemment.

Je demande à la Direction Générale de la Santé de veiller à la cohérence des ambitieux programmes nutritionnels qu'elle coordonne.

Nous nous félicitons du fait que certains professionnels de l'alimentation, conscients que leurs produits constituent des sources importantes d'apport en sel, se soient montrés ouverts à une réduction réglementaire progressive de la teneur en sel de denrées telles que le pain.

A ce titre, la sensibilisation du public et la formation des professionnels de la santé est fondamentale et doit s'intégrer dans la stratégie d'information générale du PNNS. Elle portera sur :

- la relation entre sel et santé ;
- les principales sources alimentaires de sel ;
- les comportements favorables à un apport adéquat en sel par l'alimentation.

Avec la Direction Générale de la Consommation, nous devrons étudier les modalités d'un meilleur étiquetage des aliments sur leur teneur en sodium.

Seule la combinaison de la réglementation, de l'incitation, de la formation, de l'information et de la surveillance permettra d'atteindre l'objectif visé. L'action coordonnée des Ministères de l'Agriculture, de la Consommation et de la Santé conditionnera l'impact des décisions de santé publique qui seront prises.

Je remercie donc les éminents scientifiques européens et américains, l'Afssa et son Directeur Martin Hirsch, l'INSERM et Pierre Ducimetière. En mettant en œuvre les conditions d'une expertise indépendante, tous ces acteurs concourent en effet à l'avancée de la connaissance dans le domaine de la relation entre nutrition et santé et à la formulation de recommandations essentielles de santé publique fondamentales pour la prise de décision qui m'incombera après consultation de la Direction Générale de la Santé.

Je vous souhaite la bienvenue ainsi que des travaux fructueux. Je vous remercie.

La place des études internationales en épidémiologie cardiovasculaire
L'exemple des relations "sel - santé"

Pierre DUCIMETIERE
INSERM, Villejuif, France

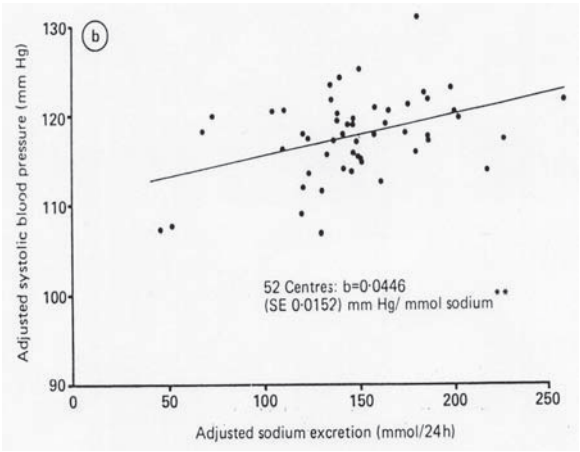
Les connaissances épidémiologiques concernant les maladies cardiovasculaires et particulièrement les maladies ischémiques du cœur ont reçu de grands développements durant les trente dernières années. Parallèlement, la mortalité cardiovasculaire a fortement diminué durant cette période dans l'ensemble des pays industrialisés à l'exception des pays de l'est de l'Europe et cette évolution a pu être documentée grâce à des projets internationaux de grande envergure comme le Projet MONICA [1].

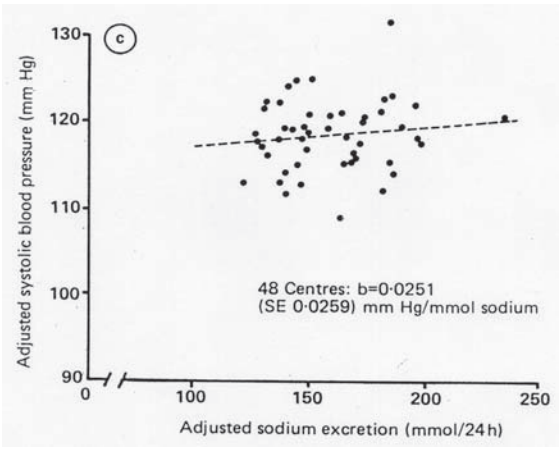
L'épidémiologie géographique a joué un rôle décisif dans le progrès des connaissances en exploitant la grande variabilité des modes de vie que l'on peut observer entre les populations humaines à une époque donnée et de leur évolution dans le temps. Au-delà des informations "écologiques" ainsi réunies, la comparaison des résultats d'études d'observation et d'études expérimentales menées dans des populations variées et la recherche de leur cohérence est une étape essentielle avant toute généralisation des mesures de prévention à l'échelle des populations.

L'étude des relations entre la consommation de sel, le niveau de pression artérielle et l'état de santé en particulier la pathologie cardiovasculaire illustre parfaitement cette démarche ainsi que le montrent plusieurs exposés effectués lors de ce colloque.

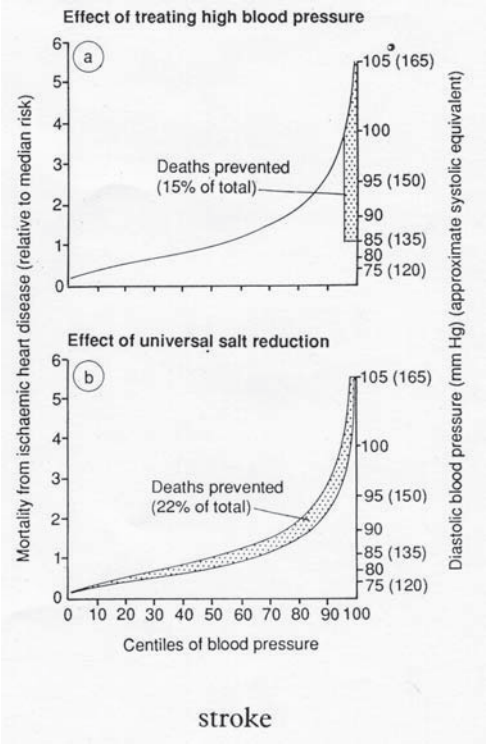
Deux travaux publiés respectivement en 1988 et 1991 dans le *British Medical Journal* ont représenté des étapes importantes dans la connaissance épidémiologique dans ce domaine.

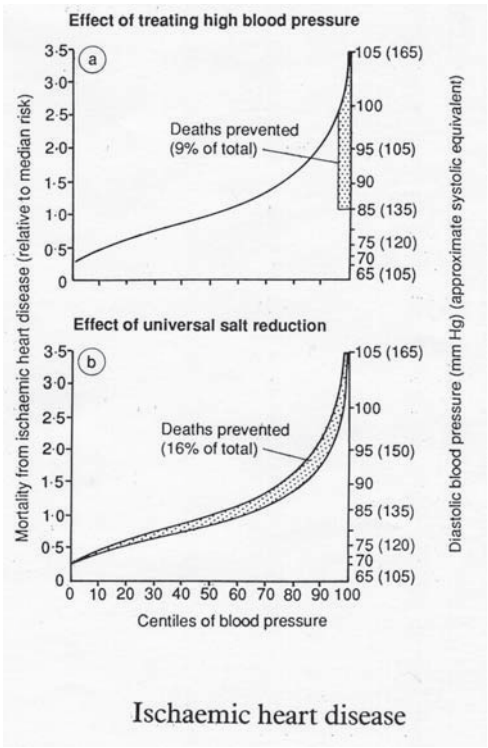
Le premier [2] a rapporté les résultats d'une étude coopérative sans précédent (INTERSALT) puisque la relation inter-groupes et intra-groupes entre l'excrétion urinaire de sodium et la pression artérielle a pu être étudiée selon un protocole commun dans 52 groupes de population dans le monde entier. Une relation cohérente a été mise en évidence mais son amplitude est faible, du moins si une correction prenant en compte la grande variabilité intra-individuelle de l'excrétion urinaire n'est pas appliquée.





Le second travail [3] représente l'exemple accompli d'une méta-analyse de données d'observation inter- et intra-populations couplée à une méta-analyse de données expérimentales de réduction de la consommation de sel chez l'homme. Son but était de rechercher la compatibilité des résultats d'observation et d'expérimentation provenant généralement d'études très différentes mais à partir desquelles il était possible d'estimer la baisse attendue de pression artérielle associée à une réduction donnée de l'apport en sel. Cette baisse, faible sur un plan individuel puisqu'elle est de l'ordre de quelques mm Hg, aurait néanmoins des conséquences importantes sur le plan de la santé publique si elle concernait l'ensemble de la population. Les auteurs ont pu calculer que la mortalité par accident vasculaire cérébral diminuerait de 22 % si la consommation moyenne de sel de la population baissait de 50 millimoles par jour alors que le traitement médicamenteux de tous les hypertendus ayant plus de 85 mm Hg de pression diastolique ne permettrait d'obtenir une baisse de seulement 15 %. Les effets attendus sur la mortalité coronaire sont plus faibles (respectivement 16 et 9 %) mais conduisent aux mêmes conclusions sur l'intérêt d'une approche collective (et donc non pharmacologique) de la prévention cardiovasculaire en plus de l'approche individuelle qui, elle, ne devrait s'appliquer qu'à des individus à très haut risque. L'exemple de la réduction de la consommation de sel dans nos pays industrialisés est, de ce point de vue, particulièrement frappant.

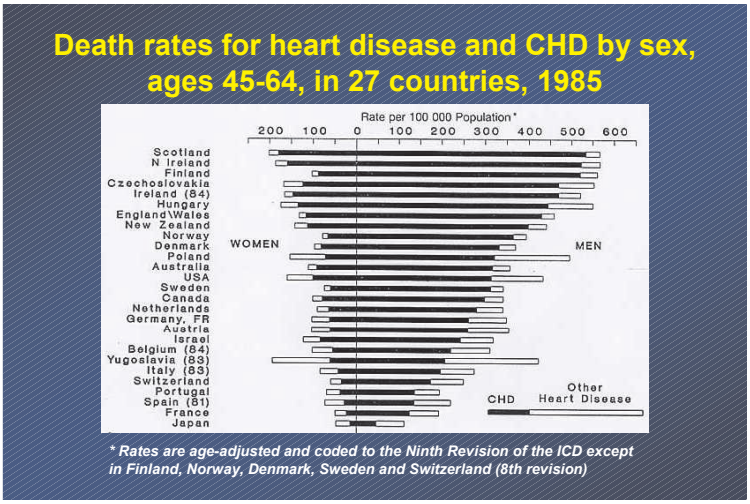


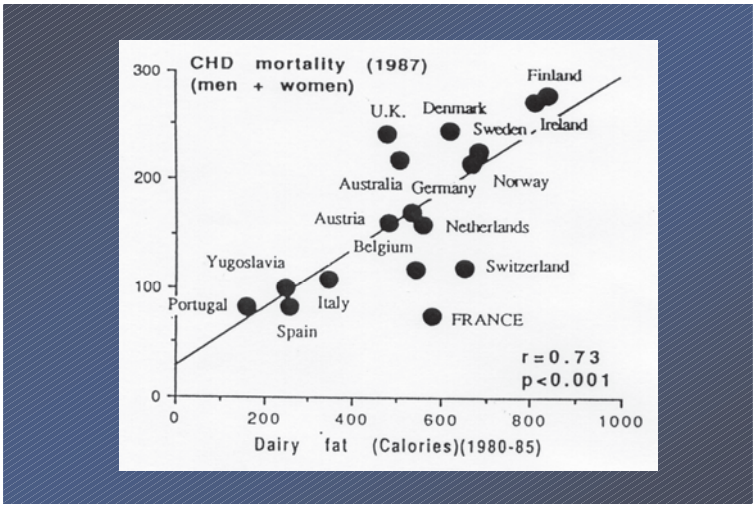


Cependant ainsi que le mentionnait le titre d'un article célèbre de J. Stamler paru en 1989 dans l'*International Journal of Epidemiology* : "Opportunities and pitfalls in international comparisons related to patterns, trends and determinants of CHD mortality" [4], les comparaisons internationales présentent des limitations et peuvent parfois conduire, si l'on n'y prend pas garde, à des hypothèses contestables qu'il est ensuite difficile d'écarter.

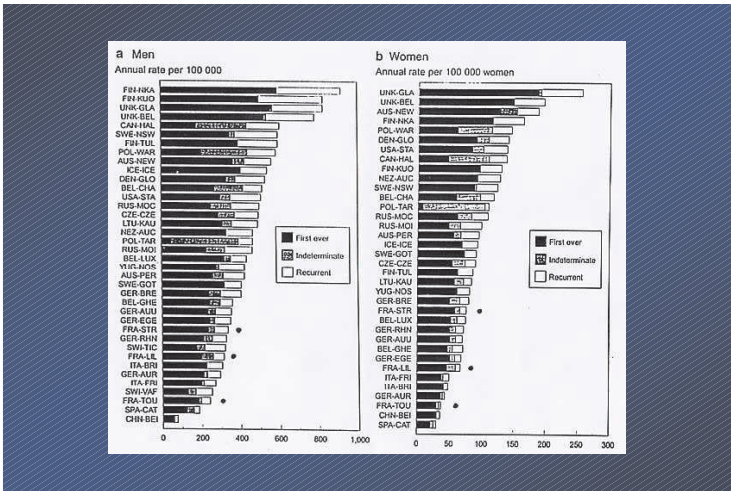
La fréquence particulièrement basse de la mortalité déclarée d'origine coronaire dans les statistiques annuelles françaises depuis les années 1950 avait attiré l'attention de nombreux observateurs. Mise en relation avec des données de consommation alimentaire issues de statistiques de l'agriculture, elle montrait la position "paradoxale" de la

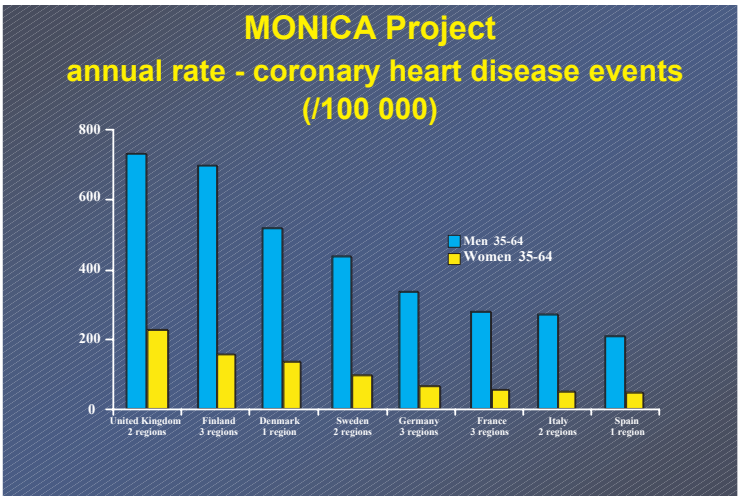
population française, dont l'alimentation en termes de macro-nutriments serait proche de celle des pays d'Europe du nord dont la mortalité coronaire est beaucoup plus élevée.





Il a fallu attendre les données comparatives d'incidence de l'infarctus du myocarde et du décès coronaire dans trois régions françaises participant au Projet MONICA pour établir que le "poids" de la pathologie coronaire y est du même ordre de grandeur que celui observé dans des régions voisines d'Europe du centre et du sud. Les résultats montrent qu'il existe en Europe de l'ouest, un gradient nord-sud de la morbidité coronaire et la population française n'est pas spécifiquement protégée compte tenu de sa position géographique [5]. Cet exemple illustre les précautions nécessaires pour interpréter des données de comparaisons géographiques lorsqu'elles ne sont pas obtenues selon des protocoles communs standardisés.





Références

1. Tunstall-Pedoe H, Kuulasmaa K, Mähönen M et al. for the WHO MONICA Project. Contribution of trends in survival and coronary event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA Project populations. *Lancet* 1999;353:1547-57

2. Intersalt Cooperative Research Group. Intersalt : an international study of electrolyte excretion and blood pressure. Results for 24-hour urinary sodium and potassium excretion. *BMJ* 1988;297:319-28

3. Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? I Analysis of observational data among populations II Analysis of observational data within populations III Analysis of data from trials of salt reduction. *BMJ* 1991;302:811-28

4. Stamler J. Opportunities and pitfalls in international comparisons related to patterns, trends and determinants of CHD mortality. *Int J Epidemiol* 1989;18:S3-S18

5. Ducimetiere P, Lang T, Amouyel P, Arveiler D, Ferrières J. Rates of coronary events are similar in France and southern Europe. *BMJ* 2000;320:249-50.

Gènes, hypertension et sensibilité au sel

Genes, hypertension and salt sensitivity

Session 1

animée par Pierre MENETON
INSERM, Paris, France

Cette session a réuni :
Xavier JEUNEMAÎTRE, Hôpital Européen Georges Pompidou, Paris, France ;
Giuseppe BIANCHI, San Raffaele Hospital, Milan, Italie ;
Pasquale STRAZZULLO, Federico II University, Naples, Italie ;
Gary K. BEAUCHAMP, Monell Chemical Senses Center, Philadelphie, Etats-Unis.

Introduction de M. Pierre MENETON

La première session est consacrée aux gènes, à l'hypertension, aux différences inter-individuelles dans la sensibilité au sel et aux différences de perception du sel. Comme tout paramètre biologique, le niveau de pression artérielle individuelle est déterminé par une interaction indissociable entre des gènes et des facteurs environnementaux. Quels gènes interviennent donc dans le contrôle de la pression artérielle ?

A priori, cette question n'a rien à voir avec le sel. Durant les dix dernières années, des individus présentant une pression artérielle basse ou élevée ont fait l'objet d'une approche génétique aveugle fondée sur les données acquises dans le cadre du programme de séquençage du génome humain pour identifier les gènes en cause dans les différences de pression artérielle observées. Aujourd'hui, une vingtaine de gènes a ainsi été identifiée, même si ces gènes sont certainement plus nombreux.

M. Jeunemaître résumera les résultats des études de génétique humaine réalisées durant les deux dernières décennies. Quant à M. Bianchi, il vous entretiendra du gène particulier qu'il a lui-même découvert. Nous débattrons ensuite tous ensemble de ces questions.

Gènes influençant le métabolisme du sel et la pression artérielle

Xavier JEUNEMAÎTRE
Hôpital Européen Georges Pompidou, Paris, France

Je remercie l'Afssa pour son invitation.

Je vais vous présenter rapidement les aspects génétiques de la pression artérielle, sachant que cette discipline a évolué à partir de collections familiales importantes et des avancées impressionnantes réalisées sur le génome humain.

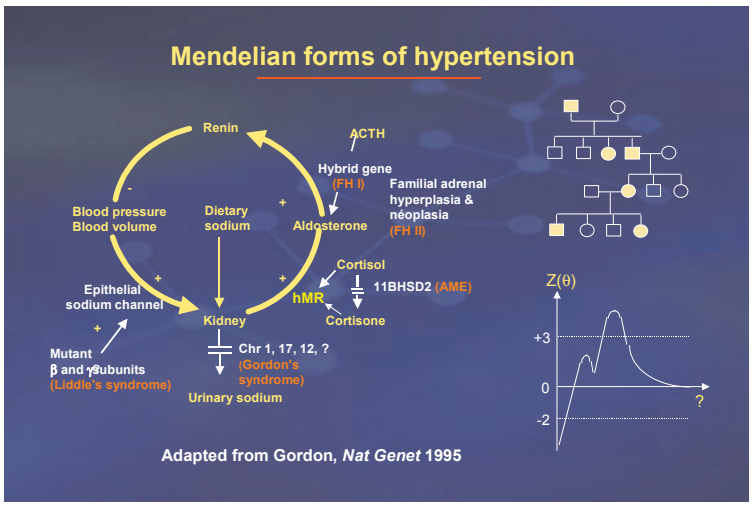
La pression artérielle subit l'influence des gènes et de l'environnement, dont l'interaction reste peu connue même si des pressions importantes de l'environnement alimentaire se manifestent à travers la relation entre le poids ou l'âge et la pression artérielle d'une part, et à travers les relations plus complexes entre l'alimentation salée et la pression artérielle d'autre part. Ces relations doivent permettre de discerner les effets entre un gène particulier, son interaction environnementale et son effet sur la pression artérielle.

L'analyse génétique humaine de la pression artérielle est effectuée schématiquement selon deux approches. L'approche populationnelle est fondée sur l'idée d'une hypertension essentielle commune, sachant que les 10, 20 ou 30 % de la population, selon les tranches d'âge, qui consultent pour hypertension artérielle sont souvent issus de familles qui possédent plusieurs gènes de susceptibilité de la pression artérielle. Or, chacun de ces gènes a souvent un effet relativement faible et donc difficile à identifier. A l'inverse, dans certaines familles caricaturales, il y a une transmission forte mendélienne de l'élévation de la pression artérielle, souvent accompagnée de troubles biologiques particuliers. Dans ce cas, la découverte des gènes impliqués dans l'augmentation de la pression artérielle se révèle plus simple grâce aux progrès de la génétique, même s'il s'agit souvent de formes rares et particulières de la maladie.

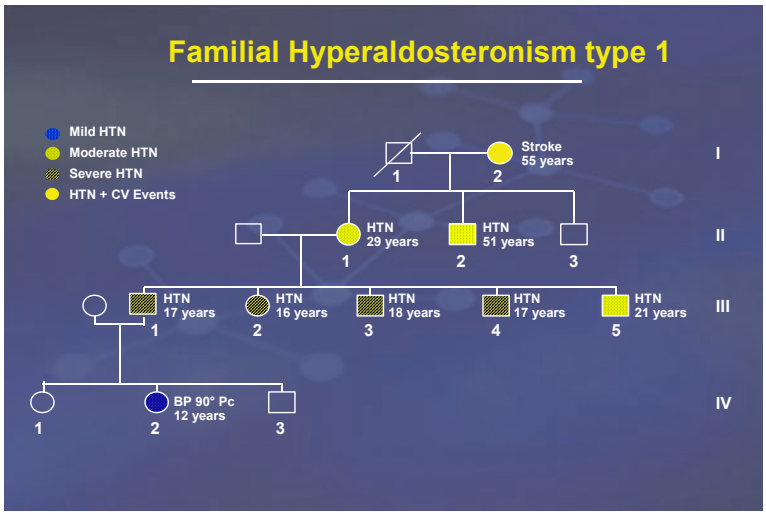
L'hypertension résultant de la combinaison de gènes correspondant au métabolisme hydrosodé et d'un environnement particulier

De nombreux sujets présentent une hypertension liée à des facteurs et gènes multiples – plus précisément à une combinaison de gènes dans un environnement particulier. Ainsi, avec un même fond génétique, vous n'élèverez pas votre tension artérielle si vous ne subissez pas le facteur environnemental qui vous rend susceptible d'élever votre tension. En revanche, pour de rares familles qui présentent un gène particulier, l'environnement joue alors un rôle moins important.

Dans les familles à transmission mendélienne de la maladie, la majorité des gènes corresponde au métabolisme hydrosodé et du tonus vasculaire, hormis un cas particulier d'hypertension décrit dans une grande famille turque et pour lequel on ne connaît pas le gène impliqué. Je voudrais vous fournir quelques exemples de ces hypertensions dites monogéniques.



Le premier exemple concerne une maman de 29 ans et ses cinq enfants de 15 ou 20 ans qui présentent une hypertension sévère. Au niveau des troubles biologiques, les sujets en question avaient une anomalie génétique particulière, correspondant à un réarrangement chromosomique qui augmente la synthèse de l'aldostérone qui est elle-même largement responsable de l'équilibre hydrosodé par les réabsorptions, notamment de sodium, au niveau du tubule distal rénal. Trente à cinquante familles de ce type ont été décrites dans le monde.



Le second exemple rare d'hypertension concerne un garçon de quatorze ans chez lequel c'est l'effecteur de l'aldostérone au niveau du tubule distal rénal qui est anormal, sachant que la transmission est autosomique dominante. Or un médicament connu peut bloquer sélectivement ce type de canal. Les anomalies génétiques ont bien été décrites : elles se traduisent par un nombre excessif de canaux à la membrane et engendrent de ce fait une rétention de sel plus importante. Par conséquent, les enfants normaux atteints de cette particularité deviennent hypertendus à vingt ans et sont généralement victimes d'accidents vasculaires cérébraux autour de quarante ou cinquante ans s'ils ne bénéficient pas d'un traitement spécifique.

LIDDLE 'S SYNDROME

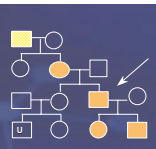
- 14 years old boy
- BP 180/120 mmHg + positive familial history of HTN
- Hypokalaemia 3.3-3.7 mEq/l
- Suppressed PRA : 0.05 ng Angl/ml/h (<<N)
- Very low aldosterone : 20 pg/ml (<<N)

- EFFICACY OF AMILORIDE (10mg/d)

	Basal	Spironolactone	Amiloride
BP (mmHg)	180/120	162/118	120/70
K+ (mmol/L)	3.3	3.3	4.0
PRA (ng Angl/ml)	0.05	0.05	1.20

Le troisième exemple illustre une nouvelle forme d'hypertension avec transmission dominante caractérisée par un taux de potassium trop élevé - même si la pression artérielle n'est pas dramatiquement élévée. Les sujets concernés répondent bien au diurétique thiazidique.

Familial Hyperkalemic Hypertension (Gordon syndrome)



	Age (years)	Sex (M/F)	BMI (Kg/m2)	BP (mmHg)	K+ (mmol/L)	Creatinine (µmol/L)
Proband	36	M	26.2	160/100	5.6-6.4	74
Mother	58	F	25.4	170/95	5.2-5.7	65
Daughter	10	F	17.8	120/80	5.3-5.5	42
Son	6	M	15.2	110/70	5.5-5.8	37

	CO2T (mmol/L)	Cl- (mmol/L)	P.R.A (ngAI/ml/h)	Aldo (pg/ml)	Response to HCTZ
Proband	18-26	111	0.08	152	++
Mother	22	112	-	-	+
Daughter	17-21	111	0.5	144	++
Son	16-20	113	0.4	91	++

Cette année, nous avons mis en évidence, en collaboration avec l'équipe américaine de Rick Lifton (Yale, USA), deux gènes placés sur le chromosome 12 et 17 et correspondant à une nouvelle famille de gènes codant pour des sérine-thréonine kinases dont le rôle reste inconnu, mais qu'il sera important de diagnostiquer dans le cadre des recherches sur l'hypertension artérielle.

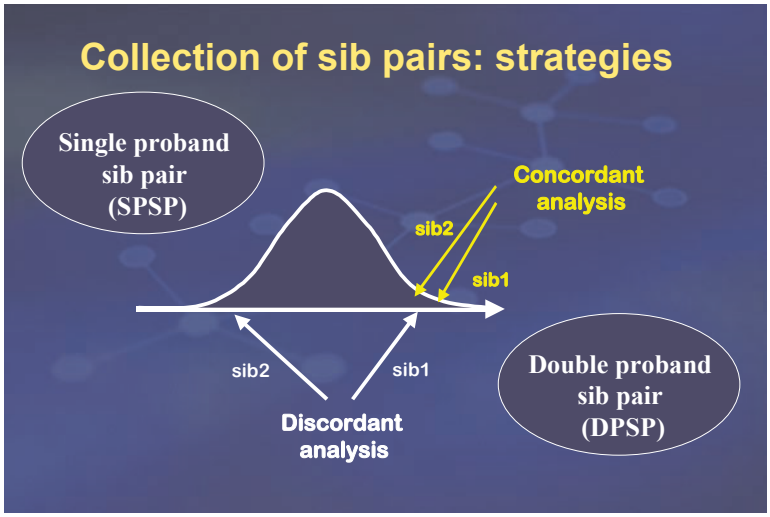
Dans l'état actuel de nos connaissances, les maladies héréditaires monogéniques avec hypertension artérielle sont reliées à des gènes qui entraînent une réabsorption de sodium ou de chlore excessive.

L'hypertension résultant seulement de gènes de susceptibilité à l'élévation de la pression artérielle

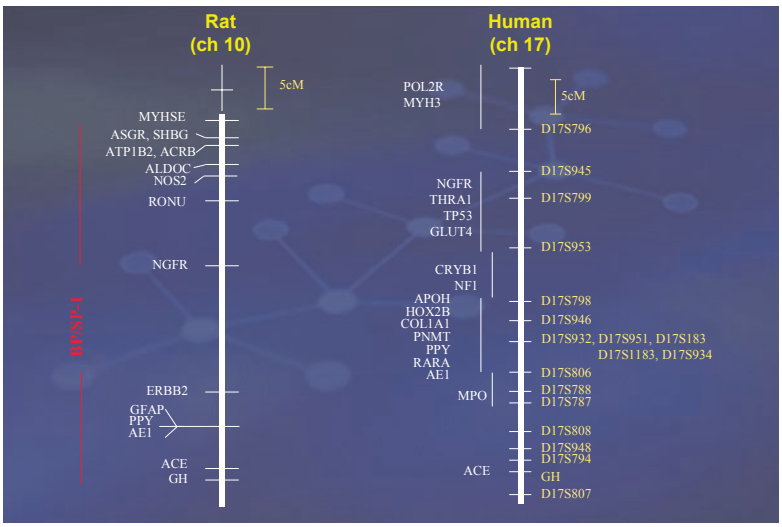
La recherche génomique « au hasard »

Sur le plan de la recherche au hasard sur l'ensemble du génome, les chercheurs tentent de retrouver les gènes de susceptibilité à l'élévation de pression artérielle présents dans l'ensemble de la population.

Les marqueurs du génome humain permettent aujourd'hui de cribler le génome sur ces familles pour savoir si les frères et sœurs hypertendus présentent un excès de concordance pour ces gènes. En analysant deux frères hypertendus ou un frère hypertendu et un frère normotendu, on espère que pour le gène de susceptibilité, ils seront concordants dans le premier cas, et discordants dans le second cas. Les résultats de ces analyses ont eu le mérite de montrer qu'il n'existe pas de gène majeur de susceptibilité à l'hypertension artérielle, mais une pluralité importante de gènes à effet faible.



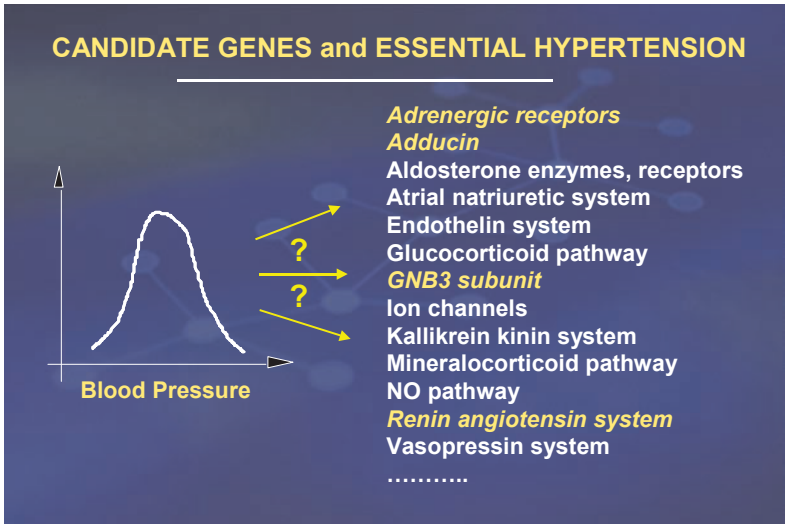
De ce fait, ces études ont en partie créé de la confusion puisqu'elles ont mis en évidence non seulement plusieurs régions chromosomiques responsables de l'hypertension, mais des régions différentes d'une étude à une autre, probablement en raison de modes différents de sélection des familles analysées, de la pluralité des effets environnementaux, de l'origine ethnique parfois différente des sujets et enfin de l'effet faible de chacun des loci putatifs. Une région récurrente dans les études et qui parait une des plus intéressantes se situe au niveau du chromosome 17, comme le montre un test statistique sur la population de Framingham. Cette région correspond également à une région du chromosome 10 de rat sur lequel les chercheurs ont montré la présence d'un locus de susceptibilité à l'hypertension artérielle à partir de l'analyse de souches hypertendues et normotendues. Par conséquent, nous partagerions apparemment avec d'autres espèces une région de susceptibilité à l'hypertension artérielle, sachant que les gènes impliqués ne sont pour le moment pas identifiés.



L'analyse de gènes connus

L'autre stratégie développée dans les populations humaines consiste à étudier des gènes dont on connaît la fonction et pour lesquels une variation génétique pourrait élever la pression artérielle, ou, en tout cas, entraîner des différences d'un sujet à un autre en modifiant le fonctionnement enzymatique d'un récepteur ou d'un peptide.

La relation entre 100 à 150 gènes et la pression artérielle a été testée sur les dix dernières années, les résultats obtenus étant parfois contradictoires.



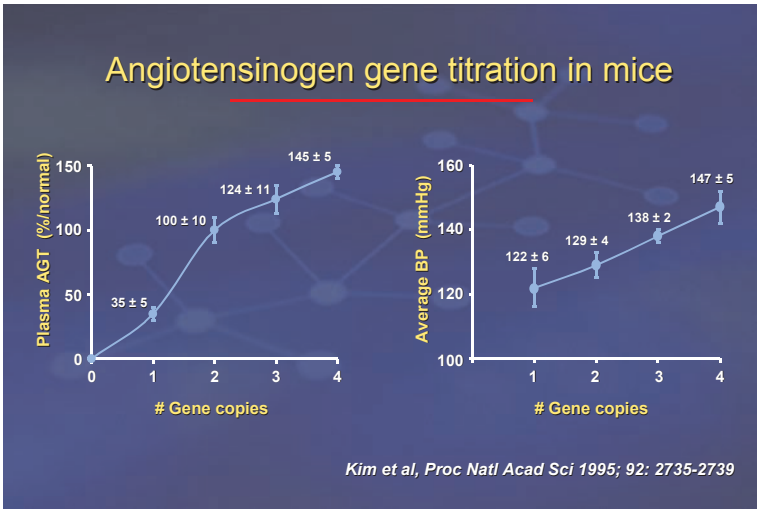
Les résultats les plus concordants portent sur les gènes codant pour l'adducine, un récepteur adrénergique, une G-protéine impliquée dans le transport ionique et le système rénine-angiotensine. Je vous fournis quelques exemples de ce dernier cas.

Le système rénine-angiotensine correspond essentiellement à une cascade enzymatique avec un substrat (l'angiotensinogène), une enzyme spécifique (la rénine) puis une autre enzyme qui clive l'angiotensine I en angiotensine II (enzyme de conversion de l'angiotensine I), et enfin un récepteur (récepteur de type 1 de l'angiotensine II).

Tous ces gènes sont désormais identifiés et nous en connaissons les variations génétiques. Nous tentons maintenant de savoir si ces variations sont fonctionnelles. Certaines le sont. Par exemple, dans le cas du gène de l'angiotensinogène, une série de variations génétiques le plus souvent associées les unes aux autres font en sorte

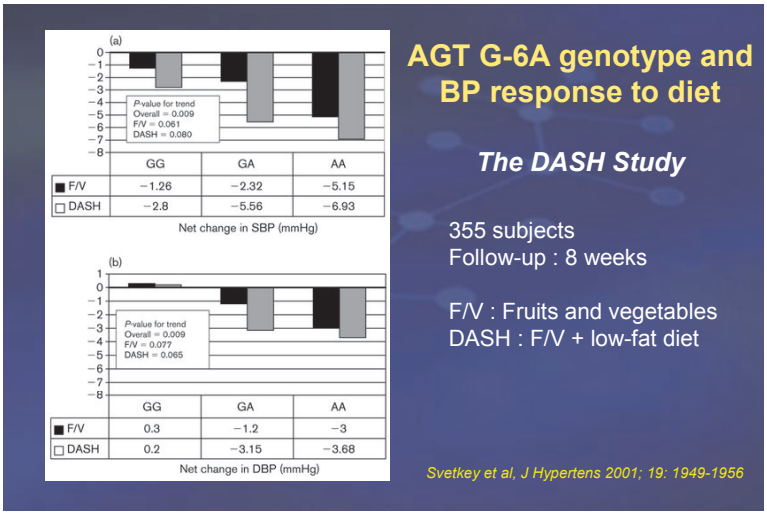
d'augmenter le taux de substrat contenu dans le sang de 10 à 20 %. L'effet de ce taux sur le plan physiopathologique est plus difficile à mettre en évidence, de nombreuses études tentant de comprendre les relations simples entre augmentation du substrat et tendance à l'augmentation de la pression artérielle.

Le travail de l'équipe de Smithies (USA) accompli il y a plus de cinq ans montre, grâce au modèle animal, que le nombre de copies du gène de l'angiotensinogène a pu être modifié chez la souris. Par suite, la production de la protéine et la pression artérielle augmentent, démontrant ainsi une relation de causalité entre augmentation du substrat et augmentation de la pression artérielle.



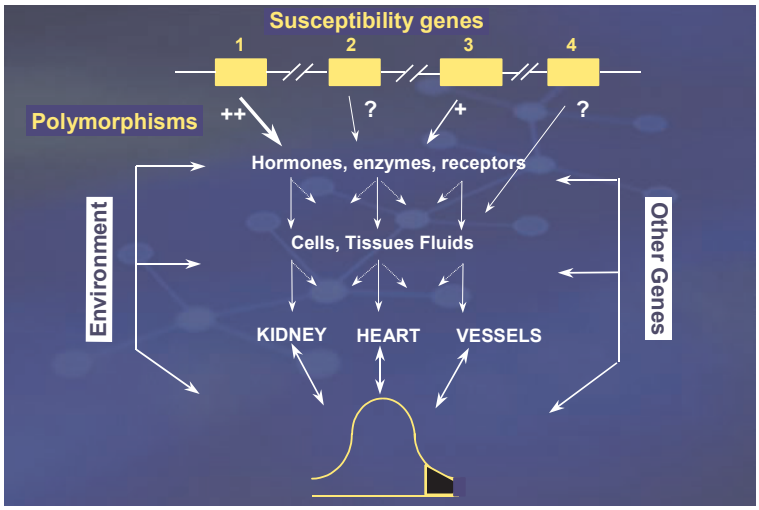
La recherche sur des gènes de susceptibilité exige donc un déchiffrage physiopathologique complexe entre les variations, leur fonctionnalité cellulaire, leur fonctionnalité au niveau d'un tissu, d'un organe complet et d'un individu.

Une étude récente sur ce polymorphisme humain partiellement associé à la pression artérielle et à la concentration plasmatique de l'angiotensinogène, met en évidence une tendance entre la présence de ce polymorphisme et le fait de suivre un régime riche en fibres et pauvre en sel.



Je ne vous ai montré que certains éléments très simples des découvertes génétiques récentes dans le domaine de l'hypertension artérielle. Nous ne disposons pas de réponse simple pour un trait complexe comme l'hypertension artérielle. Nous n'observons qu'un phénotype qui résulte d'une interaction entre gènes et environnement. Nous aurons donc des difficultés à discerner le rôle de chaque paramètre et combinaison de paramètres.

Je vous remercie.



The alpha-adducin gene's history

Giuseppe BIANCHI
San Raffaele Hospital, Milan, Italy

Many approaches to the genetics of hypertension have been proposed. Here I will illustrate our approach that consists in an integration of different disciplines. In particular:

a] pathophysiology of hypertension caused by an experimental renal injury in dogs and rats or by a genetic mechanisms in an inbred strain of rats, followed by cellular and biochemical studies aimed at detecting a primary protein alteration responsible of the sequence of events leading to hypertension. When possible, all these studies have also been performed in humans in order to provide an appropriate comparison between the two species.

b] detection of polymorphisms in the genes coding for the protein involved in the pathophysiological phenomena mentioned above and performance of the appropriate genetic studies in rats and humans to assess their role in causing arterial hypertension.

Following the demonstration that after some weeks from the initial blood pressure rise produced by renal artery constriction, the changes more directly linked to the renal injury disappear, it was hypothesized that the same pattern of changes may occur also in primary or polygenic forms of human hypertension where a subtle kidney abnormality may cause hypertension without overt renal alterations [1-3].

This hypothesis was proved with kidney cross-transplantation between MHS rats (with "genetic" form of hypertension) and its normotensive control strain (MNS) [4,5]. Also in humans, recipients of kidney from donors with hypertensive parents require larger amount of antihypertensive therapy than the recipients of kidney removed from donors with normotensive parents [6,7]. These results stimulated a series of researches both in human and rats aimed at clarifying the cellular and molecular mechanisms underlying the "genetic message" travelling with the kidney [8-15].

These researches led to the identification of adducin polymorphism, as a candidate "pressor" gene, through the following steps.

1) The comparisons between MHS and MNS carried out using different approaches (Na balance in metabolic cages, isolated kidneys, tubuli and tubular cell, erythrocytes, isolated cell membrane from both renal and red blood cells, genetic crosses) yielded data consistent with the notion that a genetic alteration in cell membrane ion transport, due to a cytoskeleton protein abnormality, could be responsible for an abnormality in renal Na handling leading to the development of at least a portion of hypertension in MHS [16].

2) Cross immunization between MHS and MNS with cytoskeleton membrane proteins stimulated the development of an antibody against a 105 KD protein subsequently identified as adducin [17].

Adducin participates in the assembly of the spectrin-actin cytoskeleton [18,19], it modulates actin polymerization and bundling [20], it binds calmodulin [21], it is phosphorylated by PKC Rho-kinase [22] and tyrosine kinase, it regulates cell signal transduction and cell ion transports [23] through changes in actin cytoskeleton. These cellular properties of adducin may be the basis of its regulatory effect on tubular sodium reabsorption and blood pressure demonstrated by our research group.

Adducin functions within the cell as a heterodimer composed by related but not identical subunits (alfa, beta and gamma) coded by specific genes mapping on different chromosomes.

Human alpha adducin (HaAd) maps in 4p16.3 [24]. Rat alpha adducin (RaAd) maps in chr 14 [25]. In HaAd two polymorphisms Gly46Trp [26] and Ser586Cys have been found associated to hypertension. Between MNS and MHS rats a Phe316Tyr (F316Y) polymorphism has been found [27]. aAd mRNA is differently expressed in all tissues investigated [28].

Human beta adducin (HbAd) maps in 2p14-p13 [29]. Rat beta adducin (RbAd) maps in chr 4 [25]. Three alternative spliced isoforms b2, b3 and b4 have been found. HbAd4 isoform results in an out-of-frame insertion of 63 aminoacids (exon 15), with an alternative stop codon leading to a truncated protein with a different C-terminus amino acid sequence [30]. RbAd4 isoform results in the expression of additional in-frame 18 aminoacids. HbAd4 is polymorphic in humans at codon 599 (silent polymorphism C599T). Between MNS and MHS rat a Gln529Arg (Q529R) polymorphism [27] has been found in RbAd1. bAd mRNA shows restricted expression mainly in brain and erythropoietic tissues [28] even if, by PCR analysis, it can be detected in additional tissues.

Human Gamma adducin (HgAd) maps in 10q24.2-10q24.3 [31]. Rat gamma adducin (RgAd) maps in chr 1 [32]. In humans an A/G polymorphism in intron 11 has been identified. Between MNS and MHS rats a Gln572Lys (Q527K) polymorphism has been found [32]. gAd mRNA is differently expressed in all tissues investigated [28].

3) In an F2 hybrid population (MHS X MNS), rat alpha-adducin (ADD1) F316Y mutation cosegregated with blood pressure [33]. Mutations in rat beta-adducin (ADD2) (Q529R) [33] and rat gamma adducin (ADD3) (Q527K) [32] were not "per se" associated with blood pressure variation but epistatically interacted with rat ADD1 mutation in determining blood pressure level. A wide genome search on the same F2 population using 245 DNA markers confirmed these data [34].

4) MHS rat ADD1 stimulates actin polymerization and enhances actin bundling in a cell free system [35]. Transfection of MHS ADD1 in kidney cells cultures increases the surface expression of Na-K pump while the transfection of the MNS ADD1 variant is without effect [35].

5) We and others detected polymorphisms in human ADD1 [26,36]. The 460Trp allele showed a positive association to hypertension in 8 out of 15 populations examined [37].

6) Hypertensives with the 460Trp allele, compared to those homozygous for the 460Gly one, are salt-sensitive [26], have less steep pressure natriuresis relationship [38], increased proximal tubular reabsorption of lithium [39], larger blood pressure fall on diuretic treatment [26,40], lower PRA [26,40]. These differences, consistent with an increased tubular reabsorption in 460Trp carriers, are also present in a population where no difference in the 460Trp frequency was found between hypertensives and normotensives [40].

7) Linkage analysis with a highly polymorphic DNA marker mapping 20Kb from the human ADD1 locus yielded positive results in two studies [41,42]. Negative results were reported in two other studies [43,44] but DNA markers mapping 660Kb from the ADD1 locus were used.

8) Compared to the "wild" variants, both human and rat "mutated" adducins (either extracted from tissues or prepared by recombinant DNA technology) bind to the Na-K

ATPase with greater affinity, in a cell free system [45]. Therefore, in spite of the difference in the mutation sites between rats and humans, the mutated variants similarly modify the interaction of adducin with the Na-K ATPase [46,47], which is the key enzyme for tubular Na transport.

9) Congenic strains are in preparation by introgressing either in MHS or MNS the ADD1, ADD2, ADD3 of the other strain alone or combined. So far we have obtained two congenic strains where the MHS ADD1 locus increases the blood pressure of MNS rats.

10) Targeted disruption of ADD2 locus (carried out by the Baralle's group) increases systolic blood pressure in mice [47].

In summary, the results on physiological genetics in human and rats and those on genetics in rats are quite consistent for a role of adducin polymorphism in body sodium and blood pressure regulation. Conversely, the data on statistical genetics in humans, summarized at points 5 and 7 seem to be less consistent as occurs for many other candidate genes when this type of approach is applied.

There are possible explanations for this discrepancy: statistical genetics is based on differences in allelic frequency between normotensives and hypertensives or on cosegregation of a given allele with hypertension in families. There are many confounding factors which may be responsible for contrasting results when the methodology of statistical genetics is applied to the dissection of complex diseases like hypertension. Context dependency (either genetic or environmental) of a given hypertension favouring allele may be so strong to blunt its pressor activity or, even, to favour an hypotensive activity. Even though this hypothesis contrasts with most of the current data and theories of statistical genetics, there are observations that suggest careful considerations before rejecting it.

1) When the influence of three polymorphisms (ACE I/D, alpha-adducin Trp/Gly and aldosterone synthase C/T) on the incidence of hypertension expressed as cumulative incidence rate per 1000 subjects/year was studied [48] on 678 normotensive subjects followed for 9.1 years, we showed that, in spite of the fact that Trp/Trp and Trp/Gly alpha-adducin and CC aldosterone synthase genotypes alone were not affecting this incidence, they were able to increase the incidence of hypertension in carriers of ACE DD genotypes (from 44.9 to 70) and decrease this value in carriers of ACE II and ID genotypes (from 34.5 to 20.2). This is clearly an opposite effect of these genotypes on the incidence of hypertension associated to ACE I/D polymorphism.

2) The ACE genotypes DD, DI and II do not have any influence on the blood pressure response to i.v. saline infusion carried out in a cohort of never treated hypertensive patients under very carefully controlled experimental conditions. Conversely, the pressor response was greater in carriers of Gly/Trp alpha-adducin genotype than in those carrying the Gly/Gly alpha-adducin genotype [38].

However, when the three ACE genotypes were splitted according to the two alpha-adducin genotypes, in the carriers of the Trp alpha-adducin, the ACE D allele was associated to an increase in blood pressure in a dose dependent manner, while in carriers of the Gly alpha-adducin genotype, there was a tendency for the D allele to decrease blood pressure in a dose dependent manner.

3) Population studies showed that Trp/Trp adducin carriers tend to have lower blood pressure than the carriers of the other two genotypes [49 and unpublished observations]. This observation is consistent in relatively young subjects (<50 years of age) but it is opposite in older subjects, that is Trp/Trp carriers have higher blood pressure at this age

(>55 years of age). These age-dependent changes in the genetic mechanisms involved in hypertension is not surprising for the experts of the clinical and pathophysiological aspects of hypertension.

Along this line, we have also extended our previous study [26] on the relationship between blood pressure response to hydrochlorothiazide (HCTZ) and alpha-adducin polymorphism in never treated patients considering also the ACE I/D polymorphism. The results of this studies [50] so far carried out in 86 patients showed remarkable influence of these two polymorphisms on the magnitude of blood pressure response. The odd of being responder to HCTZ is 15,75 (2.05-57.6, 95%) when the subgroup of patients with the most responder genotypes (ACE II and alpha-adducin Trp/Gly) was compared to the patients with the least responder genotypes (ACE DD and ID-alpha-adducin Gly/Gly). Certainly, these observations must be confirmed by further studies. However, they may be added to the endless debate lasting more than 12 years on the most appropriate statistical genetics approach to cast further doubts on the still unproved assumptions on which are based these approaches to the genetics of primary hypertension.

As already pointed out by two experts of the field [51,52], we are facing a dilemma: from one hand, we are linked to the tools of statistical genetics to define the role of a given allele on hypertension ; from the other, we do not have any established criteria to dissect the genetic complexity of hypertension. Perhaps the best way to circumvent this dilemma is to rely upon physiological or pathophysiological genetics, such as the association between a given genotype and a given phenotype in individual subjects, including pharmacogenomics, without looking for consistency with the so-called statistical genetics (that is the study of the difference in allelic frequency between normotensives and hypertensives or cosegregation in families).

Indeed the results obtained by comparing the Sassari and Milan cohorts of hypertensives and normotensives provided a message along this direction. That is in both cohorts the hypertensives carrying the Trp alpha-adducin allele have characteristics consistent with the constitutive renal Na retention of this allele that is lower plasma renin, greater fall in blood pressure with diuretics and faster ion transport across the erythrocyte membrane than hypertensive carrying the Gly/Gly alpha-adducin genotype, in spite of the fact that the frequency difference of the Trp alpha-adducin allele between hypertensives and normotensives was detected in Milan but not in Sassari.

What is the lessons I learned from the adducin studies for approaching the issue of this meeting, that is the relationship between dietary sodium and blood pressure in the population?

Besides alpha-adducin there are other genes (angiotensinogen, ACE, Na channel, aldosterone synthase) whose polymorphisms have been shown to be associated to the blood pressure or cardiac mass changes after variations of dietary Na or administration of diuretics with some controversies as discussed by others at this symposium.

In the study mentioned above [48], we have studied the interaction between ACE and alpha-adducin polymorphisms. The positive predictive values to develop hypertension for carriers of ACE DD increases from 23% to 30% when this genotype is associated to the Trp alpha-adducin genotype and to 40% when also the CC aldosterone synthase genotype is considered. The corresponding RR to develop hypertension for these combinations of genotypes were 1.2, 1.57 and 2.04 respectively.

Both population studies and intervention studies in hypertensive patients so far mentioned must be carried out in larger cohorts in order to reach conclusions about the contribution

that genetics may give to interventions regarding health policies on dietary salt at least in a subset of patients carrying some genetic risk factors.

The existing data are certainly sufficient to justify appropriate powered studies to furnish the genetic rational for reducing the Na intake in this subset of population.

References:

1. Bianchi G, Tenconi LT, Lucca R. Effect in the conscious dog of constriction of the renal artery to a sole remaining kidney on haemodynamics, sodium balance, body fluid volume, plasma renin concentration and pressor responsiveness to angiotensin. Cli Sci 1970; 38:741-766

2. Bianchi G, Baldoli E, Lucca E et al. Pathogenesis of arterial hypertension after the constriction of the renal artery leaving the opposite kidney intact both in the anesthetized and in the conscious dog. Cli Sci 1972; 42:651-664

3. Caravaggi AM, Bianchi G, Brown JJ et al. Blood pressure and plasma angiotensin II concentation after renal artery constriction and angiotensin in the dog (5-Isoleucine) angiotensin II and its breakdown fragments in dog blood. Circ Res 1976;38:315-321

4. Bianchi G, Fox U, Di Francesco GF et al. The hypertensive role of the kidney in spontaneously hypertensive rats. Clin Sci Mol Med 1973;45:135s-139s

5. Bianchi G, Fox U, Di Francesco GF et al. Blood pressure changes produced by kidney cross-transplantation between spontaneously hypertensive rats and normotensive rats. Clin Sci Mol Med 1974;47:435-448

6. Guidi E , Bianchi G, Rivolta E et al. Hypertension in man with a kidney transplant: role of familial versus other factors. Nephron 1985; 41:14-21

7. Guidi E, Menghetti D, Milani Pharm S et al. Hypertension may be transplanted with the kidney in humans. J Am Soc Nephrol 1996;7:11311138

8. Bianchi G, Cusi D, Gatti M et al. A renal abnormality as a possible cause of "essential" hypertension. Lancet 1979; I:173-177

9. Bianchi G, Cusi D, Barlassina C et al. Renal dysfunction as a possible cause of essential hypertension in predisposed subjects. Kidney Int 1983; 23:870-875

10. Bianchi G, Baer PG, Fox U et al. Changes in renin, water balance, and sodium balance during development of high blood pressure in genetically hypertensive rats. Circ Res 1975;36&37 [suppl I]:153-161

11. Baer PC, Bianchi G. Renal micropuncture study of normotensive and Milan hypertensive rats before and after development of hypertension. Kidney Int 1978; 13:452-466

12. Persson AE, Bianchi G, Boberg U. Tubuloglomerular feedback in hypertensive rats of the Milan strain. Acta Physiol Scand 1985;123:139-146

13. Parenti P, Hanozet G, Bianchi G. Sodium and glucose transport across renal brush-border membranes of Milan hypertensive rats. Hypertension 1986; 8:932-939

14. Ferrari P, Barber BR, Torielli L et al. The Milan hypertensive rat as a model for studying cation transport abnormality in genetic hypertension. Hypertension 1987;10 [suppl I]:32-36

15. Bianchi G, Ferrari P, Trizio D et al. Red blood cell abnormalities and spontaneus hypertension in the rat: a genetically determined link. Hypertension 1985;7:319-325

16. Bianchi G et al. The Milan Hypertensive strain of rats. In "Textbook of hypertension", ed. Swales JD, Blackwell Scientific Publications [Oxford, UK], 1994; 457-460

17. Salardi S, Saccardo B, Borsani G et al. Erythrocyte adducin differential properties in normotensive and hypertensive rats of the Milan strain (characterization of spleen adducin m-RNA) Am J Hypertens 1989;2:229-237

18. Bennett V. Spectrin-based membrane cytoskeleton: a multipotential adaptor between plasma nembrane and cytoplasm. Physiol Rev 1990; 70:1029-1065

19. Hughes CA, Bennet V. Adducin: a physical model with implications for function in assembly of spectrin-actin complexes. J Biol Chem 1995;270:18990-18996

20. Kuhlman PA, Hughes CA, Bennet V et al. A new function for adducin. J Biol Chem 1996;271:7986-7991

21. Gardner K., and Bennet V. A new erythrocyte membrane-associated protein with calmodulin binding activity: identification and purification. J Biol Chem 1986;261:1339-1348

22. Fukata Y, Oshiro N, Kinoshita N et al. Phosphorylation of adducin by Rho-kinase plays a crucial role in cell motility. J Cell Biol 1999; 19;145[2]:347-361

23. Kurana S. Role of actin cytoskeleton in regulation of ion transport: Examples from epithelial cells. J Membrane Biol 2000;178:73-87

24. Lin B, Nasir J, McRonald H et al. Genomic organization of the human a-adducin gene and its alternately spliced isoforms. Genomics 1995;25:93-99

25. Tripodi G, Casari G, Tisminetzky S et al. Characterisation and chromosomal localisation of the rat a- and b-adducin- encoding genes. Gene 1995;166:307-311

26. Cusi D, Barlassina C, Azzani T et al. Polymorphisms of alpha-adducin and salt sensitivity in patients with essential hypertension. Lancet 1997; 349:1353-1357

27. Bianchi G, Tripodi G, Casari G et al. Two point mutations in the adducin genes are involved in blood pressure variation. Proc Natl Acad Sci USA. 1994;91:3999-4003

28. Gilligan D, Lozovatsky L, Gwynn B et al. Targeted disruption of the b-adducin gene (Add2) causes red blood cell spherocytosis in mice. Proc Natl Acad Sci USA 1999;96:10717-10722

29. Gilligan D, Lieman J, Bennett V. Assignement of the human b-adducin gene (Add2) to 2p13-p14. Genomics 1995;28:610-612

30. Sinard J, Stewart GW, Stabach PR et al. Utilization of an 86bp exon generates a novel adducin isoform (b4) lacking the MARCKS homology domain. Biochem Biophys Acta 1998;1396:57-66

31. Citterio L, Azzani T, Duga S et al. Genomic organization of the human g-adducin gene. Biochem Biophys Res Com 1999;266:110-114

32. Tripodi G, Szpirer C, Reina C et al. Polymorphism of g-adducin gene in genetic hypertension and mapping of the gene to rat chromosome 1p55. Biochem Biophys Res Com 1997;237:685-689

33. Bianchi G, Tripodi G, Casari G et al. Two point mutations within the adducin genesa are involved inblood pressure variation. Proc Natl Acad Sci USA.1994; 91:3999-4003

34. Zagato L, Modica R, Florio M et al. Genetic mapping of blood pressure quantitative trait loci in Milan hypertensive rats. Hypertension 2000;36[5]:734-739

35. Tripodi G, Valtorta F, Torielli L et al. Hypertension-associated point mutations in the adducin alpha and beta subunits affect actin cytoskeleton and ion transport. J Clin Invest 1996;97:2815-2822

36. Halushka MK, Fan JB, Bentley K et al. Patterns of single-nucleotide polymorphisms in candidate genes for blood-pressure homeostasis. Nat Genet 1999;22[3]:239-247

37. Bianchi G, Cusi D. Association and linkage analysis of alpha-adducin polymorphism. Is the glass half full or half empty? Am J Hypertens 2000;13[6 Pt 1]:739-743

48. Barlassina C, Schork NJ, Manunta P et al. Synergetic effect of alpha-adducin and ACE genes in causing blood pressure changes with body sodium and volume expansion. Kidney Int 2000;57/3:1083-1090

39. Manunta P, Burnier M, D'Amico M et al. Adducin polymorphism affects renal proximal tubule reabsorption in hypertension. Hypertension1999;33:694-697

40. Glorioso N, Manunta P, Filigheddu F et al. The role of alpha-adducin polymorphism in blood pressure and sodium handling regulation may not be excluded by a negative association study. Hypertension 1999;34:649-654

41. Casari G, Barlassina C, Cusi D et al. Association of the alpha-adducin locus with essential hypertension. Hypertension 1995, 25:320-326

42. Busjajn A., Aydin A., von Treuenfels Net al. Linkage but lack of association for blood pressure and the alpha-adducin locus in normotensive twins. J Hypertens 1999;17:1437-1441

43. Bray M, Li L, Turner S, Kardia SL et al. Association and linkage analysis of the alpha-adducin gene and blood pressure. Am J Hypertens 2000;13(6):699-703

44. Niu T, Xu X, Cordell HJ et al. Linkage analysis of candidate genes and gene-gene interactions in Chinese hypertensive sib pairs. Hypertension 1999;33:1332-1337

45. Ferrandi M, Salardi S, Tripodi G et al. Evidence for an interaction between adducin and Na-K-ATPase: relation to genetic hypertension. Am J Physiol 1999;277:H1338-H1349

46 Tripodi G, Ferrandi M, Modica R et al. Effect of adducin gene transfer on blood pressure and Na-K pump activity in Milan Hupertensive rats (MHS). J Mol Med 2000;79(2-3):B30.

47. Marro ML, Scremin OU, Jordan MC et al. Hypertension in beta-adducin-deficient mice. Hypertension 2000;36(3):449-453

48. Staessen J, Wang GJ, Brand E et al. Effects of three candidate genes on prevalence and incidence of hypertension in a Caucasian population. J Hypertens 2001;19:1349-1358

49. Castellano M, Barlassina C, Rossi F, Perani C, Giacchè M, Rivadossi F, Muiesan ML, Beschi M, Tizzoni L, Cusi D, Bianchi G, Agabiti-Rosei E. Age-dependency of alpha-adducin polymorphism modulation of blood pressure. Abstract submitted

50. Sciarrone MT, Stella P, Barlassina C, Manunta P, Lanzani C, Tizzoni L, Ballabeni C, Bigatti G, Acquistapace I, Calvetta A, Bianchi G, Cusi D. Ace I/D polymorphism is a marker of individual response to diuretic treatment. Abstract at the Eleventh European Meeting on Hypertension. Milan, Italy. June 15-19 2001

51. Shork NJ et al. Molecular genetics of hypertension. Eds. Dominiczak, Connell, Soubrier; Bios S.P. Ltd, Oxford 1999; 9

52. Tyerwilliger JD, Goering HHH. Gene mapping in the 20th and 21st centuries: statistical methods, data anlysis and experimenta design. Hum Biol 2000; 72:63-132

Pierre MENETON

Je souhaite ajouter quelques informations importantes.

En premier lieu, la souris a fait l'objet d'approches expérimentales dans le domaine de la recherche biomédicale parce que cette espèce est la seule qui permette des manipulations génétiques dirigées et spécifiques. Ces expériences confirment les données obtenues chez l'homme. La mutation des vingt gènes montrés chez l'homme comme étant impliqués dans la régulation de la pression artérielle modifie également la pression artérielle chez la souris. Ainsi, les mécanismes génétiques impliqués dans le contrôle de la pression artérielle sont conservés d'un point de vue évolutif, ce qui n'est pas très surprenant au regard de l'évolution des mammifères terrestres.

En second lieu, ces études ont également permis de compléter ces observations. Chez la souris, quarante gènes ont été impliqués dans le contrôle de la pression artérielle, sachant que la quasi-totalité est impliquée directement ou non dans la réabsorption de sel au niveau des reins.

Enfin, ces expériences sur la souris montrent qu'il existe plusieurs dizaines de gènes qui ont chacun des effets relativement modestes et déterminent ensemble le niveau de la pression artérielle chez un individu ou une souris en fonction des conditions environnementales.

Xavier Jeunemaître, le séquençage du génome humain accélèrera-t-il considérablement la découverte des gènes manquants dans le contrôle de la pression artérielle – et si oui, à quelle échéance ?

Xavier JEUNEMAÎTRE

Le séquençage du génome humain représente un avantage considérable dans le cas de formes très rares avec la possibilité d'identifier en quelques mois les gènes et les mutations correspondantes. Nous arrivons presque au terme du séquençage pour ces formes mendéliennes et nous parvenons parfois à une dissection physiopathologique nouvelle et passionnante.

Sur le plan des études de populations, le séquençage représente également un avantage puisque nous accédons, grâce aux bases de données bio-informatiques, aux connaissances relatives aux gènes en question et à un catalogue de variations génétiques humaines. Il est également possible aujourd'hui de tester un grand nombre de ces variations en rapport avec la pression artérielle, compte tenu de tous les aléas précédemment cités.

Pierre MENETON

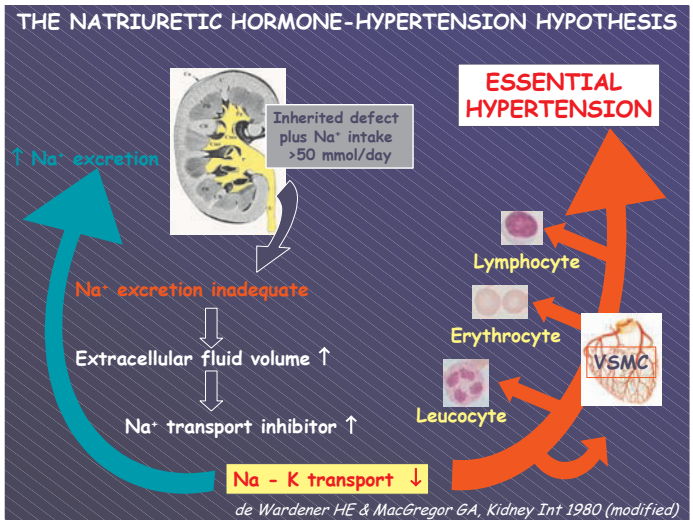
Nous entendons maintenant M. Pasquale Strazzullo, qui va nous expliquer les bases génétiques des différences interindividuelles dans la relation entre sel et pression artérielle.

Altered renal sodium handling and blood pressure : genetic and metabolic influences

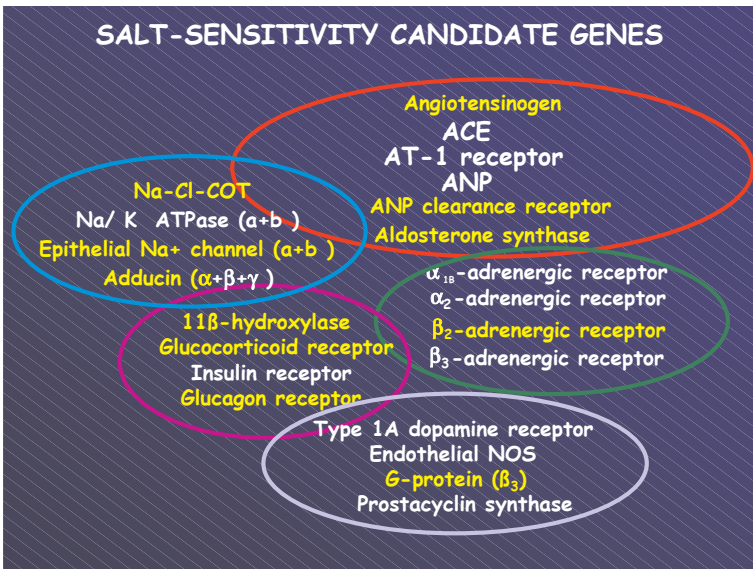
Pr. Pasquale STRAZZULLO
Federico II University, Naples, Italy

Introduction

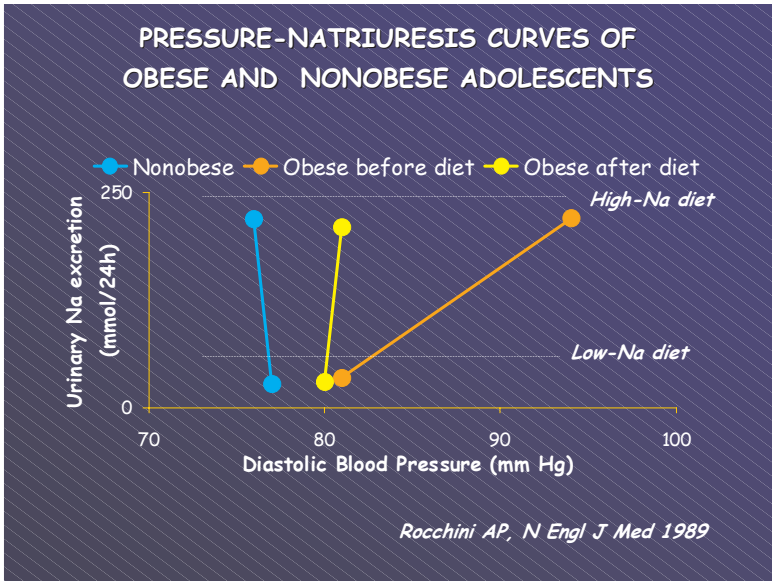
In a landmark article appeared in the *American Journal of Medicine* in 1976, Dr. Norman Hollenberg wrote that "… the pivotal role of the kidney in sustaining hypertension from any source or etiology (was) becoming increasingly clear" [1]. Over the last quarter of century, several ways have been explored in order to confirm and elucidate in more depth this pathogenic role of the kidney in sustaining high blood pressure. Fundamental steps in this direction were Guyton's observations [2] and Dahl's experimental studies on the interaction between genetic alterations in the kidney of hypertension-prone rats and excess dietary sodium intake [3]. This was also the route pursued in de Wardener and MacGregor hypothesis that sodium-dependent hypertension has its roots in the interaction between an inherited inability of the kidney to excrete a sodium load and a high-sodium environment [4]. A key question in that fascinating hypothesis was the nature of the defect in renal sodium handling underlying high blood pressure. Genetics, over the last two decades, has provided initial response to this issue.



A long list of genes that are plausible candidates for salt-dependent hypertension could be compiled. It is important to note in the first place that a few monogenic forms of hypertension have been recognised that are due to well characterised functional mutations that involve an alteration of renal sodium handling as the mechanism of the raised blood pressure [5-7]. In general, however, hypertension is the result of the synergistic action of multiple environmental and genetic factors and, actually, a large number of common genetic variants have been detected that are associated with hypertension more frequently than expected by chance [8]. This number is expected to grow considerably in the future. The large majority of these "susceptibility genes" encode for proteins that are either directly involved with sodium transport through the renal tubular epithelia or with the endocrine/paracrine regulation of renal sodium handling [9].

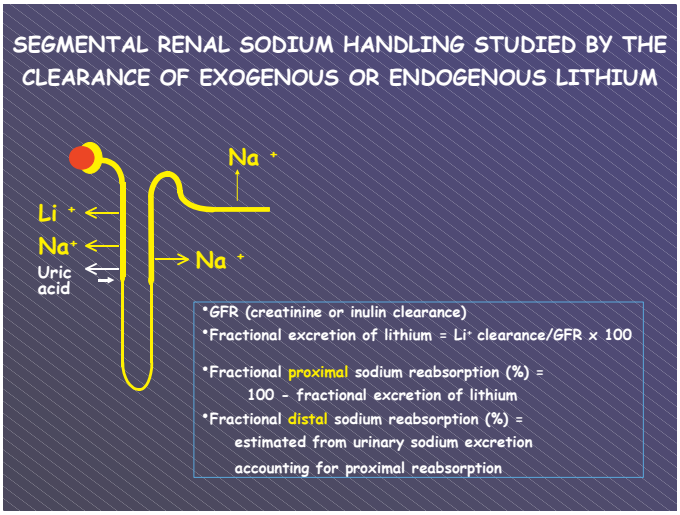


On the other hand, it may not be forgotten that, aside to direct genetic influence, other factors do influence the relationship between renal sodium handling and blood pressure. A major such factor is obesity, as shown several years ago by Rocchini and coworkers through the study of obese and control adolescents who were kept for two consecutive periods on a high- or a low- sodium intake [10]. Rocchini noted that, while on the low salt intake the blood pressures of the two groups were substantially similar, on high salt intake the obese group had a significant increase in blood pressure, which denoted a shift in the pressure-natriuresis relationship in these individuals. Noteworthy, this altered relationship was back to normal after a period of calorie restriction followed by weight loss. This is just one example of the many metabolic and neurohormonal influences that may affect the relationship between renal sodium handling and blood pressure. Other examples may be the adrenergic and dopaminergic tone, the endothelial function, that in turn is affected by the aging process and by a number of metabolic and vascular disorders, etc. A comprehensive review of all these several aspects is beyond the scope of this article, the main purpose of which is to highlight the central role of altered renal sodium handling in relation to blood pressure salt-dependence and hypertension.



Studies of segmental renal tubular sodium handling in relation to blood pressure in man

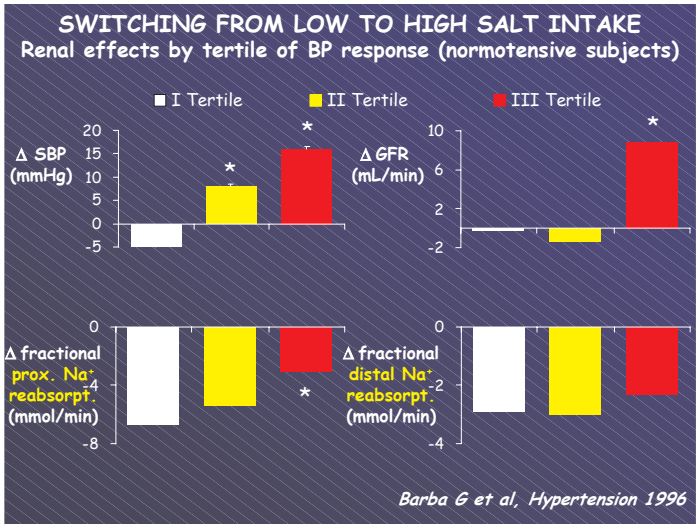
These studies have in common the investigation of the segmental renal tubular sodium handing using the lithium clearance technique. The clearance of lithium is the best available indicator of proximal tubular sodium handing for clinical studies. While sodium and water are reabsorbed at several sites along the nephron, the lithium ion is taken up almost exclusively at proximal tubular sites, so that the amount of substance escaping reabsorption at this level is quantitatively excreted in the urine. As lithium is transported by the same systems driving sodium and water, an alteration in the fractional excretion of lithium argues for an alteration in the reabsorption of sodium and water at the proximal tubule. Similar considerations, though with more limitations, can be made for the clearance of uric acid as urate transportation also occurs mainly in the proximal tubule along pathways linked to sodium and water reabsorption [11]. One limitation of these techniques is that they provide only indirect evidence of the proximal tubular sodium transport *in vivo.* However, micropuncture studies in animals showed that the lithium clearance provides a reasonably correct measure of the end-proximal delivery of sodium and fluid [12]. The reliability and accuracy of the protocols adopted was carefully investigated under various experimental conditions by our group, as previously reported [13].



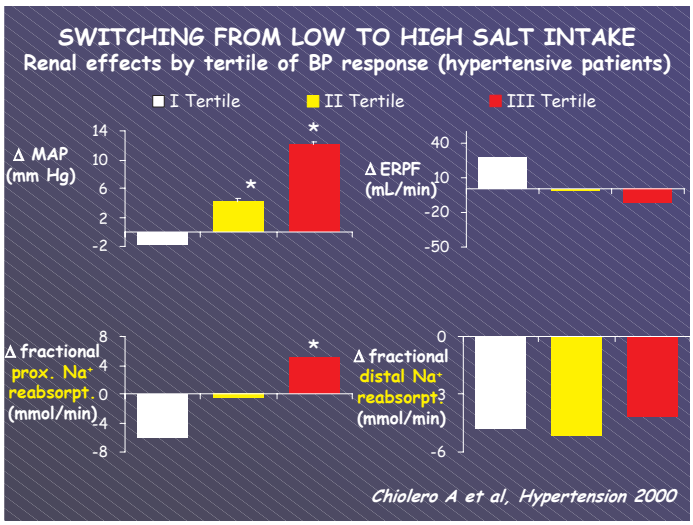
Expressing the renal clearance of lithium and uric acid as fractional excretion has the advantage of providing a measure that is independent of the glomerular filtration rate (GFR) and of possible sources of bias such as differences in flow rate and incomplete urine collection. Once the GFR and the fractional lithium clearance have been measured, it is possible to calculate the two most informative indices of tubular renal sodium handling, i.e. the fractional proximal sodium reabsorption, i.e. the proportion of filtered sodium that is reabsorbed at sites proximal to Henle's loop, and the fractional distal reabsorption, which is estimated by difference from proximal reabsorption and the actual urinary sodium excretion.

Renal sodium handling in relation to blood pressure salt-dependence in normotensive and hypertensive individuals

We used the lithium clearance technique to investigate differences in renal sodium handling according to differences in dietary sodium intake. A group of normotensive volunteers was studied on both a sodium restricted diet (average 70 mmol sodium per day) and on their habitual sodium-rich diet (average 185 mmol sodium per day) [14]. The subjects were classified according to tertiles of blood pressure response to the alteration in sodium intake. It was seen that the subjects whose blood pressure increased the most on high sodium intake were also the ones with the least reduction in the fractional proximal reabsorption of sodium. Distal reabsorption was affected to a similar extent in all subjects whereas a significant increase in the glomerular filtration rate occurred only in the group that was not able to reduce proximal sodium reabsorption appropriately, a compensation to maintain a neutral sodium balance.

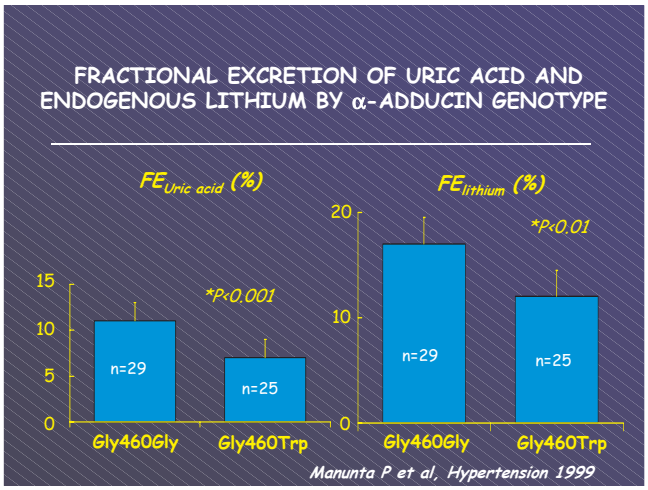


More recently, a similar study has been performed by Chiolero et al [15] with the aim to investigate the role of renal sodium handling in the blood pressure response to salt in hypertensive patients. Similarly to our results in normotensives, the authors reported a significant difference in the behaviour of proximal sodium reabsorption between groups, the most salt-sensitive patients showing a paradoxical increase in fractional proximal reabsorption on a high salt diet at variance with the other two groups. Again similarly to our study, there was no difference in the response at more distal sites and also no significant difference in the renal hemodynamic response to changing diet. Thus, the authors concluded that proximal renal sodium handling is a determinant of the shift in the pressure-natriuresis relationship that occurs in subjects with salt-dependent hypertension.



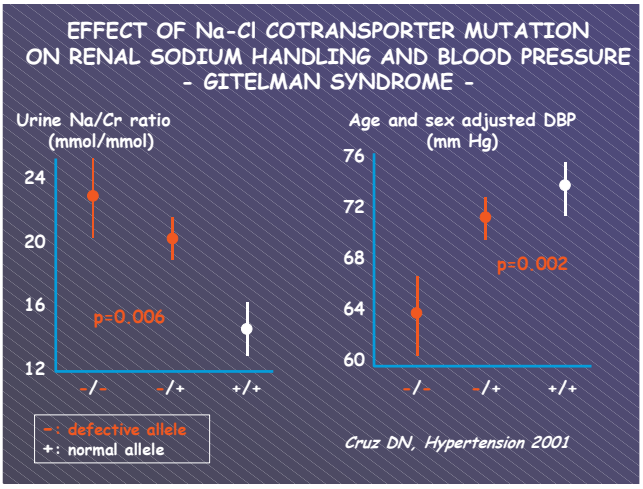
Molecular bases of the alteration in renal sodium handling in different settings

Genetic studies have provided initial responses in this regard. A number of genetic variants relatively common in the population have been shown to be associated with different predisposition to hypertension. One such example is that of polymorphic variation in the molecule of α-adducin described by Bianchi and coworkers [16]. The less frequent Gly460Trp variant has been reported to be associated with higher prevalence of hypertension in several studies [17]. By using the endogenous lithium clearance, Manunta and coworkers showed that both the fractional lithium excretion and the fractional excretion of uric acid are reduced in hypertensive patients carrying the variant, indicating an increased rate of sodium reabsorption in the proximal tubule [18]. The biochemical alteration underlying the greater avidity of the tubular epithelium for sodium appears to be in this case an enhanced activity of the Na-K pump [19].



The paradigm of a quite opposite condition is represented by Gitelman syndrome, which is the result of a group of functional mutations in the Na-Cl cotransporter at the distal convoluted tubule that lead to a reduced rate of sodium reabsorption at this level and to salt-wasting [20]. It has been seen that the individuals bearing the defective allele in either single or double dose have an increased urinary Na/Cr ratio and, at least in the homozygous condition, they also have significantly lower blood pressure [21]. The same individuals also seem to have an increased appetite for salt and actually tend to stick to a

very high sodium diet. This finding demonstrates that, while mutations that increase renal sodium reabsorption tend to elevate blood pressure, the opposite is also true, thus supporting a consistent effect of salt balance on blood pressure regulation in man.



Other interesting examples have been provided by the Olivetti Heart Study, an investigation of the genetic and metabolic determinants of cardiovascular disease. This study involved in 1994-95 the participation of over 1,000 adult male individuals in the age range 25-75 years, who are at present undergoing a further follow-up visit. The examination included complete anthropometric measurements, biochemical investigations and the study of polymorphism in several candidate genes for hypertension and various metabolic disorders. The segmental renal handling of sodium was investigated by the measurement of the clearance of exogenous lithium and of uric acid.

In this population we investigated the role of a previously described functional mutation in the GCGR gene [22], known to be associated with reduced receptor affinity for glucagon and in turn with a lower secretory rate of its second messenger cAMP. The rare Arg40Ser variant was found in 3.8% of the population examined (n=970), only in the heterozygous condition. The carriers of the variant had a very high prevalence of hypertension (40%) and a statistically significant twofold greater probability of being on drug treatment for high blood pressure compared to the rest of the population. These subjects also had significantly reduced fractional excretion of both lithium and uric acid, again supporting the hypothesis of an enhanced rate of proximal tubular sodium reabsorption [23] (Fig.1).

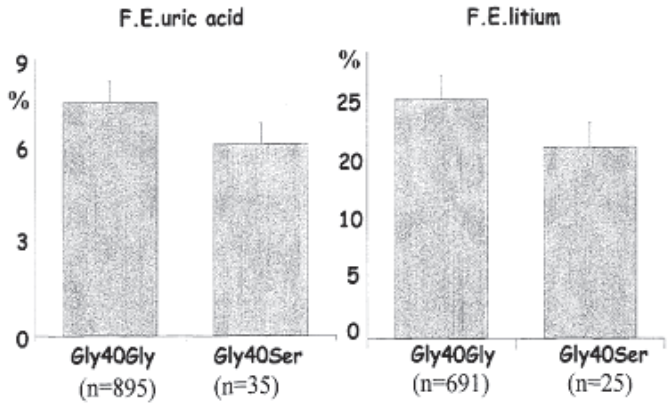


Figure 1. Fractional excretion of uric acid (left) and exogenous lithium (right) in carriers of the Gly40Ser variant versus the wild-type Gly40Gly form of the glucagon receptor gene.
Data are expressed as mean and standard error. Both differences are significant at p=0.004.
Results obtained in the Olivetti Heart Study population (ref. 23).

In the Olivetti Study the relationship of several anthropometric indices of adiposity and of fat distribution to blood pressure and renal sodium handling was also investigated in 555 untreated and otherwise unselected participants [24]. In this case, body mass index (BMI) was taken as an indicator of total fat mass, waist circumference as a measure of abdominal adiposity and arm circumference as an index of peripheral fat deposition. It was found that for increasing values of both BMI and waist circumference the rate of proximal sodium reabsorption also increased, these relationships being both statistically significant also accounting for age and for blood pressure. On the other hand, the relationship between proximal renal sodium handling and arm circumference was flat, suggesting that abdominal adiposity is specifically associated with this alteration in proximal sodium transport.

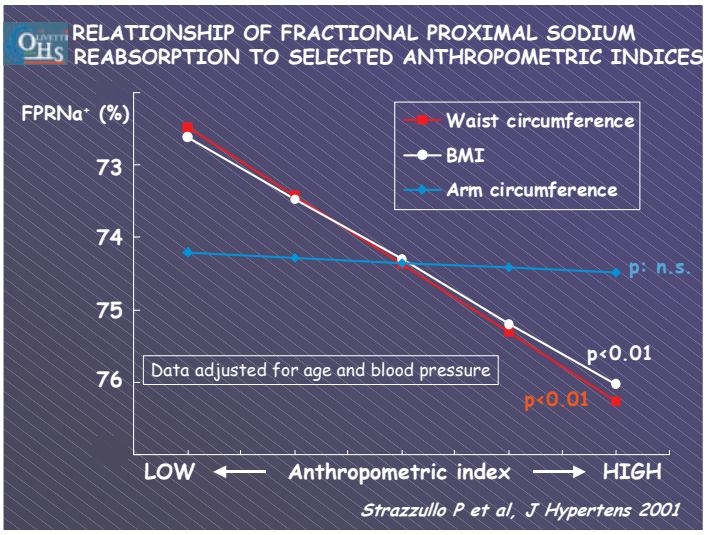


Figure 2 shows a comparison of fractional proximal sodium reabsorption in normal weight individuals versus overweight participants with waist circumferences values either below or above the median for the population. It was found that only overweight individuals with enhanced abdominal fat deposition had an increased rate of proximal sodium reabsorption and that this was associated with higher blood pressure [24].

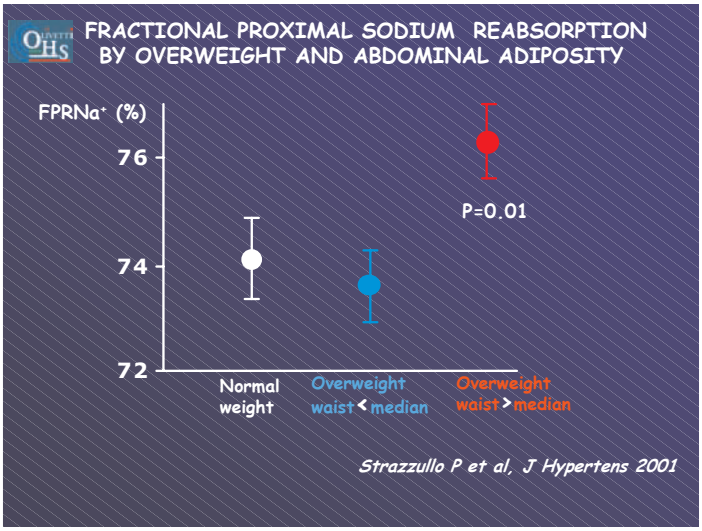
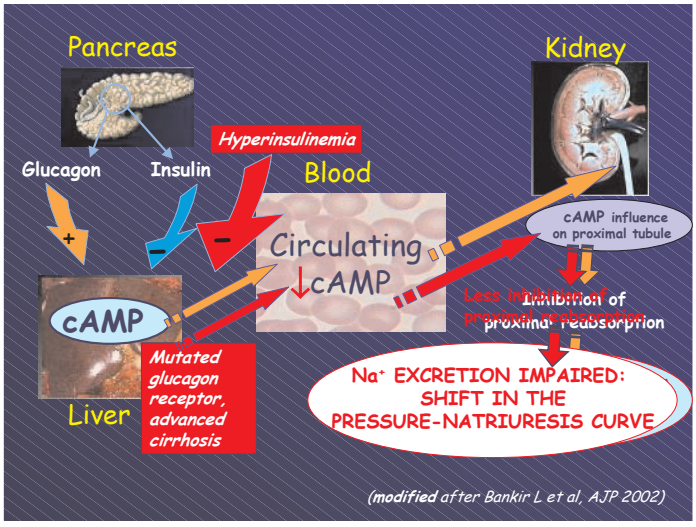


Fig. 2. Rate of fractional proximal sodium reabsorption in normal weight individuals versus overweight participants with waist circumference values either below or above the median for the population. Results obtained in the Olivetti Heart Study population (ref. 24).

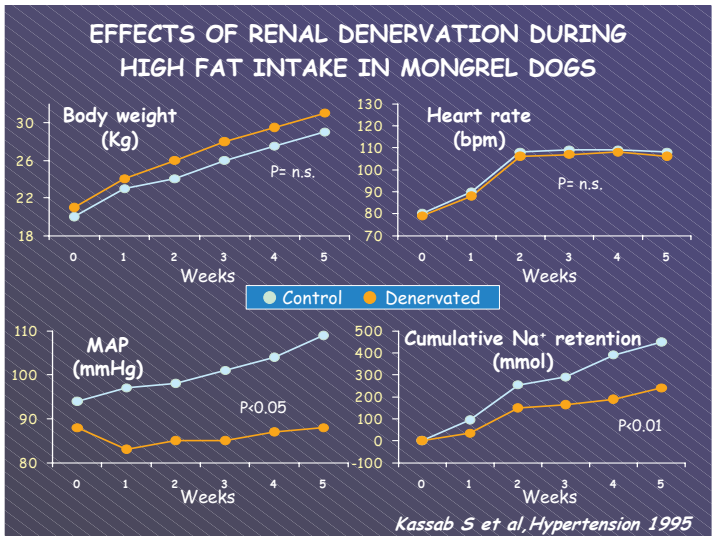
One tentative interpretation of these aggregated findings from the Olivetti Study population is based on an analysis of the possible role of extracellular cAMP on sodium transport at the renal proximal tubular level [25]. This analysis is based on the consideration that the pancreatic hormones glucagon and insulin are both regulators of the cAMP production by the liver, glucagon exerting a stimulatory effect and insulin an inhibitory influence. Under normal conditions, the hepatic production of cAMP is large enough to allow a significant amount of the substance to spill out in the systemic circulation and reach the kidney where it has been shown to affect sodium transport at the proximal tubular level and to promote sodium, phosphate and water diuresis [26]. In this physiological framework, any condition affecting the rate of cAMP production in the liver can be anticipated to bear an influence on the renal proximal tubular activity. Hyperinsulinemia, which is a frequent companion of obesity and in particular of abdominal adiposity, is expected to reduce hepatic cAMP production [27]. A mutated glucagon receptor, with reduced functional activity, will produce the same effect as well as any parenchimal disorder of the liver with impaired hepatic function. Under these conditions, the cAMP concentration in the blood is expected to decrease and so its influence on the renal proximal sodium transport with resultant impairment in sodium delivery to more distal sites and a shift in the pressure-natriuresis relationship. Further studies are in progress in order to obtain confirmatory evidence in support of this putative chain of events.



The effects of sympathetic activation on renal sodium handling in obesity

Another important pathogenic factor for the altered renal sodium handling occurring in obese individuals and probably with other insulin resistance states is the increase in the renal sympathetic drive. Aside to the clinical evidence of elevated sympathetic tone in obesity [28; 29], strong support to this concept was provided by several experimental studies such as the one by Kassab and coworkers who investigated the effects of renal denervation on sodium balance and blood pressure in mongrel dogs made obese by high fat intake [30]. The authors compared a group of dogs submitted to renal denervation with a control group of dogs, both groups receiving a high fat diet for five weeks. They reported that body weight increased during the experimental period to a similar extent in both groups. So also increased heart rate denoting a similar degree of systemic sympathetic activation. Blood pressure however did not increased in the renal denervated dogs at variance with the control group and the difference in blood pressure was paralleled by a difference in cumulative sodium balance: while in the control group a positive sodium balance developed in parallel with the increase in weight and blood pressure, the degree of sodium retention observed in the renal denervated animals was much lower, suggesting

an important role for sympathetic activation to promote sodium retention under these conditions.



Conclusion

The bulk of the evidence coming from both clinical and experimental studies supports the contention that altered renal sodium handling plays a key role in salt-dependent forms of hypertension, which indeed may represent a major proportion of so-called essential hypertension. Salt-dependence of blood pressure is the resultant of a presumably very large number of susceptibility genes with variable penetrance interacting with each other and with a series of metabolic, nutritional and neurohormonal factors. Among these factors a fundamental role is played by sympathetic and dopaminergic tone as well as by the endothelial dysfunction associated with aging and with various metabolic and cardiovascular conditions (Fig. 3). The final product of this complex network of interactions is an impairment in the natriuretic ability of the kidney and a shift in the pressure-natriuresis relationship. The elucidation of the precise role of the gene products involved in this process as well as of their interactions is the challenge we face for a thorough understanding of the molecular bases of blood pressure regulation.

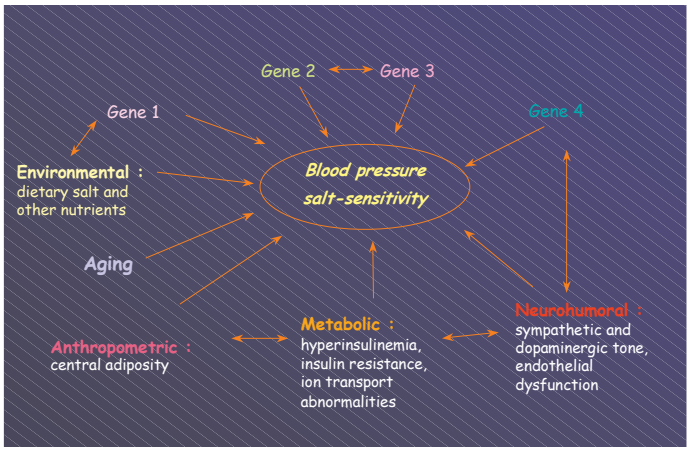


Figure 3. Interaction between genetic and non-genetic factors involved in the pathogenesis of altered renal sodium handling and sodium-dependent hypertension.

References

1. Hollenberg NK, Adams DF: The renal circulation in hypertensive disease. *Am J Med* 1976;60 :773-784

2. Guyton AC: The surprising kidney-fluid mechanism for pressure control- Its infinite gain! *Hypertension* 1990; 16:725-730

3. Jaffe D, Sutherland LE, Barker DM, DahI LK: Effects 0f chronic excess sait ingestion. Morphologic findings in kidneys of rats with differing genetic susceptibilities to hypertension. *Arch Pathol* 1970;90: 1-16

4. De Wardener HE, MacGregor GA: The natriuretic hormone and essential hypertension. *Lancet* 1982;1: 1450-1454

5. Ulick S, Ramirez LC, New MI: An abnormality in steroid metabolism in a hypertensive syndrome. *J Clin Endocrin Metab* 1977;44:799-802

6. Sutherland DJA, Ruse JL, Laidlaw JC: Hypertension, increased aldosterone secretion and low plasma renin activity reversed by dexamethasone. *Can Med Assoc J* 1966;95:1109-1119

7. Liddle GW, Bledsoe T, Coppage WS: A familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretion. *Trans Assoc Am Phys* 1963;76: 199-213

8. *Siani* A, Guglielmucci F, Farinaro E, Strazzullo P: Increasing evidence for the role of salt and salt-sensitivity in hypertension. *Nutr Metab Cardiovasc Dis* 2000;10:93-100

9. Strazzullo P, Siani A, Russo P: Salt-sensitivity of blood pressure: a paradigm of gene environment interaction. *Ital Heart J* 2000;1 Suppl 3:S15-S19

10.Rocchini AP, Key J, Bondie D, Chico R, Moorehead C, Katch y, Martin M: The effect of weight Ioss on the sensitivity of blood pressure to sodium in obese adolescents. *N Engl J Med* 1989;321 :580-585

11. Boer WH, Koomans HA, Beutler JJ, Gaillard CA, Rabelink AJ, Dorhout Mees EJ: Small intra- and large inter-individual variability in lithium clearance in humans. *Kidney Int* 1989;35:1183-1188

12. Boer WH, Fransen R, Shirley DG, Walter SJ, Boer P, Koomans HA: Evaluation of the lithium clearance method: Direct analysis of tubular lithium handling by micropuncture. *Kidney Int.* 1995;47: 1023-1030

13. Strazzullo P, Iacoviello L, Iacone R, Giorgione N: The use of fractional lithium clearance in clinical and epidemiological investigation: a methodological assessment. *Clin Sci* 1988;74:651-657

14. Barba G, Cappuccio FP, Russo L, Stinga F, Iacone R, Strazzullo P: Renal function and blood pressure response to dietary salt restriction in normotensive men. *Hypertension* 1996;27: 1160-1164

15. Chiolero A, Maillard M, Nussberger J Brunner HR, Brunner M: Proximal sodium reabsorption: An independent determinant of blood pressure response to salt. *Hypertension* 2000;36:631-637

16. Casari G, Barlassina C, Cusi D, Zagato L, Muirhead R, Righetti M, Nembri P, Amar K, Gatti M, Macciardi E, Binelli G, Bianchi G: Association of the a-adducin locus with essential hypertension. *Hypertension* 1995; 25:320-326

17. Glorioso N, Manunta P, Filigheddu F, Troffa C, Stella P, Barlassina C, Lombardi C, Soro A, Dettori F, Parpaglia PP, Alibrandi MT, Cusi D, Bianchi G: The role of alpha-adducin polymorphism in blood pressure and sodium handling regulation may not be excluded by a negative association study. *Hypertension* 1999;34:649-654

18. Manunta P, Burnier M, D'Amico M, Buzzi L, Maillard M, Barlassina C, Lanella G, Cusi D, Bianchi G: Adducin polymorphism affects renal proximal tubule reabsorption in hypertension. *Hypertension* 1999 ;33 :694-697

19. Tripodi G, Valtorta F, Torielli L, Chieregatti E, Salardi S, Trusolino L, Menegon A, Ferrari P, Marchisio PC, Bianchi G: Hypertension-associated point mutations in the adducin alpha and beta subunits affect actin cytoskeleton and ion transport. *J Clin Invest* 1996;97 :2815-2822

20. Simon D, Lifton RP: Ion transporter mutations in Gitelman's and Bartter's syndromes. *Curr Opin Nephrol Hypertens* 1998;7:43-47

21. Cruz DN, Simon DB, Nelson-Williams C, Farhi A, Finberg K, Burleson L, Gill JR, Lifton RP: Mutations in the Na-Cl cotransporter reduce blood pressure in humans. *Hypertension* 2001;37: 1458-1464

22. Chambers SM, Morris BJ: Glucagon receptor gene mutation in essential hypertension. *Nat.Genet.* 1996;12:122 (letter)-122

23. Strazzullo P, Iacone R, Siani A, Barba G, Russo O, Russo P, Barbato A, D'Elia L, Farinaro E, Cappuccio FP: Altered renai sodium handling and hypertension in men carrying the glucagon receptor gene (Gly4OSer) variant. *J Mol Med* 2001;79:574-580

24. Strazzullo P, Barba G, Cappuccio FP, Siani A, Trevisan M, Farinaro E, Pagano E, Barbato A, Iacone R, Galletti F: Altered renal sodium handling in men with abdominal adiposity: a link to hypertension. *J Hypertens* 2001;19:2157-2164

25. Bankir L, Ahloulay M, Devreotes P, Parent C: Extracellular cAMP inhibits proximal reabsorption: are plasma membrane CAMP receptors involved? *Am J Physiol* 2002;282:in press

26. Bankir L, Martin H, Dechaux M, Ahloulay M: Plasma cAMP: a hepatorenal link influencing proximal reabsorption and renal hemodynamics? *Kidney Int* 1997;59 (suppl.9) :S50-S56

27. Exton J, Lewis SB, Ho R, Robinson G, Park C: The role of cyclic AMP in the interaction of glucagon and insulin in the control of liver metabolism. *Ann N Y Acad Sci* 1971;185:85-100

28. Young JB, Landsberg L: Diet-induced changes in sympathetic nervous system activity: possible implications for obesity and hypertension. *J Chron Dis* 1982;35:879-886

29. Grassi G, Seravalle G, Dell O, Turri C, Bolla GB, Mancia G: Adrenergic and reflex abnormalities in obesity-related hypertension. *Hypertension* 2000; 36:538-542

30. Kassab S, Kato T, Wilkins FC, Chen R, Hall JE, Granger JP: Renal denervation attenuates the sodium retention and hypertension associated with obesity. *Hypertension* 1995;25 :893-897

ACKNOWLEDGMENTS

The contribution of the components of the Olivetti Study Research Team to many of the studies reviewed in this article is acknowledged. The Olivetti Study Research Team is composed by: Pasquale Strazzullo, Francesco P. Cappuccio, Eduardo Farinaro, Alfonso Siani, Maurizio Trevisan (who are all members of the Steering Committee), Gianvincenzo Barba, Ferruccio Galletti, Roberto Iacone, Ornella Russo, Paola Russo, Antonio Barbato, Maria Bartolomei, Clara Gerardi. The author is also grateful to Dr. Lise Bankir for stimulating and thought-provoking discussion about the possible role of altered cAMP metabolism in the pathogenesis of the alteration of renal sodium handling in obesity and other conditions described in this paper.

Pierre MENETON

Je propose une discussion. Au niveau des politiques de santé publique, la sensibilité au sel à long terme – sur plusieurs dizaines d'années - est très importante. La recherche en la matière est-elle similaire à celle qui est menée dans le domaine de la sensibilité au sel à court terme ?

Pasquale STRAZZULLO

L'identification de la sensibilité au sel constitue un vaste problème méthodologique. Nous devons utiliser des tests et protocoles alimentaires à court terme, parce qu'il est difficile de gagner la confiance des patients que nous souhaitons étudier de manière prolongée. Plusieurs études y sont parvenues mais l'expérience actuelle n'est globalement pas satisfaisante. C'est pourquoi nous cherchons à mettre en œuvre des tests plus rapides. L'idéal serait de pouvoir mener des études à long terme qui déboucheraient sur des évaluations.

De la salle

Vous avez remarquablement résumé vos travaux. La sensibilité au sel représente-t-elle vraiment un concept pertinent du point de vue de la santé publique ? On pourrait par exemple s'intéresser à la sensibilité aux végétaux. En réalité, nous préconiserons une réduction de la consommation de sel et de graisses. De fait, nous devrions peut-être davantage insister sur la sensibilité aux fruits et légumes, aux diurétiques, etc.

Pasquale STRAZZULLO

Je suis d'accord avec vous. Le problème de santé publique est résolu - mais pas celui de la sensibilité au sel. En fait, cette question ne doit pas devenir obsessionnelle mais elle est importante du point de vue de la compréhension des mécanismes. Les Professeurs Jeunemaître et Bianchi ont ainsi souligné que c'est la seule raison pour laquelle nous nous y intéressons. La plupart des gens sont sensibles au sel et des tests perfectionnés montreraient que ces personnes sont encore plus nombreuses que nous ne l'imaginons aujourd'hui.

De la salle

Sur quel fondement affirmez-vous que la plupart des gens sont sensibles au sel ?

Pasquale STRAZZULLO

Le test de Weinberger - qui est le plus communément utilisé, révèle une augmentation de la pression artérielle pendant les différentes phases d'apport en sel. La plupart des patients réagissent au niveau de la pression artérielle. En fait, un déplacement de la distribution tend à déboucher sur une réponse négative. C'est la raison pour laquelle nous affirmons que la plupart des gens sont sensibles au sel.

Les différentes approches pour évaluer la sensibilité au sel tendent à confirmer cette conclusion si les personnes étudiées se tiennent à leur régime.

De la salle

L'exemple d'un seul patient peut sembler étonnant mais il est significatif. Je suis depuis 1967 une personne qui est hypotendue et souffre du syndrome de Bartter. Lorsqu'elle était jeune, cette femme mangeait des quantités étonnantes de sel. Or sa pression artérielle était importante. Aujourd'hui, cette personne est diabétique. Elle a une cholestérolémie et une hypertension artérielle difficiles à contrôler. Certains diront que sa forte consommation de sel dans sa jeunesse lui permettait de maintenir sa pression artérielle. Quoi qu'il en soit, nous devons en tirer la leçon qu'une affection génétique caractérisée par l'hypotension peut se poursuivre par une hypertension.

Pasquale STRAZZULLO

Je vous remercie de cette remarque extrêmement intéressante qui montre que la nature multifactorielle de la maladie a pour effet de la faire évoluer au cours du temps. Les prédispositions génétiques jouent également un rôle.

Pierre MENETON

L'intervention de Gary Beauchamp est fondamentale parce que la réduction de l'apport en sel se traduit dans le rapport au goût des aliments et dans la consommation de nourriture au goût plus ou moins salé. Or il existe de nombreuses théories fantaisistes sur le sujet. Gary Beauchamp est le chercheur ayant le plus travaillé sur cette question chez l'homme. Nous l'accueillons donc avec un grand plaisir.

The Desire for Salt

Gary K. BEAUCHAMP
Monell Chemical Senses Center, Philadelphia, USA

It is generally believed that people consume sodium (Na, mostly as NaCl – salt) in excess of physiological need and to their detriment. It is also widely believed that a major reason for this excess consumption is that people like the taste of salt, usually in food, due to conditioning, imprinting or even addiction (e.g. Dahl, 1972; MacGregor & de Wardener, 1999). In what follows, the first belief is not discussed. However, as I discuss, the second is without strong experimental foundation. It is argued that for humans and many other species of herbivores and omnivores, the desire for salt is due in part to an innate liking for the flavor sensations associated with it. This innate liking can be modified by both physiological processes (e.g. body Na homeostasis) and by past environmental events (e.g. customary levels of intake). Experimental evidence for salt addiction (as this term is used for drug addiction) is not convincing. Thus, the desire for salt is influenced by both innate and learned factors. An appreciation of the complexity of this desire will aid in designing strategies to reduce consumption when this is warranted.

Introduction: Salt and life

Salt (sodium chloride) holds a special place in human history. It has, when available, been used extensively in human cuisine, formed a fundamental unit of exchange, and even been a cause of war. Salt has commonly been taxed because of its universal usage and value. Utensils that contained salt were often elaborate and expensive (Reviews: Denton, 1984; Beauchamp, 1987; MacGregor & de Wardener, 1998).

Sodium is required for a variety of biological functions, including nerve conduction, blood pressure maintenance, acid-based balance, and muscle contraction. Its balance in the body is finely regulated. Excess sodium is usually excreted efficiently in the urine. Elaborate hormonal mechanisms exist in many organisms for conserving sodium when intake is restricted. Sodium deprivation is quickly followed in many vertebrate species by increases both in the activity of the renin-angiotensin system and in aldosterone production; these hormones are involved in mediating inhibition of urinary sodium excretion and thereby help conserve body sodium.

There is a major behavioral component in the maintenance of sodium balance. Herbivorous animals, whose diet of plants is relatively low in sodium, are known to travel long distances to gain access to salt-rich earths or other sources of sodium. In contrast to herbivores, carnivores would presumably never suffer sodium deficiency, because their diet of muscle, viscera and blood contains relatively high amounts of sodium. The extent to which omnivorous animals would be exposed to the stress of sodium deficiency is unclear. It has been suggested that the primate ancestors of humans were likely to have been almost completely vegetarian and were thereby exposed to a potential sodium deficiency (Denton, 1984). Consequently, it is not surprising that neural, hormonal and behavioral regulatory systems have evolved in many herbivorous and omnivorous species to ensure the discovery, recognition and consumption of sufficient sodium to meet or exceed biological requirements. Those mechanisms may also be responsible, in part, for consuming much more salt than is required.

Perception of Salty Taste

One biological system to insure sodium balance is the sense of taste that serves to detect and recognize environmental sources of sodium. The salty taste is thought to be one of the few basic or primary taste qualities. Indeed, much evidence from human and non-human animal studies supports the concept that taste experience can be chunked into a rather small number of classes. This evidence will not be reiterated here; reviews and some arguments against this idea have been published (Erickson, 1982; McBurney, 1969; Scott & Giza, 1995). The existence of psychological classes of taste (namely salty, sweet, sour, bitter and perhaps a few others) does not imply that there necessarily exists a taste compound that is a pure exemplar of that quality. That is, there may or may not be a compound that is salty and has no other quality to it. Nor does it imply that within a taste class, the mechanisms that transduce the message must necessarily be the same.

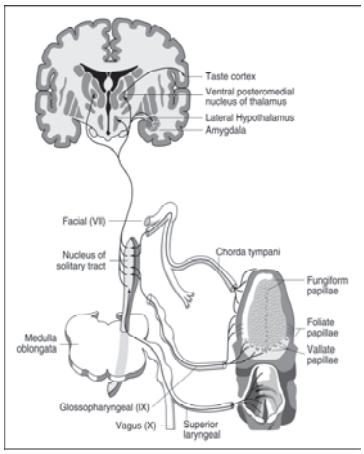
Nevertheless, there is general agreement that the taste of NaCl (herein referred to as “salt”) is almost purely salty with perhaps a side taste of sour and/or bitter; also, salt may be perceived as sweet at very low concentrations (Murphy et al, 1981). The only other compound that tastes almost purely salty is the toxic LiCl. Almost all other compounds that have a salty component (e.g. KCl, some amino acids, some other sodium salts) have prominant other taste qualities in addition to their saltiness.

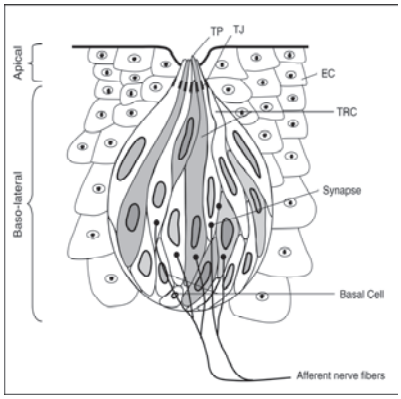
For many years there was a controversy as to which ion, the anion or the cation, was responsible for saltiness. Arguments in favor of the chloride ion centered around the observation that NaCl was much saltier than equimolar sodium salts with other anions (e.g. sodium acetate; sodium gluconate etc.). As described more fully in the next section, it is now widely believed that the Na ion is the major actor with the anion modifying intensity and non-salty quality. In general, and loosely, the larger the anion, the less salty the sodium salt.

Salty Taste Transduction

It is clear that unique receptor mechanisms exist for each taste modality. (For reviews see Brand, 1997; Dulac, 2000; Herness & Gilbertson, 1999; Lindemann, 1996; 2001) These receptor processes can be roughly divided into three types: [1] those making use of a receptor protein that transduces its interaction with a stimulus to change levels of intracellular signaling compounds (i.e., second-messenger signaling systems); [2] those making use of a stimulus-gated ion channel receptor complex and [3], those making use of existing plasma membrane-associated ion channels in taste cells, whereby the stimulus traverses the membrane through these channels or modulates the activity of these channels. Each of these transduction mechanisms ultimately alters the ion balance within the receptor cell. This change in ion balance across the membrane is thought to be a consequence of both changes in ion flux across the membrane and release of calcium from intracellular stores.

Taste receptor cells are innervated by sensory nerve fibers from one of three cranial nerves: VII, IX or X. In order to report the presence of a taste stimulus to the brain, the taste receptor cell must spill neurotransmitter across the synaptic cleft to alter the firing rate of the innervating nerve fiber. Presumably, in order to do this, sufficient changes in the activity of calcium ion must occur within the taste cell. It is probably this change in intracellular calcium ion activity that is the common signal arising from the transduction sequence.





As indicated previously, very few chemicals elicit a purely salty taste. Two of the most recognized stimuli that do impart a purely salty taste are NaCl and LiCl (Murphy et al, 1981). This stimulus specificity can be rationalized through an appreciation of the receptor mechanisms for this modality.

Saltiness (the taste of NaCl) is likely transduced by an epithelial-type ion channel located on the plasma membrane of the taste receptor cell (Avenet & Lindemann, 1988; DeSimone et al., 1981; Heck et al., 1984; Schiffman et al., 1983). In many animal models, the transduction of the signal for saltiness can be inhibited by the diuretic amiloride and some of its analogs. The existence of amiloride-inhibitable ion channels on taste cells has been inferred from psychophysical studies (McCutcheon, 1992; Schiffman et al., 1983; Tennissen & McCutcheon, 1996; but see Halpern, 1998) and from recordings of the innervating sensory nerves (Brand et al., 1985; DeSimone & Ferrell, 1985; Hettinger & Frank, 1990; Schiffman et al., 1983; Schiffman et al., 1990), and they have been directly observed using the patch-clamp technique on isolated taste cells and isolated taste buds (Avenet & Lindemann, 1988). The neural response to NaCl can also be potentiated by agents known to affect the activity of the amiloride sensitive sodium channel, including bretylium (Schiffman et al., 1986) and novobiocin (Feigin et al., 1994).

Although amiloride sensitivity of NaCl is readily demonstrable in most rodents, the phenomenon is less reliable in humans (Halpern, 1998). Indeed, several studies have failed to observe an effect of amiloride on saltiness in humans (e.g., Desor & Finn, 1989; Ossebaard & Smith, 1995). There also appear to be marked individual differences with regard to the effectiveness of amiloride on human perception of saltiness. The lack of effect of amiloride in humans does not mean that salty taste is not transduced in humans via an epithelial sodium ion channel. Rather, the implication may be that in some individuals, the sodium channel in taste cells is less amiloride sensitive than it is in rats, or than is the comparable channel in other epithelia, such as in the kidney. Salty taste can be inhibited in humans with chlorhexidine, a biguanide used as a topical antibacterial (Breslin & Tharp 2001). The mechanism of action of this agent is unknown.

Sodium salts with anions other than chloride are less salty than those of chloride. This phenomenon has been explained by noting the difference in the ability of various anions to penetrate the epithelial barrier (Ye et al., 1991). Because chloride readily penetrates the barrier by moving through the paracellular space, it creates a more negative region at the basal portion of the taste cell, promoting influx of positive charge. This additional influx of positive charge strengthens the signal for saltiness, apparently by the further influx of Na^+ into the receptor cell through amiloride-sensitive Na channels located in the apical and basal regions of the taste bud. Other larger anions, less capable of penetrating the barrier,

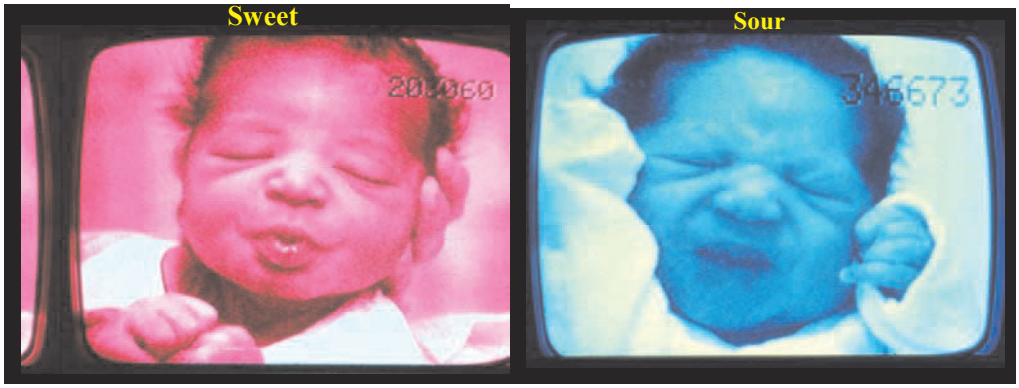
are responsible for less Na^+ crossing the barrier. As a result, these salts taste less intensely salty than NaCl.

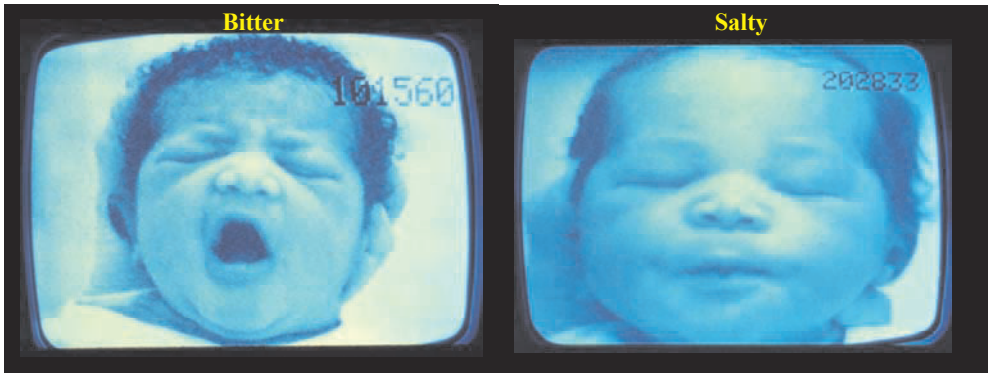
A partial clone showing homology to an amiloride-sensitive sodium channel has been cloned out of a cDNA library developed from circumvallate papillae of rat (Li et al., 1994). The hybridization studies showed the presence of message in both taste and nontaste cells of the lingual epithelium. Although this may represent the clone of the salty taste receptor, the choice of circumvallate papillae as the starting point for the library was not optimal, because it is known that NaCl stimulates the glossopharyngeal nerve in a nonamiloride-sensitive manner (Formaker & Hill, 1991), suggesting that amiloride-sensitive sodium channels may not be important for salty transduction by taste cells of the circumvallate. In addition, stimulation of single circumvallate papilla by NaCl leads to sensations of primarily sourness and bitterness, with some saltiness, whereas similar stimulation of fungiform taste papillae gives rise to primarily salty sensations (Sandick & Cardello, 1983). NaCl stimulation via the chorda tympani, which innervates taste cells of the fungiform papillae, is amiloride sensitive in some animals. Recent immunohistochemical and RT-PCR studies comparing the distribution of the three ENaC subunits in anterior tongue and posterior tongue show that all three ENaC subunits were readily observed in taste tissue of anterior tongue, whereas primarily only the α-subunit was detectable in posterior taste tissue (Kretz et al., 1999; Lin et al., 1999).

The process of transduction occurs when Na^+ in the oral cavity reaches a threshold level, that is, the activity of Na^+ in the oral cavity begins to exceed that of the intercellular space of the receptor cell. In the human, this level is near 10 mM. Sodium ions then pass into the receptor cell through open epithelial ion channels, and this influx of positive charge depolarizes the cell membrane. It is likely that this depolarization then activates other voltage-sensitive ion channels within the membrane, leading ultimately to changes in ion balance across the membrane and to an increase in calcium ion activity within the cell. An increase in the release of synaptic vesicular content results, and the innervating sensory nerve changes its firing rate.

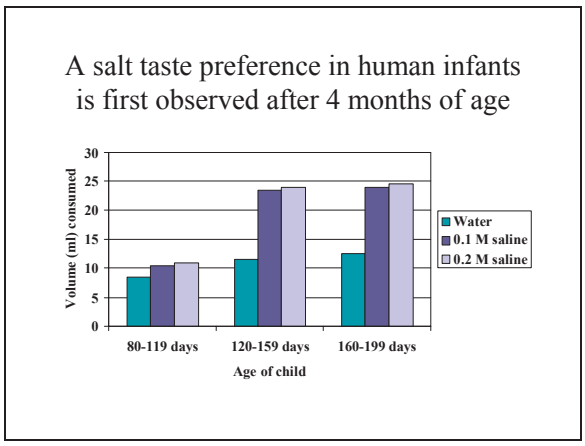
The Development of Salt Taste Perception

Newborn infants either are indifferent to or avoid moderate to high concentrations of saline solution relative to water.





By the time children are 2-3 or more years of age, preferences for salty foods over those same foods without salt are common. These two observations are consistent with the hypothesis that salt preference is learned in childhood. However, we do not believe this to be the case. A preference for salt solutions over plain water is first observed in infants four months of age and older.



Harris and Booth similarly reported that a preference for salted cereal over plain cereal was found in infants at approximately the same age. We suggest that this developmental change in response to salt represents the postnatal maturation of the ability to taste salt, an interpretation consistent with a substantial body of evidence from animal models.

Does experience with salt modulate this apparently innate preference in infants? The data are not clear with some investigators reporting a positive correlation between exposure and preference when we find no such relationship. Further longitudinal studies on the development and early modification of salt taste preference are needed. In particular, the issue of the relation between level of exposure to salt and salt preference should be explored at several ages in order to understand the origin of the very high salt preferences we have documented in some young children.

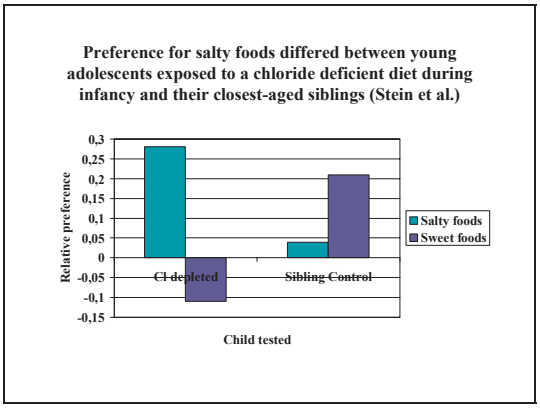
A body of evidence from studies of animal models indicates that sodium depletion early in life may have profound effects on later salt preference. Salt taste perception as measured electrophysiologically, pharmacologically and behaviorally matures postnatally. Early restriction of dietary sodium alters subsequent response to NaCl. Indeed, episodes of sodium depletion induced over a period of 1 or several days by a very high dose of diuretic combined with salt-free diets produces permanent elevation in salt intake weeks or months after recovery; this effect appears especially robust if the depletion occurs during early development.

An analysis of available clinical studies suggests that early sodium depletion may have profound effects on subsequent salt appetite in humans as well.

Research Strategy

To test the hypothesis that early sodium deficiency influences salt preferences later in life, Stein et. al. studied the food preferences of adolescents who were inadvertently fed a chloride-deficient formula (Neo-Mull-Soy) during infancy.

Plasma aldosterone levels and renin activity were activated in some of these infants, thus mimicking the hormonal state that occurs during sodium deficiency.



Modification of Salt Taste Perception and Preference

Physiological Factors: Most adults in the United States consume 6-12 g NaCl/day (100-200 meq) an order of magnitude or more above published requirements. Although it would thus appear unlikely that this level of consumption actually reflects some sort of physiological need, that has in fact been proposed despite the fact that some people live on as little as 20 meq/day or less without apparent harm.

There is little evidence that even an extremely low sodium diet and sodium depletion are followed by a greatly increased desire for salt or what has been termed "salt appetite," as distinguished from the "salt preference" (the choosing of salty food even when sodium is not needed.) To investigate this, we placed human volunteers on a very low sodium diet (5-10 meq/day) and treated them with diuretics to deplete them of sodium. Although they did not express a strong hunger for salt, when asked to rate how much they would like to eat foods varying salt content, the sodium-depleted subjects did express a greater desire for salty foods. Related work has shown that normal subjects, when administered a hydrochlorothiazide diuretic, exhibited a compensatory increase in sodium intake. Subjects expressed no obvious desire for increased salt, and in fact, it was not possible to determine the source of the increased intake.

It is generally believed that individuals in cultures in which a primarily vegetarian diet is consumed need and crave more salt than do primarily meat-eating peoples. The traditional explanation has been that meat-eaters obtain substantial amounts of sodium in meat. Although it is certainly true that meat diets generally contain more sodium than vegetable diets, there is little evidence that the low sodium diets that might exist in vegetarian cultures would lead to an elevated desire for salt. Vegetarian diets in native populations are not only low in salt but may also be low in protein: perhaps protein content, rather than sodium content, of the diet underlies an increased desire for salt, or perhaps both protein and sodium content influence this desire.

Psychological Explanations: Experimental studies have demonstrated that if salt intake is reduced by 30-50% over a period of time, the optimal level of salt in foods declines. The amount of salt required to optimize food flavor is decreased to about 65-75% of the prediet amount. Importantly, this change is gradual, taking probably 1-2 months to occur.

For several reasons, it is most likely that this change is due to the altered (decreased) experience of tasting salty foods rather than a physiological response to the change in the amount of sodium consumed. First, the gradual nature of the effect, as noted above, would suggest that experience plays the major role. Second, we found that if salt consumption was increased by requiring subjects to add approximately 10 g salt to their food, preferred levels of salt in food (but not in aqueous solution) increased. However, if

the same amount of additional salt was consumed as tablets, and thus not tasted, there were no changes in taste preferences. Apparently, a sensory adaptation to different levels of salt accompanies a change in salt intake. To some extent, people like the level of salt they taste rather than, or in addition to, choosing the taste level of salt they like.

The third reason for believing this change in optimal salt level after dietary change to be a psychological phenomenon comes from another study in which we reduced salt in the diet of subjects by 50% but allowed them continued ad libitum use of table salt. Under these conditions, their use of added salt increased almost fourfold but did not approach compensation for the amount removed. In fact, they only replaced 20% of the decrement; thus, there was an overall decrease of approximately 40% in sodium intake. In this instance, we suggest that salt as added "to taste"; this finding further implies that although the salt content of their regular food was in a range that the subjects found palatable, it was unnecessarily high, probably because it was dispersed throughout the food, rather than all being on its surface, and easily accessible to the taste receptors. This study suggests a novel technique to reduce salt intake, in that individuals were able to use as much salt as they wished while still reducing total salt intake. For this to be practical, however, it will be necessary for there to be side availability of all categories of lowered sodium foods. In terms of control of salt preference, the importance of this research is that there were no changes in taste preference, even though salt intake was decreased 40%. We suggest that subjects, by adding salt to the outside of their food, obtained sufficient salty-taste experience to prevent any preference changes.

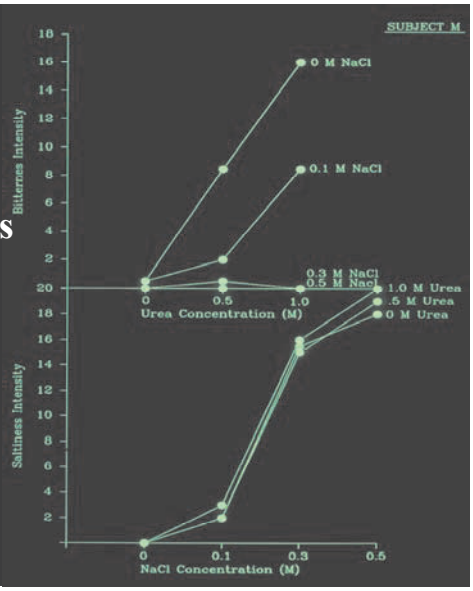
In sum, these studies suport the conclusion that changes in salt taste preferences after halving or doubling salt intake are mediated by hedonic/cognitive expectations based on current dietary experience and not by physiological changes associated with alterations in the amount of NaCl available to the body. Although more extreme depletions may raise salt preferences as described above, the extent to which this is due to depletion rather than the blandness of the foods is unknown.

Salt as a Flavor Potentiator

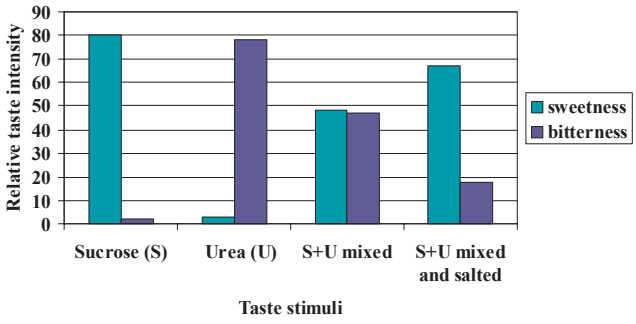
In addition to tasting salty and adding salty taste to foods and beverages, it is well known that salt enhances (improves the palatibility) food flavor. Indeed, it seems to do this even when it does not frankly make the food taste salty. Examples here include breads and other grain products as well as many vegetables. Presumably this is reflected in the very wide spread use of small amounts of salt in many recipes.

We suggested that one way salt might act as a flavor enhancer is by specifically and profoundly blocking bitter taste substances (Kemp & Beauchamp, 1994). It is not known how Na compounds block the bitterness of (only some) bitter compounds, but evidence suggests that the effect is at the receptor level (Breslin & Beauchamp, 1997). Also unknown is whether the mechanism(s) underlying the perception of the saltiness of NaCl and those underlying the efficacy on NaCl as a bitter blocker, are the same.

The sodium ion suppresses the bitterness of urea.



Salt Enhances Sweetness



Nature 387: 1997

Conclusions

Humans prefer to consume substancially more salt than is necessary for the maintenance of normal physiology. In some instances, primarily in the salt-sensitive hypertensive individual, this may lead to illness, and in other instances, it may contribute to the worsening of an existing illness (i.e., congestive heart failure, hepatic cirrhosis with fluid retention, and increased hypertension for those on antihypertensive medication). Some sensory and behavioral factors responsible for this high consumption have been identified, but a full explanation of the mechanisms is lacking. To the extent that one understands the determinants of salt intake, one may be better able to provide guidance for successful reduction of dietary salt intake where this is medically indicated.

References

N.B. : Not all of these appear in the text and not all references in the text are listed.

1. Avenet, P., & Lindemann, B. (1988). Amiloride-blockable sodium currents in isolate taste receptor cells. J. Membr. Biol. 105: 245-255.
2. Beauchamp, G.K. (1987). The human preference for excess salt. Am. Sci. 75: 27-33
3. Branco, L.G., Varanda, W.A. (1992) Toad bladder amiloride-sensitive channels reconstituted into planar lipid bilayers. J. Membr. Biol., 127(2):121-128.
4. Brand, J.G., (1997). Biophysics of taste. In: *Tasting and Smelling*, ed. By G.K.
5. Beauchamp and L. Bartoshuk, Academic Press, San Diego. Pp. 1-24.
6. Brand, J.G., Teeter, J.H., Silver, W.L. (1985) Inhibition by amiloride of chorda tympani responses evoked by monovalent salts. Brain Res. 334:207-214
7. Breslin, P.A, Beauchamp, G.K. (1997) Salt enhances sweetness by suppressing bitterness. Nature. 387(6633):563.
8. Breslin, P.A.S. & Tharp, C.D. (2001). Reduction of saltiness and bitterness after a chlorhexidine rinse. Chem Senses 26: 105-116.
9. Cahn, F.J. (1950) Sodium-free flavoring compositions. U.S. Patent #2,500,919.
10. Denton, D. (1984). *The Hunger for Salt*. Springer-Verlag, Berlin.
11. DeSimone, J.A., & Ferrell, F. (1985). Analysis of amiloride inhibition of chorda tympani taste response of rat to NaCl. Am. J. Physiol. 249: R52-R61.
12. DeSimone, J.A., Heck, G.L. (1991) Salt taste enhancer. U.S. Patent #4,997,672.
13. DeSimone, J.A., Heck, G.L., & DeSimone, S.K. (1981). Active ion transport in dog tongue: A possible role in taste. Science 214: 1039-1041.
14. Desor, J.A., & Finn, J. (1989). Effects of amiloride on salt taste in humans. Chem. Senses 14: 793-803.
15. Dulac, C. (2000). The physiology of taste, vintage 2000. Cell 100: 607-610.
16. Erickson, R.P. (1982). Studies on the perception of taste: Do primaries exist? Physiol. Behav. 28: 57-62.
17. Feigin, A.M., Aronov, E.V., Teeter, J.H., Brand, J.G. (1995) The properties of ion channels formed by the coumarin antibiotic, novobiocin, in lipid bilayers. Biochim. Biophys. Acta 1234: 43-51.
18. Feigin, A.M., Ninomiya, Y., Bezrukov, S.M., Bryant, B.P., Moore, P.A., Komai, M., Wachowiak, M., Teeter, J.H., Vodyanoy, I., Brand, J.G. (1994) Enhancement of gustatory never fibers to NaCl and formation of ion channels by a commercial preparation of novobiocin. Am. J. Physiol. 266:C1165-C1172.
19. Formaker, B.K., & Hill, D.L. (1991). Lack of amiloride sensitivity in SHR and WKY glossopharyngeal taste responses to NaCl. Physiology & Behavior, 50: 765-769.
20. Halpern, B.P. (1998). Amiloride and vertebrate gustatory responses to NaCl. Neurosci. & Biobehav. Rev. 23: 5-47.
21. Heck, G.L., Mierson, S., & DeSimone, J.A. (1984). Salt taste transduction occurs through an amiloride-sensitive sodium transport pathway. Science, 233: 403-405.
22. Herness, M.S. & Gilbertson, T.A. (1999). Cellular mechanisms of taste trasnduction. Ann. Rev. Physiol. 61: 873-900.

23. Hettinger, T.P., & Frank, M.E. (1990). Specificity of amiloride inhibition of hamster taste responses. Brain Res., 513: 24-34.

24. Kemmerer, K.S. (1958) Dietary seasoning composition. U.S. Patent #2,829,056.

25. Kemp, S.E. & Beauchamp, G.K. (1994). Flavor modification by sodium chloride and monosodium glutamate. J. Food Sci., 59: 682-686.

26. Kretz, O., Barbry, P., Bock, R. & Lindemann, B. (1999). Differential expression of RNA and protein of the three pore-forming subunits of the amiloride-sensitive epithelial sodium channel in taste buds of the rat. J. Histochem. & Cytochem. 47: 51-64.

27. Lee, T.D. (1993) Seasoned food product with a salt enhancer. U.S. Patent #5,176,934.

28. Leibrecht, A. (1932) Process for preparing suitable substitutes for table salt for flavoring purposes. U.S. Patent #1,874,055.

29. Li, X.-J., Blackshaw, S., 7 Snyder, S.H. (1994). Expression and localization of amiloride-sensitive sodium channel indicate a role for non-taste cells in taste perception. Proc. Natl. Acad. Sci., USA, 91:1814-1818.

30. Lin, W., Finger, T.E., Rossier, B. C. & Kinnamon, S.C. (1999). Epithelial Na channel subunits in Rat Taste Cells: localization and regulation by aldosterone. J. Comp. Neurol. 405: 406-420.

31. Lindemann, B. (1996) Taste Reception. Physiological Reviews 76(3):719-766.

32. MacGregor, G.A. & Wardener, H.E. (1998) *Salt, Diet & Health*. Cambridge University Press, Cambridge, UK

33. McBurney, D.H. (1969). Effects of adaptation on human taste function. In: *Olfaction and Taste III*, ed. By C. Pfaffmann, Rockefeller Univ Press, New York. pp 407- 419.

34. McCutcheon, N.B. (1992). Human psychophysical studies of saltiness suppression by amiloride. Physiol. Behav. 51: 1069-1074.

35. Mohlenkamp, Jr, M.J., Hiller, G.D. (1981) Sodium-free salt substitute. U.S. Patent #4,243,691.

36. Murphy, C., Cardello, A.V., & Brand, J.G. (1981). Tastes of fifteen halide salts following water and NaCl: Anion and cation effects. Physiol. & Behav., 26: 1083-1095.

37. Ossebaard, C.A., & Smith, D.V. (1995). Effects of amiloride on the taste of NaCl, Na-gluconate, and KCl in humans: Implications for Na^+ receptor mechanisms. Chemi. Senses, 20: 37-46.

38. Pich, C.H., Moest, T. (1982) Stringently sodium-restricted dietetic salt and its preparation. U.S. Patent #4,340,614.

39. Sandick, B., & Cardello, A.V. (1983). Tastes of salts and acids on circumvallate papillae and anterior tongue. Chem. Senses, 8: 59-69.

40. Schiffman, S.S., Booth, B.J., Carr, B.T., Losee, M.L., Sattely-Miller, E.A., Graham, B.G. (1995) Investigation of synergism in binary mixtures of sweeteners. Brain Res Bull, 38(2):105-120

41. Schiffman, S.S., Lockhead, E., & Maes, F.W. (1983). Amiloride reduces the taste intensity of Na and Li salts and sweeteners. Proc. Natl. Acad. Sci., USA, 80: 6136-6140.

42. Schiffman, S.S., Simon, S.A., Gill, J.M. & Beeker, T.G. (1986). Bretylium tosylate enhances salt taste. Physiol. & Behav., 36: 1129-1137

43. Schiffman, S.S., Suggs, M.S., Cragoe, E.J., Jr., & Erickson, R.P. (1990). Inhibition of taste responses to Na salts by epithelial Na channel blockers in gerbil. Physiol. & Behav. 47: 455-459.

44. Scott, T.R. & Giza, B. K. (1995). Theories of gustatory neural coding. In: *Handbook of Olfaction and Gustation*, ed. By R.L. Doty. Marcel Dekker, New York. pp 611- 633.

45. Tamura, M., Seki, T., Yoshihiro, K. Tada, M., Kikuchi, E., Okai, H. (1989) An enhancing effect on the saltiness of sodium chloride of added amino acids and their esters. Agric. Biol. Chem., 53(6):1625.

46. Tennissen, A.M., & McCutcheon, N.B. (1996). Anterior tongue stimulation with amiloride suppresses NaCl saltiness, but not citric acid sourness in humans. Chem. Senses, 21: 113-120.

47. Ye, Q., Heck, G.L. & DeSimone, J.A. (1991). The anion paradox in sodium taste reception: Resolution by voltage-clamp studies. Science, 254: 724-726.

De la salle

D'une part, s'agissant de la relation entre le sodium corporel et le goût du sel, l'augmentation de la teneur en sodium du corps, du fait de certains problèmes, a des répercussions sur le goût. Si vous augmentez la teneur en sodium par l'administration de corticoïdes, l'animal est en réplétion de sodium et continue pourtant à rechercher le sodium. D'autre part, la réduction du sodium corporel en deçà d'un certain seuil entraîne une excrétion très faible du sodium supplémentaire. Le corps peut donc éliminer des quantités minimes de sodium une fois qu'il y a réplétion. En revanche, si l'on réduit le sodium, le corps peut retenir le sodium. Que pensez-vous de ces relations ?

Gary K. BEAUCHAMP

Je n'explique pas les cas que vous citez. En fait, quand la teneur en sodium corporelle est alterée de façon marquée, on n'observe pas d'effet sur la réaction sensorielle. Peut-être que ces deux données ne sont pas corrélées en réalité, parce que les animaux ne sont pas vraiment sous stress.

De la salle

Les Français utilisent très peu de sel dans leur cuisine. Si l'on utilise des aliments frais et naturels tels que la viande, les fruits et les légumes, on n'a pas besoin d'ajouter du sel pour apprécier leur saveur. En réalité, c'est lorsqu'on ajoute du sel que les aliments se ressemblent. La cuisine industrielle recourt à des produits non frais et de moindre qualité exigeant d'être améliorés pour être savoureux. Si vous réalisiez vos expériences sur des aliments frais, vous aboutiriez à ce type de conclusions.

Gary K. BEAUCHAMP

Je ne m'aventurerai pas à juger la cuisine française. Mais mes lectures me laissent penser que les Français ajoutent une pincée de sel dans la plupart de leurs recettes. Quoi qu'il en soit, je ne crois pas que les quantités de sel utilisées – qui représentent trois fois celle contenue dans l'eau de mer – améliorent le goût des aliments.

De la salle

Une étude montre que sur 48 centres caractérisés par des habitudes alimentaires différentes comportant peu de sodium, la consommation de sel serait comprise entre 100 et 200 minimol par jour. Comment interprétez-vous cette donnée sous l'angle de la préférence pour le sodium ?

Gary K. BEAUCHAMP

La faiblesse de variations sur les 48 pays observés résulte certainement du fait que les mêmes fabricants produisent les mêmes aliments dans tous ces pays. Ce sont donc les

sociétés agroalimentaires qui sont responsables du niveau de sel ingéré dans ces pays. A cet égard, les populations n'ont pas le choix.

De la salle

Votre exposé devrait être replacé dans un cadre anthropologique. Il ne serait pas surprenant que la préférence pour le sel constitue une sorte d'appétit inné pour le sel. Dans les stades précoces de l'évolution humaine, l'homme vivait dans un environnement hyposodé alors que nous vivons désormais dans un environnement hypersodé. Or notre patrimoine génétique n'a pas dû évoluer. Dès lors, il est rassurant que le suivi d'un régime hyposodé fasse régresser la préférence pour le sel.

Gary K. BEAUCHAMP

Le fait de replacer ces résultats dans une perspective d'évolution est pertinent. Je souscris à vos conclusions. Il est rassurant de pouvoir s'adapter à un régime hyposodé. La difficulté consiste à maintenir ce régime parce que le changement de préférence est graduel. Mais passé un certain seuil, l'interruption de ce régime entraîne un retour au point d'origine très rapidement. Il faudrait disposer d'une grande quantité d'aliments frais pour maintenir ce régime hyposodé.

De la salle

Quel est le lien entre la température des aliments et le goût salé ?

Gary K. BEAUCHAMP

De nombreuses études ont montré que la température des aliments avait un effet faible, voire non significatif, sur le goût du sel.

De la salle

Les études effectuées chez des nourrissons tiennent-elles compte du fait que, dans certains pays, les pédiatres recommandent de nettoyer les narines des nourrissons plusieurs fois par jour avec des solutions salines - cette pratique ayant certainement un impact sur l'absorption de sel par les bébés ?

Gary K. BEAUCHAMP

C'est la première fois qu'une telle question m'est posée. Il est probable que cette pratique contribue à l'absorption de sel.

Apport en sel et hypertension

Les études d'observation et d'intervention

Salt intake and hypertension

Observational and intervention studies

Session 2

animée par M. Alberto ZANCHETTI
University Major Hospital, Milan, Italie,

et M. Theodore A. KOTCHEN,
Medical College of Wisconsin, Milwaukee, Etats-Unis

Cette session a réuni :
Paul ELLIOT, Imperial College of Science, Technology and Medicine, Londres, Royaume-Uni ;
Graham A. MacGREGOR, St George's Hospital Medical School, Londres, Royaume-Uni ;
Alexander G. LOGAN, Mount Sinaï Hospital, Toronto, Canada ;
Eva OBARZANEK, NHLBI, Bethesda, Etats-Unis ;
Johanna M. GELEIJNSE, Wageningen University, Pays-Bas.

Introduction par M. Alberto ZANCHETTI (VF)

Je remercie le Directeur général de l'Afssa, M. Martin Hirsch, le Pr. Ducimetière et mon ami Joël Ménard de m'avoir aimablement invité à présider cette séance avec le Dr. Théodore Kotchen.

J'ai passé quinze ans en Toscane, où les populations mangent du pain sans sel. Dante lui-même s'est plaint dans ses poèmes de manger du pain salé lors de son exil au Nord de l'Italie, même si nous ne savons pas si Dante souffrait de ce fait d'hypertension. En fait, c'est la cour de Catherine de Médicis qui a exporté le pain italien en France. Nous nous réjouissons donc de pouvoir discuter de la question de l'exportation du pain italien en France.

Après avoir évoqué ce matin les gènes impliqués dans la régulation de la balance sodée, nous abordons maintenant la relation entre apport en sel et hypertension, grâce à cinq experts intervenants.

Je demande immédiatement au Dr. Paul Elliot de l'Imperial College of Science, Technology and Medicine de Londres de nous parler des études Intersalt et Intermap.

INTERSALT and INTERMAP studies

Paul ELLIOT
Imperial College of Science, Technology and Medicine, London, United Kingdom

---

Raised blood pressure in the population is a major cause of stroke and coronary heart disease worldwide. Data from migrant studies indicate that environmental factors underlie the rise in blood pressure with age and the high prevalence of high blood pressure and hypertension at older ages seen in most populations around the world. Dietary sodium intake is one of the key factors underlying these unfavourable patterns of population blood pressure.

Results from two large population-based studies giving data on 24-hour urinary sodium excretion and blood pressure are presented: the INTERSALT and INTERMAP (International Cooperative Study of Macronutrients and Blood Pressure) studies. INTERSALT included analyses for 10,074 men and women in 52 population samples from 32 countries. It found highly significant positive associations of urinary sodium excretion with blood pressure of individuals, as well as with the slope of blood pressure with age across the population samples. INTERMAP included data on 4,680 men and women aged 40-59, from 17 population samples in Japan, the PRC, UK and USA. As well as obtaining 24-hour urinary data, INTERMAP collected 4 x 24-hour dietary recalls based on in-depth dietary interview, with high levels of standardisation and quality control. Results are presented from INTERMAP on urinary sodium excretion and blood pressure based on the INTERSALT model. Results from the two studies are considered with reference to results from other observational studies, as well as clinical trial and other data on sodium and high blood pressure. Implications for the prevention of unfavourable blood pressure patterns and high prevalence of high blood pressure in populations are discussed.

References

Intersalt Cooperative Research Group - Intersalt : an international study of electrolyte excretion and blood pressure: results for 24-hour urinary sodium and potassium excretion. BMJ 1988; 297:319-328

Salt and Cardiovascular Disease

Graham A. MACGREGOR
St George's Hospital Medical School, London, United Kingdom

Summary

Increasing blood pressure throughout the range found in developed countries is one of the main causes of premature death. It is the major cause of strokes and heart failure. It is also a very important cause of coronary heart disease. These together account for just under half of all deaths in the UK and are the major cause of disability. Blood pressure lowering trials demonstrate the immense benefits of reducing blood pressure in both preventing strokes and heart failure and coronary heart disease. There are no differences in outcome between the different methods used to lower blood pressure and the benefit is proportional to the degree of blood pressure lowering.

Evidence that relates salt intake to increases in population blood pressure, the increase in blood pressure with age and the number and severity of those with high blood pressure are described from six different lines of evidence - epidemiology, migration, intervention, treatment and animal studies and genetics. Evidence from these different sources all suggests that salt intake is important in blood pressure regulation and a reduction in salt would lead to a reduction in population blood pressure, a reduction in the rise in blood pressure with age and a reduction in blood pressure in those with high blood pressure whether on or off treatment.

This evidence has been strongly reinforced by some important studies over the last few years. Salt intake can be easily reduced in all western countries, firstly by a public campaign providing education about the dangers of salt, in turn leading to less use of table and cooking salt in the home. Secondly, as 70 to 80% of salt intake comes from processed foods, this must be combined with a gradual and sustained reduction in the salt concentration of all processed, ready prepared, restaurant and catering foods. Average salt intake in western countries lies between 10 to 12 grams per day. This should be reduced to 5 to 6 grams per day.

This reduction in salt intake will carry large benefits to the health of the population by reducing strokes, heart failure and heart attacks. If this reduction in salt intake was also combined with an increase in fruit and vegetable consumption and a reduction in saturated fat intake, there would be even larger benefits.

Importance of Cardiovascular Disease

Cardiovascular disease is the commonest cause of death and disability in the western world, accounting for just under half of all deaths. The major underlying cause of cardiovascular disease is atherosclerosis. The three major established risk factors are cigarette smoking, abnormal lipid profiles and blood pressure. Increasing blood pressure throughout the range in developed countries is a major accelerating factor (1). Blood pressure also has direct effects. It is the main cause of strokes, both through cerebral haemorrhage and small vessel disease, in addition to the atherosclerosis that it causes. Blood pressure is now the main cause of heart failure.

Some of the best evidence for primary prevention of disease comes from the many blood pressure lowering trials that have been carried out over the last 30 years, which

demonstrate that lowering blood pressure is of great benefit in reducing strokes, heart failure and coronary heart disease (2). Recent meta-analyses of these studies have shown that there is equal benefit whatever means is used to lower blood pressure, and that the benefit is proportional to the degree of lowering of blood pressure (3).

High blood pressure is extremely common in western countries. For instance, in the UK just under 40% of the entire adult population have high blood pressure (systolic ≥ 140 mmHg and/or diastolic ≥ 90 mmHg), at the age of 50-59 years approximately 50% have high blood pressure, and at the age of 60-79 years 70% have high blood pressure (4). At the same time, studies in developed countries have shown a consistent pattern of an increase in blood pressure with increasing age.

Benefits of Reducing Blood Pressure in the "Normal" Range

Whilst these primary prevention studies have been performed in people with high blood pressure, ie with a systolic greater than 140 mmHg or a diastolic greater than 90 mmHg, the risk of blood pressure is throughout its range. Recent studies have reconfirmed there are very significant risks to those people whose blood pressure is in the upper range of normal[5]. Indeed, the greatest number of strokes and heart attacks attributable to blood pressure occur in the upper range of normal, although the risk is less than in those with high blood pressure, the numbers exposed are much greater (Fig 1; 1) (Fig 2; 6).

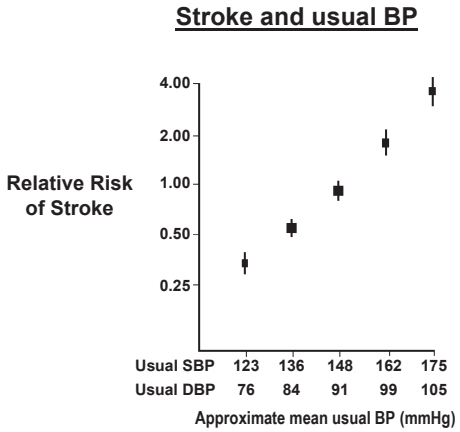


Figure 1. Relative risk of stroke in relation to systolic and diastolic blood pressure. (From Ref.1).

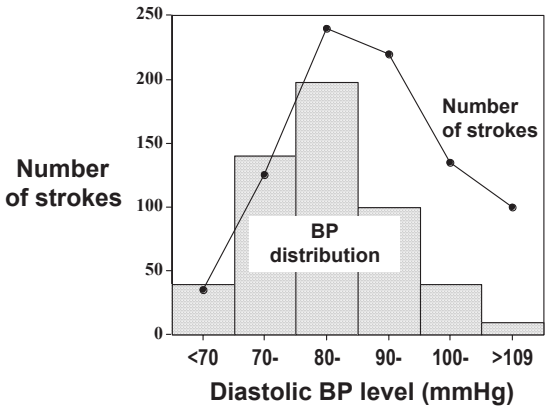


Figure 2. Absolute number of strokes in 405000 individuals in seven prospective observational studies by baseline diastolic blood pressure. Approximately three-quarters of all strokes occurred among individuals classified as "normotensive". (Redrawn from Ref.6).

Any intervention therefore, that would lower blood pressure in the general population, even by small amounts, is likely to be of immense benefit in preventing both strokes and

heart attacks and would, over a period of time, have even more benefit if it slowed down the rate of increase in blood pressure with age. Geoffrey Rose pointed out many years ago that a 2 mmHg reduction in systolic pressure in the whole population would carry more benefit than all of the current blood pressure treatment (7). Two recent studies in individuals at high risk of cardiovascular disease have demonstrated the very large benefits of reducing blood pressure in the "normal" range (8,9).

Underlying Factors

The mechanisms whereby blood pressure in developed countries is raised and the rise in blood pressure that occurs with age are not fully understood. However, there is a wealth of evidence to suggest that obesity coupled with a lack of exercise are important factors. There is also very strong evidence to suggest that salt intake is related to the development of hypertension (10), and that potassium intake has the opposite effect and may, in certain circumstances, reverse the effects of a high salt intake (11). Excess alcohol intake is epidemiologically related to blood pressure, but the effect appears to be transient and there is debate as to whether excess alcohol intake causes a sustained increase in blood pressure. Other minerals, eg calcium, magnesium and fat and protein intake have also been studied but so far the results are inconsistent.

This paper will only consider the evidence relating salt intake to blood pressure.

Evidence on Salt and Blood Pressure

There are six different types of evidence that relate salt to the development of high blood pressure:

- Epidemiological Studies
- Migration Studies
- Intervention Studies
- Treatment Studies
- Animal Studies
- Genetic Studies

Epidemiological Studies

There are now over 40 reports and studies in undeveloped societies who do not or did not have access to salt. These societies have low blood pressure compared to developed societies and no rise in blood pressure with age (12-17). Whilst there may be other factors that also account for the lower blood pressure, several studies have clearly demonstrated the profound importance of salt (16,17). A study in the Pacific Islands where one undeveloped community used salt water in their food and the other did not, showed the community using salt had higher blood pressure (16). Another study in Nigeria of two rural communities, one of which had access to salt from a salt lake and the other did not, showed differences in salt intake and differences in blood pressure, and yet in all other aspects of lifestyle and diet the two communities were similar (18). The Qash'qai, an undeveloped tribe living in Iran who have access to salt deposits on the ground, develop high blood pressure and a rise in blood pressure with age similar to that which occurs in western communities, but in all aspects live a lifestyle similar to undeveloped countries (17).

The InterSalt Study (19) was a carefully controlled study of 52 communities throughout the world with measurements including blood pressure, weight, 24 hour urinary sodium and potassium. The original intention of the InterSalt study was to study communities with a wide range of salt intake, ie from 0.5 grams per day to 25 grams per day.

However, only four communities studied had a low salt intake and the rest lay between 6 and 12 grams of salt per day. The study showed when all the communities were considered there was a positive relationship between salt intake (as judged by 24 hour urinary sodium excretion) and blood pressure (19). There was a positive and highly significant relationship between the increase in blood pressure with age and salt intake (Fig 3; 19). This relationship showed that an increase in 6 grams of salt over 30 years would lead to an increase in systolic pressure in the whole population by 9 mmHg.

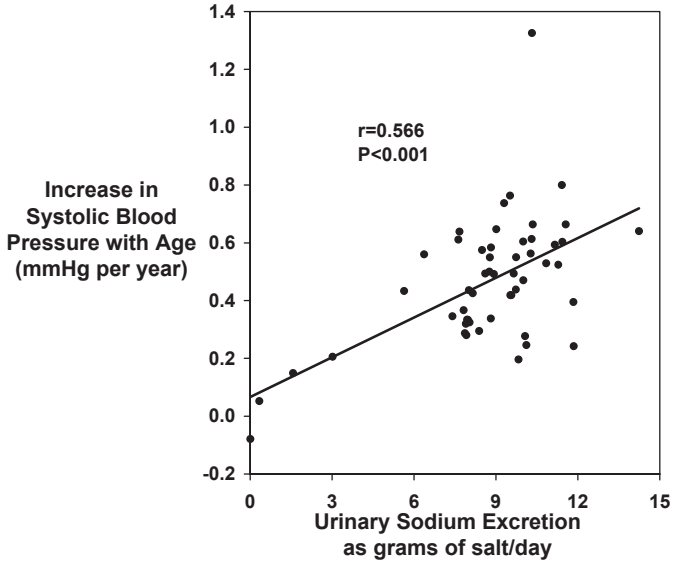


Figure 3. The relation of salt excretion to the slope of the rise in systolic blood pressure with age in 52 centres in the INTERSALT study. (Adapted from Ref.19).

One criticism of the InterSalt study was that when the four communities consuming less salt were excluded, there was no overall relationship remaining between salt intake and blood pressure in these 48 communities. However, the variability of salt intake in developed countries from day to day is large. Blood pressure is also variable. Given that in these communities the range of salt intake was only from 6 to 12 grams per day, it is not surprising that there was only a positive relationship in just under half of the communities studied.

The Salt Institute published a paper criticising the statistics of the study (20). The InterSalt Study's authors re-analysed their findings and the results were published simultaneously (21). The conclusion was that the re-analysis strengthened their results and their conclusions still stood that salt intake was related to blood pressure throughout different populations in the world, and that there was a robust relationship between the rise in blood pressure with increasing age and salt intake (21).

Migration Studies

A well controlled migration study of a rural tribe in Kenya showed that on migration to an urban environment, there was an increase in salt intake and a reduction in potassium intake and blood pressure rose compared to those in a similar controlled group who remained in the rural environment (22). It was suggested that the change in electrolyte

intake was an important factor in the increase in blood pressure and furthermore, that the stress of the urban environment may have caused additional retention of sodium above that which would have occurred with the increase in salt intake.

Intervention Studies

A well controlled double-blind study in just under 500 new born babies (23) showed that when salt intake was reduced by about 30% in the reduced salt group, as judged by spot urinary sodium concentrations, there was a progressive difference in systolic blood pressure. At the end of six months the babies on the lower salt intake had a 2.1 mmHg lower systolic blood pressure (P<0.01). The study was discontinued at six months.

Many of these babies were restudied 15 years later (24). There remained a significant difference in blood pressure, when adjusted, between those babies who in the first six months of life had had a reduced salt intake compared to those that had not, suggesting that there was a programming effect of salt intake in early life, which fits with several studies in animals (Fig 4).

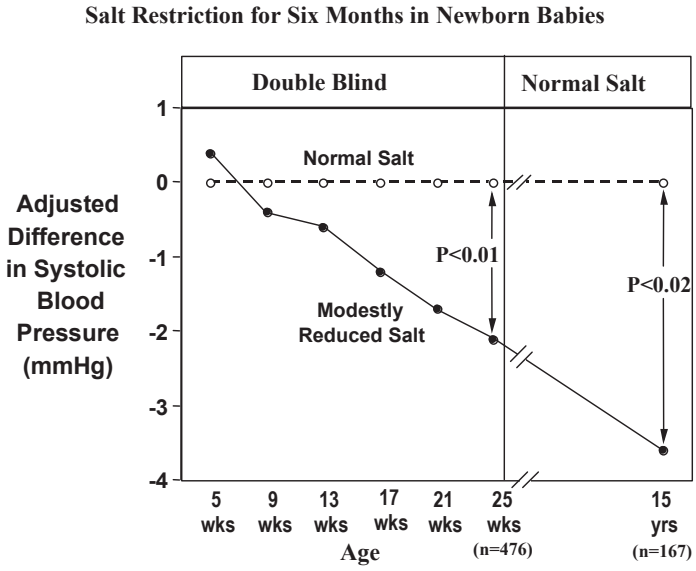


Figure 4. Difference in systolic blood pressure in newborn babies, randomised to either a normal salt intake or a moderate reduction in salt intake over the first six months of life. At six months, the study was discontinued, with all participants resuming a normal salt intake. Fifteen years later, a subgroup of those in the study had blood pressure re-measured. (Adapted from Ref.23,24)

The other intervention study which successfully managed to reduce salt intake is a study of two villages in Portugal (25). One village was given information on how to reduce salt intake, and given processed foods with less salt. Salt intake was reduced by just under half, as judged by 24 hour urinary sodium excretion. After one year, there was a difference in blood pressure and at two years both systolic and diastolic pressure showed highly significant falls compared to the control village where no reduction in salt intake was made (Fig 5).

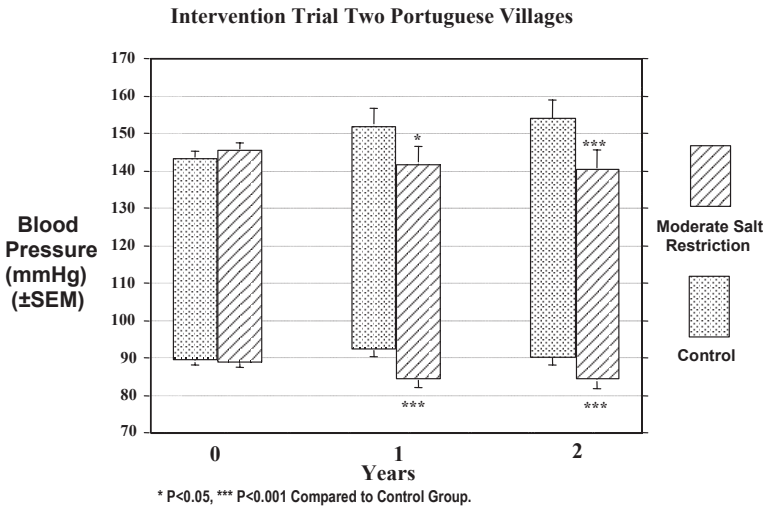


Figure 5. Blood pressure changes with time in two Portuguese villages, one of which was advised on how to reduce salt intake and given processed foods with a reduced salt content, the other had similar measurements of blood pressure but no advice on diet. Note the significant differences in blood pressure at 1 year and continuing differences at 2 years. (Adapted from Ref.25).

Two other intervention studies are often quoted as being negative (26, 27). Neither were successful in reducing salt intake and it is not surprising that there was no change in blood pressure in these studies between the community that was instructed on reducing salt, but failed to do so, and those that were not given such instructions. The only conclusions from these latter studies is that in western countries it is difficult to reduce salt intake unless processed foods with no or much less salt are provided.

Population Studies

Japan: In the late 1950s the Japanese became aware that certain parts of Japan, particularly the north, had a high salt consumption and deaths from stroke due to brain haemorrhage were amongst the highest in the world. It was then found that the number of strokes in different parts of Japan were directly related to the salt intake. In view of these findings, there was a Government campaign to reduce salt intake, which was successful in reducing salt intake over the following decade from an average of 13.5 grams per day to 12.1 grams per day. However, in the north of Japan the salt intake fell from 18 grams per day to 14 grams per day. At the same time, there was a fall in blood pressure both in adults and children, and an 80% reduction in stroke mortality (28). At the time of this fall and the reduction in stroke mortality, there were large population increases in fat intake, cigarette smoking, alcohol consumption and an increase in weight, along with a reduction in fruit and vegetable consumption and less exercise being taken. It would appear that the Western influence which was rapidly overtaking Japan seemed to have little effect on blood pressure, provided salt intake was reduced.

North Karelia: In this study, 14,000 men aged 35-64 years were given advice about reducing fat and salt intake, increasing fruit and vegetable consumption and decreasing smoking. In co-operation with the food industry in Finland, they were given processed foods with less salt. Over the 20 years of the study which started in 1972, cholesterol was reduced by 13%, diastolic pressure by 9% and smoking by 15%. At the same time, there was a reduction in stroke mortality by 66% and coronary heart disease mortality by 55%. The reduction in the three major risk factors explained four-fifths of the fall in coronary heart disease mortality and two-thirds of the fall in stroke mortality (29,30). It has been estimated that about half of these changes were due to the change in diet and that the

reduction in salt intake played an important role in the fall in blood pressure and the reduction in strokes that occurred.

Both the Japanese and North Karelia experience suggest that where the right advice is given to the public and where processed foods are provided with less salt, it is relatively easy for the whole population to reduce their salt intake.

Treatment Trials

Studies since the early 1900s have shown that in those subjects with high blood pressure, restricting salt intake causes large falls in blood pressure. The classic studies of Kempner clearly showed major effects (31), even in accelerated hypertension, which was subsequently shown by carefully controlled studies to be due to the reduction in salt intake (32).

More recently, more modest reductions in salt intake, ie to around 5 to 6 grams per day from an intake of 10 to 12 grams per day, have been shown to cause falls in blood pressure in hypertensives equivalent to single drug therapy (33). These falls are larger in those subjects with lower levels of plasma renin activity or angiotensin II, for example those of African origin (34) or older subjects. Furthermore, modest reductions in salt intake have been shown to be additive to drug treatment (35).

A double blind study of salt reduction with three sodium intakes - 10, 5 and 3 grams per day in subjects with mild untreated essential hypertension showed a clear dose response to the salt reduction (36) with large falls in blood pressure on 3 grams of salt per day. Furthermore blood pressure remained controlled on the lower salt intake at one year of follow up.

Three longer term studies from the USA have also demonstrated that quite small reductions in salt intake not only lower blood pressure, but may also prevent the development of hypertension, and may allow the withdrawal of drug therapy (37-39).

Given that 30 to 40% of the adult population have high blood pressure, this in itself could be seen as sufficient reason for a reduction in population salt intake, particularly as many subjects are unaware that they have high blood pressure and as people become older, the risk of stroke become greater and the immediate benefits of even small reductions in blood pressure would be large.

Some controversy has surrounded the effect of modest salt reduction in those with "normal" blood pressure. Meta-analyses of a variety of studies that have been undertaken in normotensives have shown small, but consistent, reductions in systolic pressure (40-43). Two recent meta-analyses of the effect of salt restriction on blood pressure showed that whilst the fall in blood pressure was again significant in normotensive subjects, it was, according to the authors, of insufficient degree to be of public health importance (41, 43). Close examination of these two meta-analyses shows that they are seriously flawed as they included many normotensive studies where salt intake had only been reduced for five days and there were very large reductions in salt intake, eg from 20 grams per day to less than 0.5 grams of salt per day over five days. This is known to cause stimulation of the sympathetic nervous system and brisk activation of the renin-angiotensin system (44). These very short acute reductions in salt intake are not relevant to the public health recommendations of a more modest reduction in salt intake from 9-10 grams per day to 5-6 grams per day over a lifetime.

A more recent meta-analysis looked only at studies of one month or more in duration and only included studies with modest reductions in salt intake similar to the public health recommendations (45). This meta-analysis demonstrated a significant fall in blood pressure, both in systolic and diastolic blood pressure, not only in hypertensives but also in normotensive individuals (Fig 6). The meta-analysis also showed a dose response so that a 6 gram reduction in salt intake, would result in a fall in systolic blood pressure in the normotensive subjects of 4.0 mmHg.

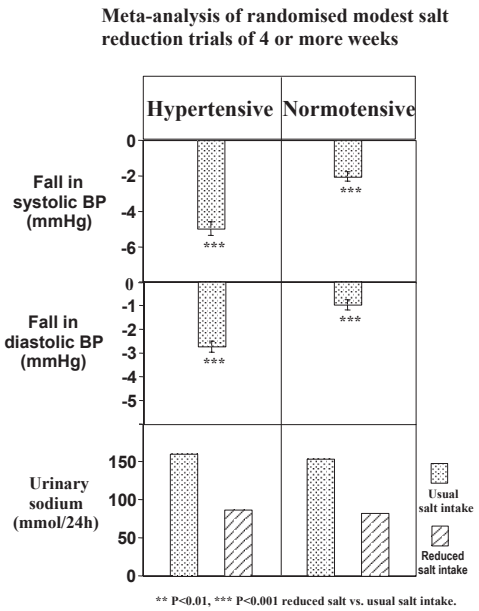


Figure 6. Effect of modest salt reduction on blood pressure in hypertensive and normotensive individuals in a meta-analysis of 28 randomised controlled trials of 4 or more weeks. (Note average salt intake was reduced from 10 to 5 grams/day).

A double-blind study in older subjects (46) demonstrated that the fall in blood pressure in normotensive individuals with a modest reduction in salt intake from 10 to 5 grams of salt per day, was the same as those with high blood pressure. This suggested a large potential benefit of salt reduction in preventing strokes in this vulnerable elderly group who have blood pressure in the upper range of normal.

More recently, the DASH Sodium Study (34), a well controlled feeding study, has clearly demonstrated that reducing salt intake lowers blood pressure substantially, not only in hypertensives but also in normotensives, and importantly there was a dose response. Furthermore, there was a further fall in blood pressure with the salt restriction when a separate group of patients were fed a DASH diet consisting of more fruit and vegetables, less saturated fat. This study is of importance in that it demonstrates that not only would there be benefit from reducing salt intake on the diet that we currently consume, but there would be additional effects of consuming more fruit and vegetables and reducing saturated fat intake and reducing salt intake (Fig 7, Table below).

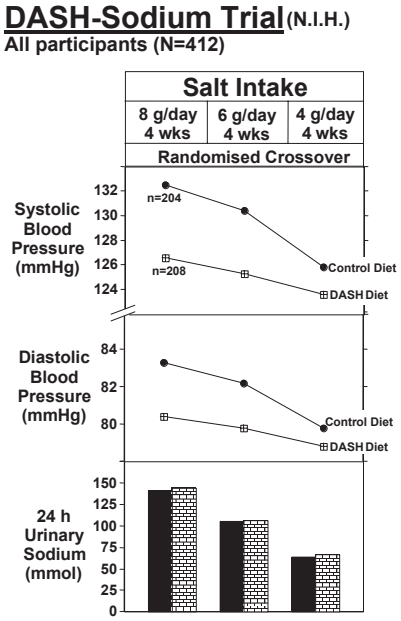


Figure 7. Changes in blood pressure and 24 h urinary sodium excretion with the reduction in salt intake in all participants (hypertensives: n=169; normotensives: n=243) on the normal American diet (i.e. control diet) and on DASH diet. (Redrawn from Ref. 34).

Table : Fall in blood pressure with salt restriction alone or the combination of salt restriction DASH-diet in hypertensive and normotensive individuals in the DASH-Sodium study.

	Hypertensives (n=169)	Normotensives (n=243)
Salt restriction alone	8.3/4.4 mmHg	5.6/2.8 mmHg
Salt restriction + DASH diet	11.5/5.7 mmHg	7.1/3.7 mmHg

Most studies have been for one month only and it is likely that a longer duration of salt reduction would have a greater effect, particularly if it also prevented or slowed down the rise in blood pressure with age.

Animal Studies

Studies in animals have demonstrated that in the inherited hypertension in the rat, all require a high salt intake to develop high blood pressure. The higher the salt intake, the greater the rise in pressure. Furthermore, all forms of experimental hypertension require a high salt intake to develop high blood pressure. In addition, many normal animals also have large rises in blood pressure when exposed to an increased salt intake. For instance, a study in chimpanzees (98.8% genetic homology with man) where one group was maintained on their normal diet of around half a gram of salt per day was compared with a randomly selected group that had salt intake increased to 10 to 15 grams per day over 20 months (47). There was a substantial rise in blood pressure in those chimpanzees on the high salt diet, which fell back to control levels when salt intake was returned to their normal intake (Fig 8).

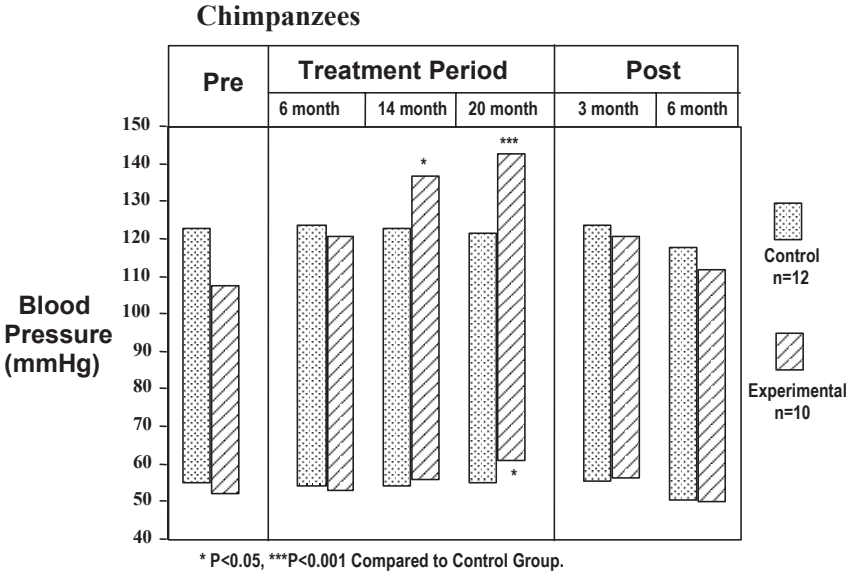


Figure 8. Blood pressure in chimpanzees who either continued on their usual diet (10 mmol sodium per day) or were given an increased salt intake (200 mmol sodium per day). At the end of the 20-month study, the salt supplements were stopped and blood pressure declined to that of the control group. (Adapted from Ref.47).

Human Genetic Studies

All of the monogenic causes of high blood pressure described so far reduce the kidney's ability to excrete sodium and cause high blood pressure if salt is consumed. Rare monogenic causes of low blood pressure have also been described which result in the kidney being unable to hold on to sodium normally, thereby resulting in low blood pressure. These forms of low blood pressure are ameliorated by a high salt intake. Overall they clearly indicate the importance of salt in regulating blood pressure in humans (48).

Mortality Studies

One of the difficulties of drawing conclusions about the importance of dietary or other lifestyle changes in cardiovascular disease is the gap in the evidence that relates to mortality. One has to accept that outcome studies in the population are extremely difficult and there is unlikely to ever be outcome evidence on mortality for any dietary variable, eg saturated fat, fruit and vegetables or other lifestyle changes eg losing weight, or taking exercise. For instance, a study on salt would need to randomise subjects at the time of conception to a lower and higher salt intake and then follow up the two groups of offspring on a high and low salt intake for the rest of their lives. Such studies are impractical and would be unethical in the light of current knowledge.

Alderman has attempted to look at the effect of salt on outcome in cardiovascular disease (49,50). The first study was in hypertensives who had renin profiling performed prior to entering a study of long term follow up on blood pressure lowering drugs. In order to perform the renin profiling, all subjects had their salt intake restricted for five days to stimulate renin release. This enabled the subjects to be sub-grouped into low, normal or high renin groups. Alderman found that the 24 hour urinary sodium excretion on the fifth day of a reduced salt intake was related to subsequent myocardial infarction and made the extraordinary claim that a lower salt intake led to more heart attacks (49). However, no measurement of salt intake had been carried out on the subject's normal diet. Furthermore, no attempt was made to monitor salt intake during the follow-up period. Analysis of the 24 hour urinary sodium data also revealed severe methodological

problems as the lowest salt quartile had a much lower 24 hour urinary creatinine excretion. This demonstrated that many of those who had been attributed to the lowest salt quartile on the fifth day of a reduced salt intake were there not because they had been successful in reducing their salt intake more, but had collected incomplete 24 hour urine collections (51,52).

Alderman's second study (50) involved the NHANES 1 - a dietary survey of US adults from the mid 1970s. However, any analysis of salt intake from this study is difficult to judge as 24 hour urinary sodium excretion was not measured and dietary salt was assessed by dietary history with no account taken of discretionary salt (ie salt added at the table or in cooking), which at this time would have accounted for more than half of the salt intake. Alderman claimed that salt intake was inversely related to cardiovascular disease. However, examination of the data showed major discrepancies, eg subjects in the lower salt intake were on a calorie intake that was near starvation levels compared to the higher salt group and yet the lower calorie group weighed 4 kgs more than those on the higher salt and calorie intake (53-55).

A well controlled study from Finland using a random sample of the Finnish adult population showed that salt intake is related to increased cardiovascular mortality and total mortality (56). For a 6 gram increase in salt intake there were large increases in both coronary heart disease, cardiovascular disease and total mortality. (Fig 9)

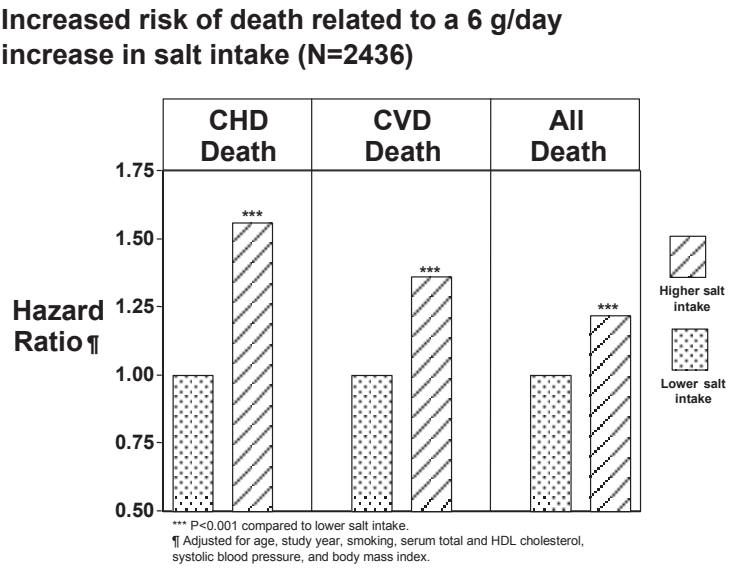


Figure 9. The hazards ratios for coronary heart disease (CHD), cardiovascular disease (CVD), and all-cause mortality associated with a 6 g/day increase in salt intake as judged by 24 hour urinary sodium excretion. (Adapted from Ref.56)

Other Adverse Effects of Salt

Much of the focus on salt has been on blood pressure. There is now increasing evidence that salt has other deleterious effects of health, independent and sometimes additive to that of blood pressure (57). When humans go from a low to a high salt intake, there is retention of sodium and thereby water and this expands the extra cellular volume. This increase in extra cellular volume is a trigger for various compensatory mechanisms to allow an increase in urinary sodium excretion but at the expense of continued retention of sodium and water. Approximately 1.5 litres of extra cellular fluid is retained and this continues as long as a higher salt intake is consumed. This increase in extra cellular fluid

exacerbates all forms of sodium and water retention, eg heart failure and is a major cause of oedema in women, aggravating both cyclical and idiopathic oedema.

Animal studies and human epidemiological evidence suggests that a high salt intake has a direct effect on strokes (58), independent and additive to salt's effect on blood pressure (Fig 10).

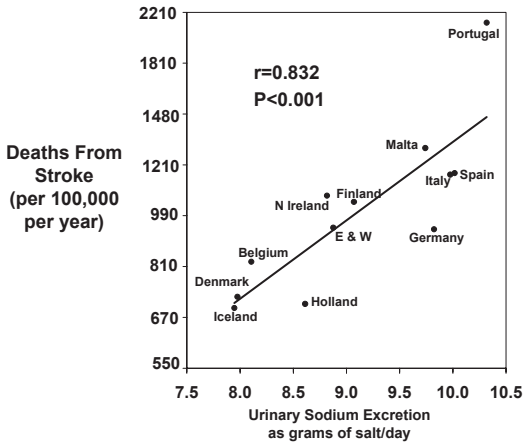


Figure 10. Relationship between salt intake as judged by 24h urinary salt excretion and stroke mortality in Western Europe (Adapted from Ref.58).

Salt intake relates directly and independently to enlargement of the heart and reducing salt intake reduces left ventricular hypertrophy (59-61). Left ventricular hypertrophy is a major risk factor for cardiovascular disease.

Salt intake is closely related to cancer of the stomach (Fig 11) and is likely to be an important pre-disposing cause (62). Salt in the concentration found in many processed or instant foods, eg instant soups, is a profound gastric irritant and may pre-dispose the individual to *Helicobacter pylori* infection.

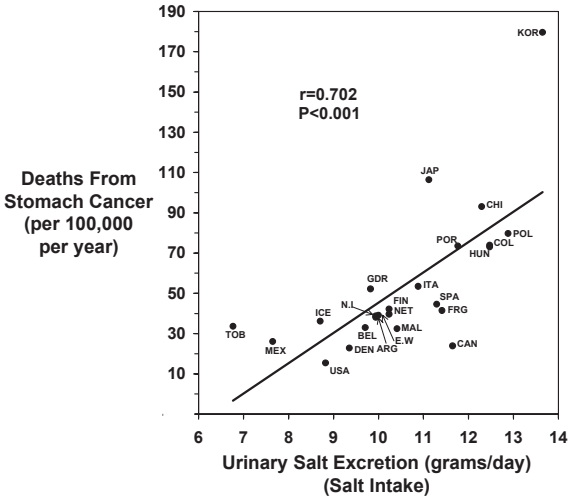


Figure 11. Relationship between salt intake as judged by 24h urinary salt excretion and stomach cancer mortality in 24 countries. (Adapted from Ref.62)

Increasing salt intake exacerbates proteinuria and the rate of deterioration of renal function in experimental forms of renal disease. Reducing salt intake in these animals markedly slows the rate of deterioration. In humans, increasing salt intake exacerbates proteinuria and reducing salt intake, particularly in conjunction with an ACE inhibitor, causes large falls in protein excretion.

Salt intake is a major cause of renal stones in humans. This is likely to be due to the effect salt has on urinary calcium excretion. The higher the urinary sodium excretion, the higher the urinary calcium excretion. Until recently, it was assumed that when salt intake was increased, the increase in calcium excretion was compensated for by an exact increase in intestinal calcium absorption. There is now evidence to suggest that this is incorrect and that there is a negative calcium balance with stimulation of mechanisms not only to increase intestinal absorption of calcium, but to mobilise calcium from bone. A study in post-menopausal women showed that the loss of hip bone density over two years was related to the 24 hour urinary sodium excretion at entry to the study and was as strong as that relating to calcium intake (63). Diuretics, through a reduction in extra cellular volume, reduce calcium excretion leading to a positive calcium balance, increase bone density and reduce bone fractures. Salt reduction is likely to do the same but there are as yet no trials of salt reduction in osteoporosis or vulnerable groups.

Specific Groups - Children

The Dutch study in new born babies has already been referred to (23,24). There are no other well-controlled studies of salt intake in this age group. However, a study in older children (mean age 13 years) suggested that both dietary potassium and dietary sodium are related to the rise in blood pressure in childhood and may be important in the early pathogenesis of primary hypertension (64). Intervention studies in adolescence showed that reducing salt intake did lower blood pressure (65).

A study in 1984 collected 24 hour urines in four to five year old primary school children (66) and showed that the average sodium excretion was 4 to 5 grams of salt per day, which if expressed for adults on a height basis is equivalent to 15 to 20 grams per day. This was at a time when consumption of processed foods by young children was not high. Since then, children are eating more processed, ready prepared and takeaway foods - most of which are very high in salt, saturated fat and sugar. It is now likely that salt intake in children from the age of three to four onwards is the same as in adults, ie 9 to 10 grams of salt per day.

Ethnic Variations

Afro-Caribbeans or people of African origin are more likely to have high blood pressure. In black adults between 40 and 60 years of age, more than half have high blood pressure (67). Studies have shown that Afro-Americans and Afro-Caribbeans are more sensitive to salt. In the DASH Sodium Study, Afro-Americans showed a greater fall in blood pressure with salt restriction (34). In the UK, high blood pressure in Afro-Caribbeans and those of African origin is a major cause of premature strokes and renal disease. A reduction in salt intake in this group is likely to be of particular benefit.

High blood pressure in South Asians is more common (67), with approximately 40% of adults between the age of 40 and 60 years having high blood pressure. There are no studies looking at the effect of salt in South Asians.

Conclusion

The evidence that relates to dietary nutrients, such as salt, potassium, saturated fat, fruit and vegetables, has to rely on weighing all of the evidence from various types of studies - epidemiological, migration, intervention, treatment trials as well as animal evidence. When all of the evidence is considered, the evidence for salt intake, particularly when judged against other nutrients appears to be robust. The benefits of reducing salt intake, even modestly, from 9 to 10 grams per day to 5 to 6 grams per day, could be of immense benefit in reducing and preventing cardiovascular disease. For instance, Law calculated from his analysis of the relationship between salt and blood pressure that a 3 gram per day reduction in salt intake in the whole adult population would cause a 22% reduction in stroke and a 16% reduction in coronary heart disease (68). Based on all of this evidence, most western countries have recommended a reduction in salt intake from 9 to 10 grams per day to 5 to 6 grams per day.

Background to COMA and subsequent recommendations on salt

In the United States, there has been consistent advice to reduce salt intake since the 1980s. In the UK, the COMA report of 1994, having assessed the evidence, recommended a population reduction in salt intake from 9 grams of salt per day to 6 grams per day (69).

Several other important dietary recommendations were also advised to try to reduce the very high cardiovascular mortality in the UK. These recommendations were initially endorsed by Conservative Ministers and the Department of Health, but according to a leading article in the *British Medical Journal* (70), huge pressure was exerted by the food industry on the Conservative Government to withdraw the specific recommendations on salt. In 1996 the Chief Medical Officer said there was continuing controversy concerning the relationship between salt and blood pressure. At this time, a group of scientists, many of whom were either on the UK COMA Committee or Sub-Committee on Minerals, set up a Consensus Action Group on Salt and Health (CASH) to try and establish a dialogue with the food industry to reduce the salt content of processed foods (71).

The Department of Health informally set up a meeting in 1997 with the help of the Faculty of Public of Health Medicine at the British Heart Foundation to reconsider all of the evidence relating salt to blood pressure since the COMA report. The recommendations of the Committee were that they re-endorsed the COMA recommendations on reducing salt as part of a more healthy eating strategy and that it should be accompanied by a reduced saturated fat intake and increased consumption of fruit and vegetables, as also recommended in the COMA report.

In January 2000 a large meeting was organised by the National Heart, Lung and Blood Institute (NHLBI) in Washington where all of the evidence on salt was reconsidered (72). There was representation from the food industry and Salt Institute. The conclusion of this meeting was that "Americans consume more sodium than they need and a population wide strategy of reducing salt in the food supply is an important public health strategy that can lower blood pressure among populations".

Most developed countries in the world who have considered the problem have now recommended a reduction in salt intake and these recommendations are fairly consistent, recommending salt intake be reduced from an average intake of 9 to 10 grams per day to 5 to 6 grams or less per day. The recommendation as acknowledged in the UK COMA report that salt intake should be reduced to 6 grams is not thought as an ideal level, but

was a practical reduction that could be achieved. The evidence suggests that if it was possible to reduce salt intake further, eg 4 grams per day, there would be further benefits, as demonstrated in the DASH Sodium Study (34), but these reductions would be difficult to achieve given the current amount of salt in processed foods.

One point of confusion is the different recommendations for salt intake in men and women which emerged from the UK COMA report, ie women should reduce their salt intake to 5 grams per day, whereas men should reduce their intake to 7 grams per day. This was based on the fact that women eat less calories than men. However, there is no evidence to suggest that men are less salt sensitive than women. Indeed, all of the evidence suggests that there is no difference between men and women in relation to salt, and that the recommendation for salt intake should be the same.

Recommendation

Based on the above evidence, all developed countries should reduce their salt intake to a level of 6 grams or less per day. This should not vary between men and women. When this target is near achievements, consideration should then be given to recommending a lower intake, that is 4 grams of salt or less per day.

The recommendations for salt intake for children are difficult to formulate, but should, in our view, be adjusted by height as a proportion of the adult figure of 6 grams per day. Intake should ideally be below these calculated. For example, at the age of four years salt intake should be less than 2 grams per day, at the age of 10 less than 4 grams per day and at the age of 15 less than 5 grams per day.

Other Issues

Labelling

In the UK, there is no need to label the sodium content of food unless a health claim is made. However, many manufacturers and retailers voluntarily label their foods with the sodium content per 100 grams. A variety of surveys has shown that this method of expressing sodium or the salt content of food is completely meaningless to the public. Firstly it requires knowledge of the difference between sodium and sodium chloride (salt), and secondly how to convert sodium concentration to salt (x 2.5), and thirdly a knowledge of the weight in grams of the serving size to be consumed.

Several of the UK leading food retailers are now labelling their foods with the salt content per serving, that is showing the amount of salt contained in a serving and followed by the recommended salt intake for the day.

Example - "One serving of 320 grams of this product contains 3.2 grams of salt. Recommended intake 6 grams per day."

Many leading UK retailers have adopted this easily understood labelling but, up to now, this has been rigorously opposed by several food industry organisations who claim that it is scientifically incorrect as not all of the sodium in foods is in the form of sodium chloride. In the majority of foods, over 99% of the sodium content **is** in the form of sodium chloride and it is only in mineral waters where there are high concentrations of sodium bicarbonate, or in products that use baking powder, eg scones where some of the sodium content is in the form of non-chloride salts. In these specific products it would be relatively easy to label additional sodium salts as and when they occur if the food industry so wishes. The very

small differences in the sodium chloride that would occur in other foods are trivial compared to the variation of salt added to branded processed food which shows quite large standard deviations.

A simple labelling system as adopted by some of the UK supermarkets of the salt content of processed foods would immediately lead to much greater understanding by the public of the salt content of the foods, and a very clear guide as to how much of the recommended salt intake would be taken up by eating that particular food or serving.

A further point to note is that if chloride, not in the form of sodium choloride, eg potassium chloride, is consumed, non-chloride sodium salts will be perceived by the body as NaCl, eg $NaHCO_3 + 2KCl = NaCl + K_2HCO_3$.

Action That Has Occurred since 1994 on Salt

In the UK, table salt sales have shown a dramatic reduction (60 to 70%) since 1986. This is in part due to the greater understanding the public has of the dangers of salt intake, and that less salt should be added in cooking and at the table. However, the reduction has also been due to the fact that less food is cooked at home, as consumers choose ready prepared and processed foods that already contain large amounts of salt. Indeed, on average 70 to 80% of salt intake in the UK now comes from salt added to processed, ready prepared and restaurant foods, etc (73,74).

Any reduction in the salt content of foods must involve the co-operation of the food, catering and restaurant industries.

In the mid 1990s the UK Federation of Bakers, in conjunction with the Department of Health, carried out experiments that clearly demonstrated it was possible to reduce the salt content of bread further, without technical difficulties and without affecting taste.

Recently some of the leading UK supermarkets have started salt reduction programmes. ASDA was the first large supermarket to reduce the salt content of nearly all of their own label processed foods by 10 to 25%, with an average reduction of 12%. ASDA were followed by Marks & Spencer who adopted a policy of introducing new recipes with lower salt content and then Sainsbury's, Safeway, Waitrose and Iceland followed suit. Kellogg's and Heinz have also made small reductions in the salt concentration of some of their products. The UK Federation of Bakers has also made small reductions in the salt content of plant breads.

One important aspect of the reductions made by the supermarkets and plant breads is that it has shown how it can easily be done. According to ASDA, there were few technical problems in reducing the salt content of all their processed foods by 10 to 25%, and ASDA, Sainsbury and Marks & Spencer all report that there have been no complaints about the reduced salt content of their foods. Therefore, claims by some food industry organisations that there are technical problems involved when making small reductions in the salt content of processed foods are incorrect and the claim that these modest reductions in salt intake lead to rejection of the foods are wrong. There is therefore no reason whatsoever why small reductions in the salt content of all processed and ready prepared foods could not be made.

A reduction of 10 to 25%, with say an average reduction of 15%, of salt in all processed and ready prepared foods, combined with a publicity campaign about the dangers of salt and educating the public to use less salt in cooking and at the table, could cause an immediate reduction in salt intake by 15%. Without active public participation, or at the very least only small active public participation, a further reduction could be made in a few

year's time of all processed foods so that a worthwhile reduction of 30% could be made over the next five years, and this could be followed by further gradual reductions. If this strategy was adopted by the whole of the world's food industry, the target of 6 grams of salt or less per day could be easily achieved.

One important fact is that as salt intake falls, the salt taste receptors become more sensitive, adjusting within one to two months. This means that lower concentrations of salt then taste as salty as the higher concentrations. It is therefore very unlikely that this lowering in salt intake will lead to rejection of foods. Indeed, all of the evidence suggests that once salt intake is reduced, individuals much prefer food with less salt and reject the highly salted foods that they ate previously.

Why are some members of the food industry so reluctant to reduce the salt content of processed foods?

The preservative properties of salt were discovered by man approximately 5,000 years ago and salt then became of great economic importance as it was possible to preserve food during the winter and allowed the development of settled communities (73). Salt was the most traded commodity in the world, with intake reaching a peak around the 1870s. However, with the invention of the deep freezer and the refrigerator salt was no longer required as a preservative. Salt intake has been declining but with the recent large increase in consumption of very highly salted processed food, salt intake is now increasing to levels that can approach those of the 1870s.

The reasons that the food industry adds salt in such a large amounts to processed foods are mainly because it makes cheap, unpalatable food edible at no cost. If high salt foods are consistently consumed, the salt taste receptors are suppressed and habituation to high salt foods occurs, with greater demand for high salt processed foods.

However, salt has two other important properties - one is in meat products where increasing the salt concentration in conjunction with other water binding chemicals increases the amount of water than can be bound into the meat product and the weight of the product can be increased by up to 20% with water. The other important property is that salt is a major determinant of thirst and any reduction in salt intake will reduce fluid consumption with a subsequent reduction in soft drink and mineral water sales (75). Many of the largest snack companies in the world are part of companies selling soft drinks. Salt manufacturers and extractors also have a major interest in the salt used in processed foods as approximately 40% by value of their sales of salt go to the processed food industry (Fig 12).

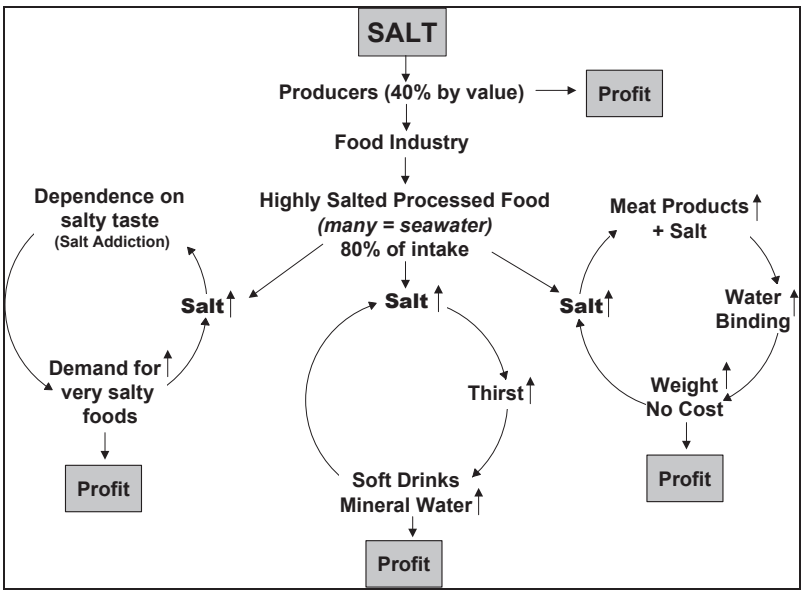


Figure 12. The commercial importance of salt in processed food

It is therefore not surprising that the salt industry and some members of the food industry are very reluctant to see any reduction in salt intake and have, in our view, been largely responsible for making salt such a controversial issue relative to other dietary changes. However, the vast majority of the food industry has no reason to fear a small consistent reduction in the salt content of foods, as already carried out by many of the supermarkets own label products. In the UK approximately two years ago, the Department of Health and the Food Standards Agency requested the Food and Drink Federation to report on the feasibility of small reductions in the salt content of processed foods. This report, which was meant to be in the public domain but has remained confidential, shows that in nearly all sections of the food industry represented by the Food and Drink Federation small reductions in salt content can easily be achieved. However, some sections of the UK food industry, particularly as represented by the Food and Drink Federation and the Salt Manufacturers' Association, have so far vigorously opposed any reduction of salt intake in the UK. The same sections of the salt, soft drink and food industry have adopted identical tactics in all other western countries. Commercial opposition by a small section of the food industry needs to be acknowledged, but should not be allowed to stand in the way of a reduction in salt intake, as this reduction will be of major benefit to the future health of developed countries. This will be particularly so if this reduction in salt intake is accompanied by a reduction in saturated fat intake and an increase in fruit and vegetable consumption.

References

1. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in BP: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765-73.
2. MacMahon S, Rodgers A. Blood pressure, antihypertensive treatment and stroke risk. *J Hypertens* 1994;12 (suppl 10):S5-14.
3. Staessen JA, Wang J, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* 2001;358:1305-15.
4. Primatesta P, Brookes M, Poulter NR. Improved Hypertension Management and Control: Results from the Health Survey for England 1998. *Hypertension* 2001;38:827-832.

5. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;345:1291-7.

6. MacMahon S. Blood pressure and the prevention of stroke. *J hypertens* 1996;14(suppl)S39-S46.

7. Rose G. Strategy of prevention: lessons from cardiovascular disease. *BMJ* 1981;282:1847-51.

8. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; 355: 253-59.

9. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;358:1033-41.

10. MacGregor G. Nutrition and blood pressure. *Nutr Metab Cardiovasc Dis.* 1999; 9: Suppl:6-15.

11. He FJ, MacGregor GA. Potassium intake and blood pressure. Editorial. *Am J Hypertens.* 1999;12:849-51.

12. Eaton SB, Konner M. Paleolithic nutrition. *N Eng J Med* 1985;312:283-288.

13. Oliver WJ, Cohen EL, Neel JV. Blood pressure, sodium intake and sodium related hormones in Yanomamö Indians, a 'no-salt' culture. *Circulation* 1975;52:146-151.

14. Chagnon NA. Yanomamö. The Fierce People. Holt, Rinehart & Winston, 1968,New York.

15. Denton D. *The hunger for salt*. Springer Verlag,1982, Heidelberg.

16. Page LB, Damon A, Moellering RC. Antecedents of cardiovascular disease in six Solomon Island societies. *Circulation* 1974;49:1132-1146.

17. Page LB, Vandevert DE, Nader K et al. Blood pressure of Qash'qai pastorall nomads in Iran culture, diet and body form. *Am J Clin Nutrit* 1981;34:527-538.

18. Uzodike VO. Epidemiological studies of arterial blood pressure and hypertension in relation to electrolyte excretion in three Igbo communities in Nigeria. (dissertation). London: University of London, 1993.

19. Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *BMJ.* 1988;297:319-28.

20. Hanneman RL. Intersalt: hypertension rise with age revisited. *BMJ* 1996;312:1283-4.

21. Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, Marmot M, for the Intersalt Cooperative Research Group. Intersalt revisited: further analyses of 24-hour sodium excretion and blood pressure within and across populations. *BMJ* 1996;312:1249-53.

22. Poulter N, Khaw KT, Hopwood BEC, Mugambi M, Peart WS, Rose G, Sever PS. The Kenyan Luo migration study: observations on the initiation of a rise in blood pressure. *BMJ.* 1990;300:967-72.

23. Hofman A, Hazebroek A, Valkenburg HA. A randomized trial of sodium intake and blood pressure in newborn infants. *JAMA.* 1983;250:370-3.

24. Geleijnse JM, Hofman A, Witteman JCM, Hazebroek AAJM, Valkenburg HA, Grobbee DE. Long-term effects of neonatal sodium restriction on blood pressure. *Hypertension.* 1996;29:913-7.

25. Forte JG, Pereira Miguel JM, Pereira Miguel MJ, de Padua F, Rose G. Salt and blood pressure: a community trial. *J Human Hypertens.* 1989;3:179-84.

26. Staessen J, Bulpitt CJ, Fagard R, Joossens JV, Lijnen P, Amery A. Salt intake and blood pressure in the general population: a controlled intervention trial in two towns. J Hypertens 1988;6:965-73.

27. Tuomilehto J, Puska P, Nissinen A, Salonen J, Tanskanen A, Pietinen P, Wolf E. Community-based prevention of hypertension in North Karelia, Finland. Ann Clin Res1984;16(Suppl 43):18-27.

28. Sasaki N. The relationship of salt intake to hypertension in the Japanese. *Geriatrics* 1964;19:735-44.

29. Vartiainen E, Puska P, Pekkanen J, Tuomilehto J, Jousilahti P. Changes in risk factors explain changes in mortality from ischaemic heart disease in Finland. *BMJ* 1994;309:23-7.

30. Vartiainen E, Sarti C, Tuomilehto J, Kuulasmaa K. Does changes in cardiovascular risk factors explain changes in mortality from stroke Finland. *BMJ* 1994;310:901-4.

31. Kempner W. Treatment of hypertensive vascular disease with rice diet. *Am J Med* 1948;4:545-77.

32. Watkin DM, Froeb HF, Hatch FT, Gutman AB. Effects of diet in essential hypertension: II. Results with unmodified Kempner rice diet in fifty hospitalised patients. *Am J Med* 1950;9:441-93.

33. MacGregor GA, Markandu ND, Best FE, Elder DM, Cam JM, Sagnella GA, Squires M. Double-blind randomised crossover trial of moderate sodium restriction in essential hypertension. *Lancet.* 1982;1:351-5.

34. Sacks R M, Svetkey LP, Vollimer VM et al. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *N Eng J Med* 2001; 344: 3-10.

35. MacGregor GA, Markandu ND, Singer DRJ, Cappuccio FP, Shore AC, Sagnella GA. Moderate sodium restriction with angiotensin converting enzyme inhibitor in essential hypertension: a double blind study. BMJ 1987;294:531-4.

36. MacGregor GA, Markandu ND, Sagnella GA, Singer D, Cappuccio FP. Double-blind study of three sodium intakes and long-term effects of sodium restriction in essential hypertension. *Lancet.* 1989;2:1244-7.

37. The Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmarmacologic interventions on blood pressure of persons with high normal levels: results of the Trials of Hypertension Prevention, phase I. *JAMA* 1992;267:1213-20.

38. The Trials of Hypertension Prevention Collaborative Research Group. Effect of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, Phase II. *Arch Intern Med* 1997;157:657-67.

39. Whelton PK, Appel LJ, Eepeland MA, Applegate WB, Ettinger WH, Kostis JB, Kumanyika S, Lacy CR, Johnson KC, Folmar S, Cutler JA, for the TONE Collaborative Research Group. *JAMA* 1998;279:839-46.

40. Law MR, Frost CD, Wald NJ. Analysis of data from trials of salt reduction. *BMJ.* 1991;302:819-24.

41. Midgley JP, Matthew AG, Greenwood CM, Logan AG. Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomised controlled trials. *JAMA.* 1996;275:1590-1597.

42. Cutler JA, Follmann D, Alleder PS. Randomized trials of sodium reduction: an overview. *Am J Clin Nutr.* 1997;65(suppl):643s-51s.

43. Graudal NA, Galloe AM, Garred P. Effect of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride: a meta-analysis. *JAMA.* 1998;279:1383-91.

44. He FJ, Markandu ND, MacGregor GA. Importance of the renin system for determining blood pressure fall with acute salt restriction in hypertensive and normotensive Whites. *Hypertension.*2001;38:321-5.

45. He F, MacGregor G. Effect of longer-term modest reduction on blood pressure. A meta-analysis. Implications for public health. *J Human Hypertens* 2000;18 (Suppl. 4):S126 (Abstract)

46. Cappuccio FP,Markandu ND, Carney C, Sagnella GA, MacGregor GA. Double-blind randomised trial of modest salt restriction in older people. *Lancet.* 1997;350:850-4.

47. Denton D, Weisinger R, Mundy NI, Wickings EJ, Dixson A, Moisson P, Pingard AM, Shade R, Carey D, Ardaillou R, Paillard F, Chapman J, Thillet J, Michel JB. The effect of increased salt intake on blood pressure of chimpanzees. *Nature Medicine.* 1995; 1:1009-16.

48. Lifton RP. Molecular genetics of human blood pressure variations. *Science.* 1996;272:676-80.

49. Alderman MH, Madhaven S, Cohen H, Sealey JE, Laragh JH. Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men. *Hypertension* 1995;25:1144-1152.

50. Alderman MH, Cohen H, Madhaven S. Dietary sodium intake and mortality. The National Health and Nutrition Examination Survey (NHANES 1). *Lancet* 1998;351:781-785.

51. MacGregor G. Low urinary sodium and myocardial infarction. Letter. *Hypertension* 1996;27:156

52. de Wardener H. Salt reduction and cardiovascular risk: the anatomy of a myth. *J Human Hypertens.* 1999;13:1-4.

53. de Wardener H, MacGregor GA. Sodium intake and mortality. Letter. *Lancet* 1998;351:1508.

54. Engelman K. Sodium intake and mortality (Letter) *Lancet* 1998;351:1508.

55. Karppanen H, Mervaala E. Sodium intake and mortality (Letter) *Lancet* 1998;351:1509.

56. Tuomilehto J, Jousilahti P, Rastenyte D, Moltchanov V, Tanskanen A, Pietinen P. Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. *Lancet 2001:357;848-51.*

57. Antonios TF, MacGregor GA. Salt--more adverse effects. *Lancet* 1996; 348:250-1.

58. Perry IJ, Beevers DG. Salt intake and stroke: a possible direct effect. J Hum Hypertens 1992;6:23-5.

59. Kupari M, Koskinen P, Virolainen J. Correlates of left ventricular mass in a population sample aged 36 to 37 years. Focus on lifestyle and salt intake. *Circulation* 1994;89:1041-50.

60. Jula AM, Karanko HM. Effects on left ventricular hypertrophy of long-term nonpharmacological treatment with sodium restriction in mild-to-moderate essential hypertension. *Circulation* 1994;89:1023-31.

61. Schmieder RE, Messerli FH. Hypertension and the heart. *J Human Hypertens* 2000;14:597-604.

62. Joossens JV, Hill MJ, Elliott P, Stamler R, Stamler J, Lesaffre E, Dyer A, Nichols R, Kesteloot H on behalf of European Cancer Prevention (ECP) and the Intersalt Cooperative Research Group. Dietary salt, nitrate and stomach cancer mortality in 24 countries. *Int J Epidemiol* 1996;25:494-504.

63. Devine A, Criddle RA, Dick IM, Kerr DA, Prince RL. A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. *Am J Clin Nutr* 1995;62:740-5.

64. Geleijnse JM, Grobbee DE, Hofman A. Sodium and potassium intake and blood pressure change in childhood. *BMJ* 1990;300:899-902.

65. Ellison RC, Capper AL, Stephenson WP, Goldberg RJ, Hosmer DW, Humphrey KF, Ockene JK, Gamble WJ, Witschi JC, Stare FJ. Effects on blood pressure of a decrease in sodium use in institutional food preparation: The Exeter-Andover project. J Clin Epidemiol 1989;42:201-8.

66. De Courcy S, Mitchell H, Simmons D, MacGregor GA. Urinary sodium excretion in 4-6 year old children: a cause for concern. *BMJ.* 1986:292:1428-9.

67. Cappuccio FP, Cook DG, Atkinson RW, Wicks PD. The Wandsworth Heart and Stroke Study. A population-based survey of cardiovascular risk factors in different ethnic groups. Methods and Baseline findings. *Nutr Metab Cardiovas Dis* 1998;8:371-85.

68. Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? *BMJ* 1991;302:811-24.

69. COMA report 46: Nutritional Aspects of Cardiovascular Disease: 1994.

70. Godlee F. The food industry fights for salt. *BMJ.* 1996;312:1239-40.

71. MacGregor GA, Sever PS. Salt-overwhelming evidence but still no action: can a consensus be reached with the food industry? CASH (consensus Action on Salt and Hypertension). *BMJ* 1996;312:1287-9.

72. Chobanian AV, Hill M. National Heart, Lung and Blood Institute Workshop on Sodium and Blood Pressure: a critical review of current scientific evidence. *Hypertension.* 2000:35;858-63.

73. MacGregor GA, de Wardener HE. Salt, diet and health. Cambridge University Press, 1998.

74. Sanchez-Castillo CP, Warrender S, Whitehead TP, James WP. An assessment of the sources of dietary salt in British population. *Clin Sci (Colch)* 1987;72:95-102.

75. He FJ, Markandu ND, Sagnella GA, MacGregor GA. Effect of salt intake on renal excretion of water in humans. *Hypertension.* 2001;38:317-20.

Relationship between salt sensitivity and diseases and its correction by dietary interventions

Alexander G. LOGAN
Mount Sinaï Hospital, Toronto, Canada

The current salt debate is fuelded by two fundamentally different views on the role of sodium in the pathogenesis of primary hypertension. Some argue that salt intake above some arbitrary level is the principal cause of hypertension (1). Proponents of this viewpoint claim that the prevalence of hypertension in developed countries is directly related to their average salt intake and recommend life-long restriction of sodium intake to prevent its development in people with normal blood pressure (2). Others state that factors inducing salt-sensitivity is the primary culprit, causing hypertension by mechanisms that are mainly independent of sodium (3). In this viewpoint, salt is an important accomplice, but on its own it does not cause hypertension, even when consumed in large amount (4). Supporting evidence includes the heterogeneous response of blood pressure to increased (5-7) or decreased (8) intake of dietary salt, the failure to find a relationship between salt intake and blood pressure in most intrapopulation studies (9), and the observation that the rise in blood pressure with age is not inevitable in modern societies (10) and occurs principally in salt-sensitive individuals (11).

Being overweight or obese is strongly associated with hypertension and salt-sensitivity, and weight loss mitigates these associations (12). Higher salt-sensitivity is also found in older subjects, blacks and persons with initial higher blood pressures. The importance of mineral deficiency (potassium, calcium and possibly magnesium) in causing blood pressure to rise and salt-sensitivity to develop is now well documented (13). Epidemiological studies indicate an inverse relationship between dietary potassium intake and blood pressure (14). Clinical studies have shown that normotensive individuals placed on a low potassium diet are unable to excrete sodium normally and have a significant rise in blood pressure (15). These undesirable effects are quickly reversed when a normal potassium diet is resumed. In a recent landmark metabolic unit study (16), normotensive black subjects fed a potassium deficient diet (30 mmol per day) had a high frequency of salt-sensitivity (79 %) that fell dramatically in a stepwise manner to < 20 % on a high potassium diet (120 mmol per day). While the frequency of salt-sensitivity in white normotensive subjects on a low potassium diet was lower than that in blacks, it also fell significantly with increases in dietary potassium intake (70 mmol per day). Epidemiological and clinical studies have also shown that the influence of dietary calcium on renal sodium handling and blood pressure is similar to that of potassium (3,4,13).

Recent clinical trial evidence, most notably the Dietary Approaches to stop Hypertension (DASH) trials (17,18), clearly illustrates the importance of nutrient interactions on blood pressure and salt-sensitivity. These trials compared a potassium-deficient [39 mmol per day in DASH-I and 40 mmol per day in DASH-II], nutritionally poor diet (the ‘control’ diet) against one that emphasized fruits and vegetables and promoted low-fat dairy, high-fiber grains and reduced dietary fat (the full ‘DASH’ diet). In the original trial (DASH-I), sodium intake and body weight were not altered, but in the follow-up trial (DASH-II) sodium intake varied from normal levels to severe restriction. In DASH-I, the group consuming the full DASH diet had the greatest fall in blood pressure, and the magnitude of the change was greater in hypertensive than in normotensive individuals and in blacks than in whites (17). In DASH-II, reducing dietary salt intake in the control diet from 8.4 g/d to less than 4 g/d lowered blood pressure to a similar degree to that observed on the DASH diet without salt

restriction (18). However, for those already on the DASH diet, the imposition of severe dietary salt restriction had limited additional effect on blood pressure.

Collectively, the studies highlight the importance of dietary deficiencies (such as potassium and calcium) as well as excesses (such as weight and sodium) in the prevention and treatment of hypertension. They demonstrate the need to carefully assess diet quality and tailor interventions to meet specific nutritional needs. They vividly illustrate the advantages of a comprehensive dietary approach rather than intervening on individual nutrients. For example, the blood pressure-lowering action of the DASH diet without salt restriction was more than twice that observed when the salt content in the control diet was reduced to the current government recommended level of 6 g/d (18). They show that salt sensitivity is not an immutable trait, but is often an acquired abnormality that can be modified by improving the overall diet quality. The fact that the DASH diet combined with a low-salt diet had limited additional benefits on blood pressure strongly suggests that DASH mitigates salt-sensitivity (18). Not surprisingly, the characteristics of DASH participants (overweight or obese, older, predominantly black) mirror the profile of those most likely to respond to dietary salt restriction (19). Finally, and possibly most importantly, promoting a diet that meets current dietary guidelines for healthy living has a wide range of benefits beyond lowering blood pressure that include reducing insulin resistance improving lipid metabolism, decreasing the risk of cardiovascular disease and some types of cancer, and enhancing bone mineral metabolism.

References

1. Stamler J. Dietary salt and blood pressure. Ann NY Acad Sci 1993; 676:122-156
2. L'enfant C. Salt wars. Science 1998; 281:1961
3. Logan AG. The DASH trials implicate dysfunction in calcium regulation in the pathogenesis of human hypertension. Curr Hyperten Rep 2001; 31:367-370
4. Logan AG. Sodium sensitivity, not level of salt intake, predicts salt effects. Curr Hypertens Rep 2000; 2:115-119
5. Kirkendall WM, Connor WE, Abboud F, Rastogi SP, Anderson TA, Fry M. The effect of dietary sodium chloride on blood pressure, body fluids, electrolytes, renal function and serum lipids of normotensive man. J Lab Clin Med 1976; 87:418-434
6. Dustan HP, Kirk KA. Corcoran lecture: the case for or against salt in hypertension. Hypertension 1989; 13:696-705
7. Luft FC, Rankin LI, Bloch R, Weyman AE, Willis LR, Murray RH, Grim CE, Weinberger MH. Cardiovascular and humoral responses to extremes of sodium intake in normal black and white men. Circulation 1979; 60:697-706
8. Midgley JP, Matthew AG, Greenwood CMT, Logan AG. Effect of reduced dietary sodium on blood pressure. A meta-analysis of randomised controlled trials. JAMA 1996; 275: 1590-1597
9. Smith WCS, Crombie IK, Tavendale RT, Gulland SK, Tunstall-Pedoe H. Urinary electrolyte excretion, alcohol consumption and blood pressure in the Scottish heart health study. BMJ 1988; 297:329-330
10. Timio M, Lippi G, Venanzi S, Gentili S, Quintaliani G, Verdura C, Monarca C, Saronio P, Timio F. Blood pressure trend and cardiovascular events in nuns in a secluded order: a 30-year follow-up study. Blood Press 1997; 6:81-87
11. Weinberger MH, Fineberg NS. Sodium and volume sensitivity of blood pressure. Age and pressure change over time. Hypertension 1991; 18:67-71

12. Rocchini AP, Key J, Bondie D, Chico R, Moorehead C, Katch V, Martin M. The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. N Engl J Med 1989; 321:580-585

13. McCarron DA. Diet and blood pressure - the paradigm shift. Science 1998; 281:933-934

14. McCarron DA, Morris CD, Henry HJ, Stanton JL. Blood pressure and nutrient intake in the United States. Science 1984; 224:1392-1398

15. Krishna GG, Miller E, Kapoor S. Increased blood pressure during potassium depletion in normotensive men. N Engl J Med 1989; 320:1177-1182

16. Morris RC Jr, Sebastian A, Forman A, Tanaka M, Schmidlin O. Normotensive salt sensitivity. Effects of race and dietary potassium. Hypertension 1999; 33:18-23

17. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med 1997; 336: 1117-1124

18. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER 3rd, Simmons-Morton DG, Karanja N, Lin PH. Effects on blood pressure of reduce dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med 2001; 344:3-10

19. Muntzel M, Drueke T. A comprehensive review of the salt and blood pressure relationship. Am J Hypertens 1992; 5:1s-42s

Alberto ZANCHETTI

Après ces exposés forts intéressants, qui nous ont présenté les forces et les faiblesses des études épidémiologiques, je suis certain que vous avez des questions à poser ou des remarques à formuler.

De la salle

Pr. Logan, vous n'avez pas parlé du rôle du calcium. Quelle est selon vous la quantité de calcium qu'il faudrait consommer dans un régime idéal ?

Alexander G. LOGAN

L'amélioration du régime alimentaire doit être générale et ne pas s'attacher à un nutriment en particulier. Jouer uniquement sur le potassium par exemple peut avoir un effet, mais jouer sur le régime dans son ensemble me paraît préférable.

De la salle

Je souhaiterais toutefois savoir quelle est la quantité de calcium optimale dans l'alimentation.

Alexander G. LOGAN

Cette quantité dépend de l'âge et du sexe des sujets. Les recommandations varient entre 1 et 2 g/j.

De la salle

En ce qui concerne le sel, de nombreuses méthodes d'analyse ont été publiées ces dernières années. Toutefois, l'utilisation de l'une ou de l'autre n'a pas d'effet sur la variabilité de la pression artérielle mesurée.

Alexander G. LOGAN

Il est difficile de comparer les études aléatoires dont j'ai parlé et les études analytiques réalisées par Paul Elliott.

De la salle

Ce colloque a pour thème le sel, mais d'autres éléments du régime alimentaire peuvent intervenir quand on cherche à faire baisser la pression artérielle.

Graham A. MacGREGOR

Je suis d'accord avec vos propos. Il faut modifier le régime alimentaire dans son ensemble, en augmentant la consommation de fruits et de légumes et en diminuant la consommation de graisses. L'apport en sel n'est certainement pas le seul élément à prendre en compte pour faire diminuer la pression artérielle : par exemple, le potassium est également très important. Cependant, il est difficile de convaincre une population qui ne consomme aucun fruit et légume de manger 7 à 10 fruits ou légumes par jour.

Au Royaume-Uni, le sel a été diminué dans l'alimentation sans que le public s'en rende compte et change son régime. Seule l'industrie alimentaire utilise moins de sel. Cette solution est plus facile à mettre en œuvre que le changement de régime alimentaire.

De la salle

L'institut dans lequel je travaille recommande non seulement une baisse de la consommation de sel en cas d'hypertension, mais également une perte de poids, la pratique d'exercices physiques et la baisse de la consommation d'alcool. J'aimerais savoir quel est le niveau optimal de consommation de potassium.

Alexander G. LOGAN

Je ne suis pas un spécialiste des aliments, mais l'industrie agroalimentaire peut certainement favoriser une augmentation de la consommation de potassium en augmentant la teneur en potassium des aliments. Toutefois, ces modifications de la composition des aliments ont un coût. En outre, 40 % de la population canadienne consomment moins de 75 millimol de potassium par jour, car les aliments à forte teneur en potassium sont plus coûteux que les autres. Je pense que les efforts en matière de santé publique doivent aller dans le sens de régimes alimentaires plus sains et plus imaginatifs. Actuellement, la population ignore que du sel est ajouté dans l'alimentation et que le traitement des aliments supprime une partie du potassium présent à l'origine. Par exemple, les *corn flakes* ne contiennent qu'un tiers du potassium du maïs naturel, mais beaucoup plus de sel.

Graham A. MacGREGOR

Il est difficile d'améliorer la qualité des aliments, de même qu'il est difficile de s'en tenir à un régime DASH. J'ai moi-même du mal à le respecter, alors que j'y suis très favorable. Le respect des recommandations nutritionnelles est un problème majeur, qu'il s'agisse du sodium ou du potassium. En réalité, il faudrait trouver les meilleurs outils pour modifier les comportements alimentaires.

Alexander G. LOGAN

Le potassium est un élément important dans l'alimentation, mais pour parvenir au rapport idéal entre potassium et sodium, il est impératif de diminuer la consommation de sodium.

Paul ELLIOT

Un grand nombre d'études témoigne d'une réduction de l'hypertension quand la consommation de sel diminue. La consommation de potassium a également des effets, mais ils sont moindres.

Cependant, il faut augmenter la consommation de potassium, et, dans le même temps, diminuer l'apport en graisses et augmenter la consommation de fruits et de légumes. Il faudrait trouver un accord avec l'industrie agroalimentaire, qui a tendance à diminuer la teneur en potassium et augmenter la teneur en sel de ses produits. Je ne doute pas que la tendance s'inverse dans les années à venir.

Alexander G. LOGAN

Les fruits et les légumes sont en effet très importants dans l'alimentation.

En outre, des recommandations visant à la perte de poids dans la population britannique existent depuis de nombreuses années, mais il a été constaté une prise de poids dans

cette population. Compte tenu de cela, il paraît donc préférable de faire diminuer les quantités de sel utilisées par l'industrie agroalimentaire de façon graduelle, sans que la population soit informée.

De la salle

Le consensus sur l'intérêt de la diminution de la consommation de sel ne me paraît pas certain. Notre but est que la pression artérielle diminue. Or la baisse de consommation de sel n'a d'effet qu'à court terme. Je ne pense pas que des messages portant sur le sel permettent de gérer les problèmes d'hypertension.

Graham A. MacGREGOR

En réalité, 80 % du sel consommé provient de l'industrie agroalimentaire. Une population comme celle des Etats-Unis a alors du mal à réduire sa consommation de sel par elle-même.

Lors d'une étude, nous avons réussi à maintenir une population à 3 grammes de sel par jour, mais cela a nécessité un effort de la part des diététiciens et des infirmières. Il est en effet difficile de convaincre les patients de se restreindre.

Par ailleurs, les graisses saturées et les autres nutriments ou aliments n'ont pas une influence aussi marquée que le sel sur la pression artérielle.

De la salle

Il y a quelques années, nous avons montré qu'en augmentant la consommation de potassium pendant un an dans une population d'hypertendus, il devenait possible de diminuer la prise de médicaments hypotenseurs. On peut certainement obtenir les mêmes résultats en réduisant la consommation de sodium.

Par ailleurs, je suis d'accord avec le Pr. MacGregor au sujet du rôle de l'industrie agroalimentaire. Il faudrait également prendre en compte l'industrie pharmaceutique. Les représentants de cette dernière ne rappellent jamais l'importance des modes de vies des hypertendus aux médecins, alors qu'ils devraient le faire. L'industrie pharmaceutique tire un profit des médicaments hypotenseurs.

The DASH-Sodium trial results : the effects on blood pressure of dietary sodium and the DASH dietary pattern

Eva OBARZANEK, PhD
National Heart, Lung and Blood Institute, Bethesda, Maryland, USA

The Dietary Approaches to Stop Hypertension (DASH) Trial is a multi-center feeding study examining the effects of diet on blood pressure. It was carried out at 4 clinical centers (Brigham & Women's Hospital, Boston, Massachusetts (F.M. Sacks, MD); Duke Medical Center, Durham, North Carolina (L.P. Svetkey, MD; Johns Hopkins Medical Institutions, Baltimore, Maryland (L.J. Appel, MD). A coordinating center, Kaiser-Permanente Center for Health Research (V.M. Vollmer, PhD), and the U.S. agency which supported the study, the National Heart, Lung, and Blood Institute, of the National Institutes of Health, Bethesda, Maryland (E. Obarzanek, PhD) also participated.

Research Questions Related to Sodium:

Although several health organizations in the United States recommend for the general public moderate levels of sodium, approximately 100 mmol (2400 mg sodium or 6 g salt) (1; 2), the optimal level has not been established. Observational studies (3) and a clinical trial (4) suggest that the blood pressure-lowering effect of reduced sodium becomes stronger at lower intakes, for example, at 50 mmol (1200 mg, or 3 g salt). Also, it is still uncertain how much sodium reduction lowers blood pressure in people without hypertension.

Research Question Related to the DASH Diet:

It has been previously shown that the DASH dietary pattern, with a sodium content of 135 mmol/d (3500 mg sodium or 9 g salt) substantially lowered systolic and diastolic blood pressure by 5.5/3.0 mm Hg (5). An unanswered question is whether the DASH diet will lower blood pressure at lower sodium levels.

The DASH diet emphasizes fruits, vegetables, low-fat dairy foods, includes whole grains, nuts, poultry, and fish, and is reduced in fats, red meat, sweets, and sugar-containing beverages. It is reduced in saturated fat, total fat, and cholesterol, and increased in potassium, calcium, magnesium, fiber, and protein.

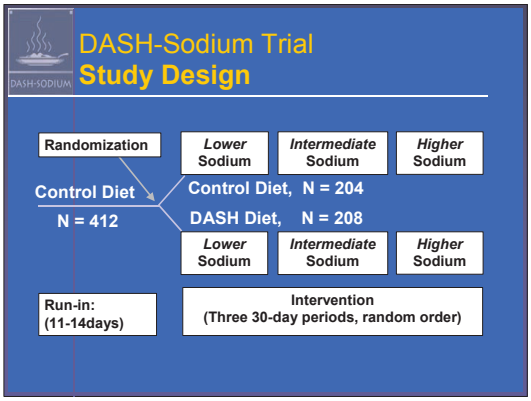
Specific Aims of the DASH-Sodium Trial:

- ¥ Determine the effect on blood pressure of 3 levels of dietary sodium:
  - o In a typical U.S. diet (control diet)
  - o In the DASH dietary pattern
- ¥ Determine the effect on blood pressure of the DASH diet at reduced levels of dietary sodium
- ¥ Determine the effect on blood pressure of the combination of the DASH diet and lower sodium.

Methods:

The design and methods of the trial have been previously described in detail (6)

Study Design: Eligible participants underwent a 2-week run-in period during which they ate a control diet, typical of what many Americans eat, at a higher level of sodium (see below). They were then randomly assigned to consume the control diet or the DASH diet for 3 months. Participants were fed their assigned diet at 3 levels of sodium for 30 days, each in random order, in a crossover design: higher, 142 mmol/day (3300 mg sodium or 8 g salt), which is a little below typical U.S. consumption levels; intermediate, 107 mmol/day (2400 mg sodium or 6 g salt), which is the upper limit of U.S. sodium recommendations; and lower, 65 mmol/day (1500 mg sodium or 4 g salt), which reflects a potentially more optimal level. All foods were provided to the participants, and adherence to the diets were monitored by observation, daily logs, and 24-hour urinary excretion. Body weight was measured on weekdays, and individual calorie levels of the diets were adjusted to assure constant body weight.



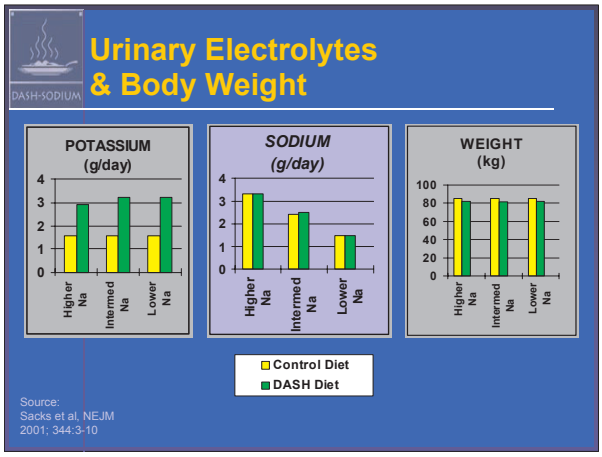
The primary outcome variable was systolic blood pressure. Diastolic blood pressure was a secondary outcome variable. The trial was powered for separate analyses in 3 specified subgroups: people with and without hypertension; African-Americans and other racial groups; women and men.

Measurements: Blood pressure was measured by random zero sphygmomano-meters. Two readings of blood pressure were taken, 30 seconds apart, on five non-consecutive days during screening and run-in (baseline blood pressure). Five pairs of blood pressure measurements were taken during the last 9 days of each sodium period, at least two of which were taken during the final 4 days.

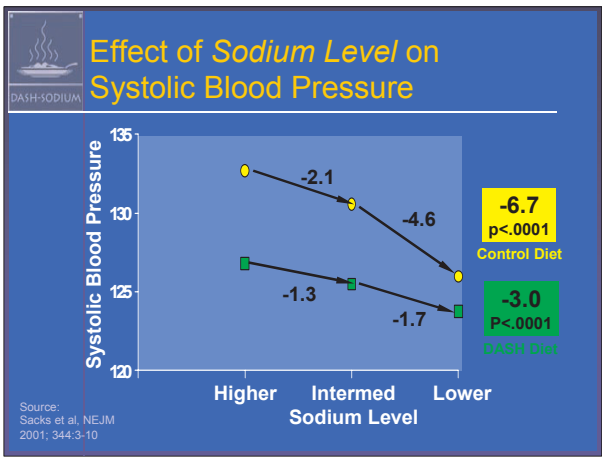
Subjects: Participants were eligible if they were at least 22 years old, had systolic blood pressure of 120-159 mm Hg and diastolic blood pressure 80-95 mm Hg, and were not taking any antihypertensive medication. A total of 412 participants were randomized, 57% were women, and 57% were African American. Mean age of the participants was 48 years, mean blood pressure at baseline was 135/86 mm Hg, and 41% had hypertension (SBP> 140 mm Hg or DBP> 80 mm Hg). Usual sodium intake, as measured by 24-hour urinary excretion taken during screening, was 155 mmol/day (3565 mg sodium or 9 g salt).

Results:

Results have been published (7;8). Twenty-four hour urinary excretions collected at the end of each feed period indicated good adherence to the diets. Urinary potassium was higher in the participants on the DASH diet than those on the control diet during all 3 sodium levels, reflecting the higher consumption of fruit and vegetables; at each sodium level, urinary sodium excretion was the same for participants on the DASH and control diets; and body weight remained constant during the 3 sodium levels for participants on each diet.

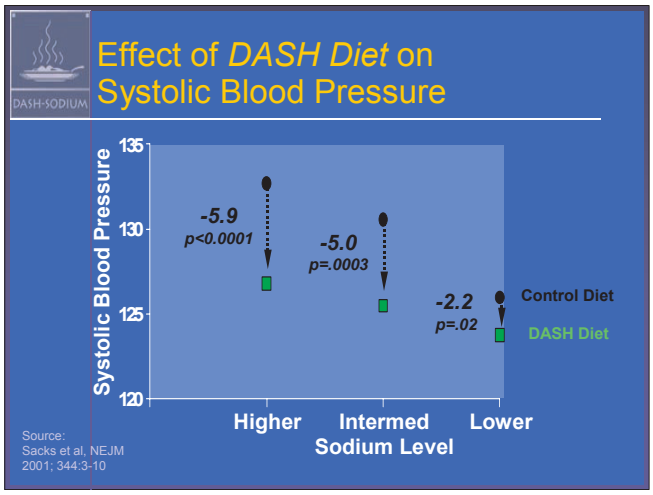


Sodium: Systolic and diastolic blood pressure progressively decreased as sodium intake decreased. On the control diet, systolic and diastolic blood pressure decreased 2.1/1.1 mm Hg when participants changed from the higher to the intermediate sodium level, and decreased another 4.6/2.4 mm Hg when participants changed from the intermediate to the lower sodium level. Thus, a difference of 77 mmol sodium (1800 mg sodium or 4 g salt) resulted in a *6.7/3.5* mm Hg reduction in systolic blood pressure (P<.001). A reduction of sodium intake of about 40 mmol/day from the intermediate sodium level lowered systolic and diastolic blood pressure more than a similar reduction in sodium intake from the higher sodium level (P<.05).

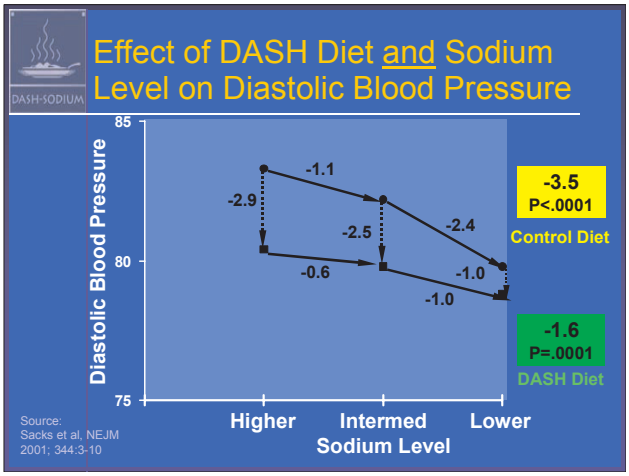


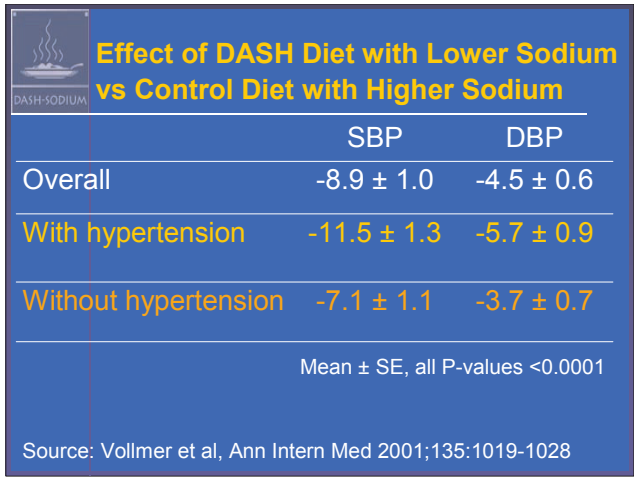
Dietary sodium had about twice the effect on blood pressure with the control diet as it did with the DASH diet (P<.001 for the interaction). For participants on the DASH diet, blood pressure decreased 1.3/0.8 mm Hg from the higher to the intermediate sodium level, and an additional 1.6/1.0 mm Hg from the intermediate to the lower sodium level. A difference of 77 mmol sodium resulted in a 3.0/1.6 mm Hg reduction in systolic blood pressure in participants on the DASH diet (P<.001).

DASH Diet: The DASH diet lowered systolic and diastolic blood pressure at every level of sodium: 5.9/2.9 mm Hg at the higher sodium level; 5.0/2.5 mm Hg at the intermediate sodium level; and 2.2/1.0 at the lower sodium level.

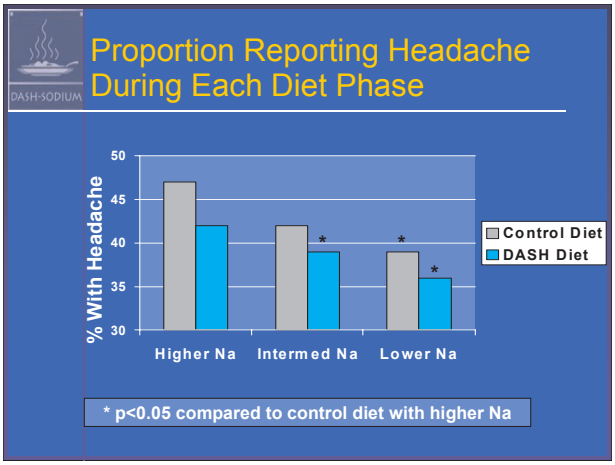


Combination of DASH Diet at Lower Sodium: Overall, compared to participants on the control diet at higher sodium blood pressure, participants following the DASH diet at lower sodium had a blood pressure reduction of 8.9/4.5 mm Hg (P<.001). Corresponding results were 11.5/5.7 mm Hg for participants with hypertension and 7.1/3.7 mm Hg for participants without hypertension (P<. 001).



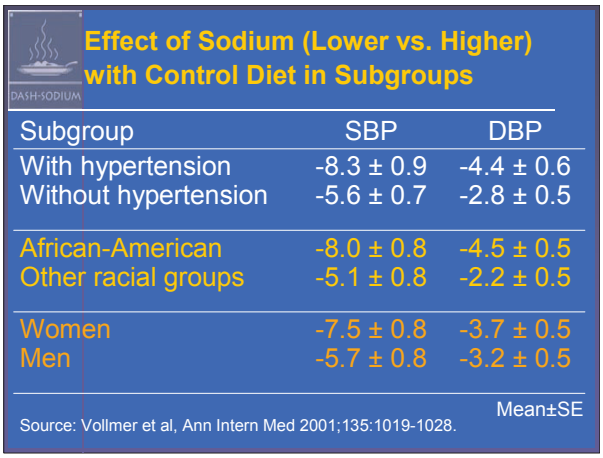


Other Health Effects: A systolic blood pressure of more than 170 mm Hg or a diastolic blood pressure of more than 105 mm Hg occurred in 12 participants on the control diet at higher sodium and to no participant on the DASH diet at lower sodium. Participants tended to report fewer symptoms during periods of reduced sodium intake. Headache was reported at least once by 47% of the participants on the control diet when consuming the higher sodium level. Compared to this group, a smaller percentage of participants on the control diet at the lower sodium level (39%), and a smaller percentage on the DASH diet at the intermediate (39%) and tower sodium level (36%) reported headaches (all P<.05).



Discussion and Conclusion:

The results of this study showed that sodium reduction lowers blood pressure in persons eating either the DASH diet or a typical U. S. diet, and the lower the sodium the lower the blood pressure. Blood pressure reduction was enhanced at the lower compared to the intermediate sodium level on the control diet. Blood pressure was reduced by lower sodium intake in all subgroups examined: those with and without hypertension, African Americans and other racial groups, and men and women.



The results of the DASH-Sodium trial also demonstrated that the DASH diet lowered blood pressure at all levels of sodium, and the combination of the DASH diet and reduced sodium lowered blood pressure more than either dietary approach alone.

Based on drug trials of blood pressure reduction, a 5 mm reduction in systolic blood pressure has been associated with 27% fewer strokes and 15% less coronary heart disease (9). If people followed the combination of the DASH diet at lower sodium, we could expect substantial risk reduction in strokes and coronary heart disease.

References

(1) Krauss Rivi, Eckel RH, Appel LJ, Daniels SR, Deckelbaum RJ, Erdman JWJr et ai. AHA Dietary Guidelines. Revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. J Nutr 2001; 131:132-146.

(2) Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1997; *157:2413-2446.*

(3) Intersalt Cooperative Research Group. Intersalt an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Br Med J 1988; 297:319-328.

(4) MacGregor GA, Sagnella GA, Markandu ND, Singer DRJ, Cappuccio FP. Double-blind study of three sodium intakes and long-term effects of sodium restriction in essential hypertension. Lancet 1989; ii:1244-1247.

(5) Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM et al. A clinical trial of the effects of dietary patterns on blood pressure. N Engl J Med 1997; 336:1117-1124.

(6) Svetkey LP, Sacks FM, Obarzanek E, Vollmer WM, Appel LJ, Lin P-H et al. The DASH diet, sodium intake and blood pressure trial (DASH-Sodium): rationale and design. J Am Diet Assoc 1999; 99(8):S96-S104.

(7) Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med 2001; 344(1):3-1O.

(8) Vollmer WM, Sacks FM, Ard J, Appel LJ, Bray GA, Simons-Morton DG et al. Effects of dietary patterns and sodium intake on blood pressure: subgroup results of the DASH-Sodium Trial. Ann Intern Med 2001; 135(12):1019-1028.

(9) Cutler JA, Psaty BM, MacMahon S, Furberg CD. Public health issues in hypertension control: what has been learned from clinical trials. In: Laragh JH, Brenner BM, editors. Hypertension: Pathophysiology, Diagnosis, and Management. New York: Raven Press, Ltd., *1995:* 253-270.

De la salle

Je vous remercie de nous avoir présenté une étude complexe et particulièrement intéressante. Il me paraît important de savoir que l'extrapolation des résultats obtenus en matière de consommation de sel et de risque d'accidents vasculaires doit être relativisée. L'étude est en effet réalisée sur une courte période et il faudrait une étude réalisée sur une plus longue durée pour savoir si l'espoir de changement peut devenir une réalité. L'éditorial de la publication de l'étude DASH incitait d'ailleurs à la prudence en matière d'extrapolation aux traitements hypertenseurs. La réduction de l'apport en sel peut intervenir tardivement lors de la prise en charge des patients hypertendus.

Eva OBARZANEK

Lors des tests concernant des médicaments, on cherche à connaître les autres facteurs expliquant les effets observés. Nous avons fait de même dans le cadre du régime alimentaire. Un certain nombre de facteurs de risques permettent d'estimer la morbidité, notamment les facteurs d'environnement. En outre, il est difficile de changer de régime pour modifier les facteurs de risques.

De la salle

L'essai DASH Sodium permet à mon avis de prendre des décisions. Il met en avant la sensibilité au sel. Des populations de même type ne répondent pas toutes de la même manière, en termes de pression artérielle, à la réduction de l'apport de sel. Le régime DASH est également l'occasion de constater que des nutriments autres que le sel jouent un rôle dans la réduction des facteurs de risques. Par ailleurs, vous avez pris en compte des intervalles de confiance plus larges pour l'étude DASH Sodium que pour l'étude DASH.

Eva OBARZANEK

Nous avons utilisé des groupes randomisés pour les deux études, mais les populations étaient différentes, ce qui rend difficile les comparaisons entre l'étude DASH et l'étude DASH Sodium.

De la salle

Je vous remercie pour cette étude particulièrement intéressante. Je voudrais intervenir au sujet des données, sans réaliser d'extrapolation. Avez-vous constitué des sous-groupes en fonction de l'âge des patients ? Sans ces groupes, des résultats importants n'ont peut-être pas été recherchés. Par ailleurs, le Dr. MacGregor a démontré qu'il y avait une corrélation entre le volume urinaire et l'excrétion de sodium. J'aimerais connaître l'évolution des volumes urinaires dans l'échantillon étudié, qui disposait d'un accès libre à l'eau, en fonction du régime.

Par ailleurs, pourriez-vous développer vos résultats concernant les maux de têtes ?

Eva OBARZANEK

Nous disposons de l'information concernant le volume urinaire. Au cours des deux premiers jours suivant le début du régime, ce volume augmente. Par ailleurs, nous avons divisé l'échantillon en sous-groupes en fonction de l'âge et nous avons constaté que l'effet

du sel sur la pression artérielle était plus marqué chez les personnes de plus de 45 ans. Toutefois, je ne me rappelle plus si les résultats étaient significatifs. Concernant la qualité de vie, nous avons principalement demandé aux patients s'ils appréciaient le régime DASH. La plupart l'ont apprécié, mais nous n'avons pas réalisé d'étude plus fine sur l'appréciation de chaque niveau de sodium.

De la salle

J'aimerais savoir si la pression artérielle des normotendus a varié lors du passage d'un niveau de consommation de sodium élevé à un niveau de consommation faible.

Eva OBARZANEK

Les normotendus qui suivaient le régime DASH ont vu leur pression artérielle baisser de 1,1 mm Hg. La diminution de la consommation de sodium a moins d'effets sur la pression artérielle quand une personne suit le régime DASH. En effet, cette diminution d'apport réduit la sensibilité au régime DASH. Il faut tenir compte de l'interaction entre le régime DASH et le régime à faible teneur en sodium.

De la salle

L'interaction entre ces deux régimes a-t-elle une signification statistique ? Les effets du régime DASH semblent supérieurs quand la quantité de sodium absorbée est importante.

Eva OBARZANEK

L'interaction entre les effets du régime DASH et les effets de la diminution de consommation de sodium n'a pas pu être démontrée de manière significative d'un point de vue statistique. Nous n'avons pas comparé les effets sur la pression artérielle du régime DASH et du régime à faible teneur en sodium. Notre but était de mesurer la pression artérielle chez des patients suivant le régime de contrôle et le régime DASH. L'interaction n'a pas été testée.

Un intervenant

Le suivi du régime DASH peut permettre de réduire la probabilité de diabète, d'obésité, etc. Une variation de l'apport calorique a-t-elle été nécessaire dans le régime DASH pour maintenir la masse corporelle des patients ?

Eva OBARZANEK

Nous avons examiné ce point lors de la première étude DASH. Nous n'avons pas observé de différence dans la capacité à maintenir le poids constant dans le cas du régime contrôle ou du régime DASH.

Salt intake early in life: does it increase the risk of hypertension?

Johanna M. GELEIJNSE, PhD [1]
Division of Human Nutrition & Epidemiology,
Wageningen University, Wageningen, The Netherlands

and Diederick E. GROBBEE, MD
Julius Center for Patient Oriented Research,
Utrecht University, Utrecht,The Netherlands

The roots of essential hypertension extend back into the first two decades of life. Insight into the role of sodium in blood pressure regulation at (very) young age is important, because factors that underly the sodium-blood pressure relationship may operate differently during various stages of hypertension development. Therefore, etiologically important relationships may only be detectable early in life. Furthermore, if blood pressure in childhood tracks into adulthood, intervention measures to lower blood pressure (or prevent a further rise) should be applied as early as possible, which calls for a clear understanding of the blood pressure determinants at young age. At present, it is unknown whether salt intake early in life, or early dietary exposures in general, have an independent effect on adult blood pressure level. The current evidence on the relation of sodium with blood pressure in infancy and childhood, and how this may influence future risk of hypertension, will be discussed.

The relationship between sodium and blood pressure is debated in any age group, including children and adolescents. Observational studies have yielded conflicting results, and randomized trials of sodium reduction and blood pressure in children are scanty. Geleijnse *et al* examined the effect of habitual sodium and potassium intake on annual blood pressure change in 233 Dutch youngsters. The findings from this study indicated no significant role of sodium in the early pathogenesis of hypertension (Geleijnse *et al*, 1990). The majority of randomized trials of sodium reduction in children and adolescents show little effect on blood pressure. Sinaiko *et al* selected 210 children with blood pressures in the upper part of the distribution, who were randomly assigned to a low sodium, high potassium, or placebo diet. Blood pressure slopes did not significantly differ among the intervention groups (Sinaiko *et al*, 1993). Apart from the possibility that no relationship between salt and blood pressure exists, there could be methodological difficulties in disclosing a relationship between dietary sodium intake and blood pressure. Imprecise measurement of habitual sodium intake and resulting misclassification may dilute the association with blood pressure. Furthermore, inadequate adjustment for confounding factors in observational studies may distort the sodium-blood pressure association. Finally, the effect of dietary sodium on blood pressure may only be detectable in populations in which the range of sodium intake is sufficiently large.

---

[1] Speaker of the conference

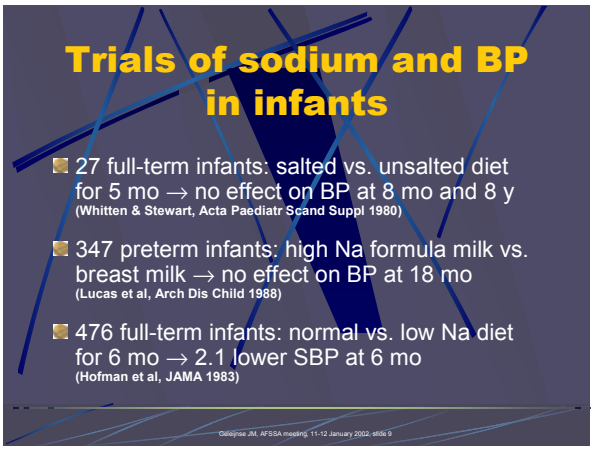
Address correspondence to:

Dr. J.M. Geleijnse, Wageningen University, Division of Human Nutrition & Epidemiology,

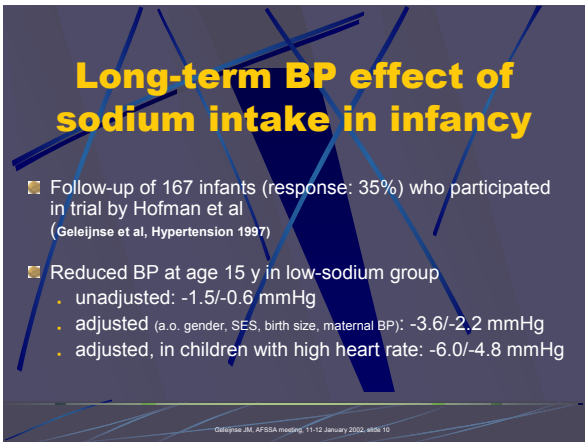
P.O. Box 8129, 6700 EV Wageningen, The Netherlands;

Phone: +31 317 482574, Fax: 31 317 483342; E-mail: Marianne.Geleijnse@staff.nutepi.wau.nl.

Sodium may not be an important modulator of blood pressure in childhood and adolescence, but could possibly play a role earlier in life. Whitten & Stewart were the first to conduct an intervention study in infants on early sodium intake and blood pressure in later life. Salted and unsalted diets were administered for 5 months (starting at age 3 months) to 27 babies who were born at term, and blood pressure was examined at 8 months and 8 years of age. No blood pressure effect was found on either occasion (Whitten & Stewart, 1980). A study among 347 preterm infants on the effect of high sodium formula milk on blood pressure at 18 months of age neither showed an effect during this relatively short follow-up period (Lucas *et al*, 1988). However, Hofman *et al* found a 2.1 mmHg lower systolic blood pressure in infants who had been given a diet with one-third regular sodium intake for 6 months (Hofman *et al*, 1983).

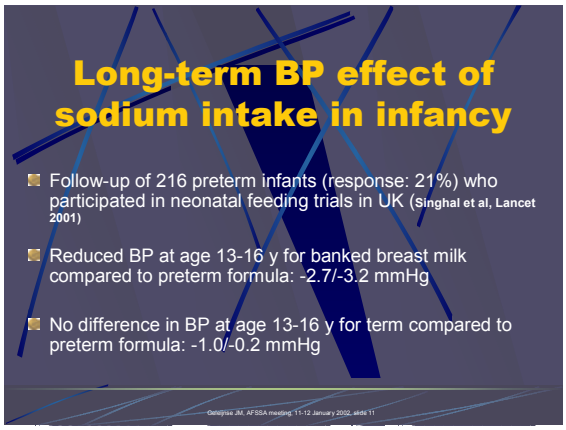


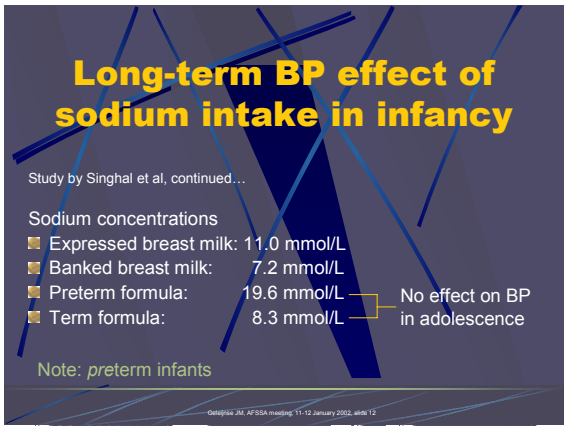
When 167 of these children (35%) were checked again after 15 years, the low-salt group still had 3.6/2.2 mmHg lower blood pressures (Geleijnse *et al*, 1997). In this study, however, the initial randomization was lost and significant associations of neonatal salt intake with blood pressure in adolescence only emerged after adjustment for confounders.



Recently, Singhal *et al* examined dietary exposures in infancy in relation to blood pressure later in life in 130 teenagers who, as premature infants, had participated in a randomized trial of preterm formula milk and banked breast milk (Singhal *et al*, 2001). Blood pressure levels in adolescence were reduced (-2.7/-3.2 mmHg) for breastmilk compared to preterm formula. These findings suggest that programming of blood pressure by early diet occurs, but sodium intake is unlikely to have played a role because it did not differ between the intervention groups. More data from long-term randomized trials are needed to conclude whether early sodium exposure is an important determinant for adult hypertension and, more important, (cardiovascular) mortality. However, starting new trials in neonates is complicated by the fact that sodium concentrations in formula milk are reduced to levels of breast milk nowadays. The question remains whether there is biological plausibility for a

lifelong, independent blood pressure effect of early sodium exposure and, if so, whether such effect is reversible. A number of hypotheses, none of which have been proven, can be postulated.

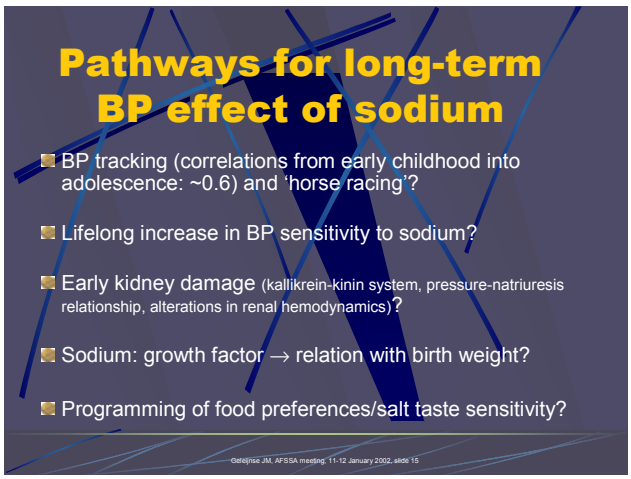




Firstly, sodium may have a small (even undetectable) effect in early life, which could track into adulthood. Especially when 'horse-racing' occurs, with amplification of blood pressure elevations, a minor increase in blood pressure early in life may eventually yield blood pressure differences over 10 mmHg in adulthood. Repeated studies in children have shown significant and sizeable correlation coefficients (~0.6) between blood pressure measured on multiple occasions from infancy through adolescence (Cook *et al*, 2000). However, correlations with adult blood pressure, probably lower, are less well studied.

Secondly, it is possible that postnatal exposure to high levels of sodium causes early kidney damage which may, for example, alter the setpoint of the pressure-natriuresis relationship. This may (irreversibly?) influence sodium handling and salt sensitivity, which could give rise to blood pressure elevations during susceptible periods in adult life. An important role for the kidney has also been suggested by Brown *et al*, who hypothesized that renal changes at early age, resulting from small rises in blood pressure caused by autonomic nervous overactivity, could form the basis for adult hypertension (Brown *et al*, 1976). A study in Dutch youngsters at higher risk for familial hypertension supported the hypothesis that alterations in renal hemodynamics occur at an early stage in the development of hypertension (van Hooft *et al*, 1991). It has also been postulated that the formation of fewer nephrons at birth (favoring sodium retention) is a risk factor for hypertension, which may partly explain the association between low birth weight and elevated blood pressure later in life (Mackenzie & Brenner, 1995). A blunted pressure natriuresis curve has been observed in children and adolescents with low birth weight (Lurbe *et al*, 1998), indicating suboptimal kidney development and abnormal renal sodium handling.

Thirdly, programming of food preferences and/or salt taste sensitivity may be established early in postnatal life or even during the intrauterine stage. If the preference for (a slightly) higher sodium intake persists throughout life, this chronic exposure may eventually increase the risk of hypertension in adulthood. During early human postnatal development, transductive elements sensitive to saltiness mature, and this process is possibly influenced by exposure to sodium at that time (Beauchamp *et al*, 1994). Furthermore, prenatal mineralofluid loss (*e.g.,* due to excessive maternal vomiting) has been shown to increase the lifelong avidity for salt in human offspring (Chrystal *et al*, 1998; Leshem, 1998). It has also been suggested that electrolyte depletion due to chloride-deficient feeding formula is related to increased liking for salty foods in adolescence (Stein *et al*, 1996).



Additional research in this field could focus on the role of the kidney in blood pressure development and how this is influenced by sodium early in life. Furthermore, the interaction between sodium and the sympathetic nervous system in blood pressure regulation warrants further study (Zhou L, *et al*. 2000, Geleijnse *et al*, 1997). Finally, more data are needed on the blood pressure effect of other dietary factors early in life, *e.g.* potassium (Geleijnse *et al*, 1990, MacGarvey *et al*, 1991, Ray *et al*, 2001).

When studying salt intake early in life, a distinction should be made between preterm and full-term infants, as bodily requirements and renal handling of sodium may largely differ between these groups. Preterm formula milk could contain doubled amounts of sodium (Singhal *et al*, 2001). In the Netherlands, as in other Western countries, the sodium concentration in term formulas has been reduced to levels of breast milk (yielding intakes around 10 mmol/d in 3-months-old children). However, sodium intake dramatically increases after the age of 4 months, when table foods are introduced. Salt intake in children, as in adults, largely depends on the amounts that are used in industrial and household food processing (Yeung *et al*, 1982). In the STRIP trial among Finnish children, the mean daily salt consumption amounted to 4.0, 4.8 and 5.5 g/d at the ages of 13 months and 3 and 5 years, respectively (Heino *et al*, 2000).

In conclusion, it remains unclear whether a high intake of sodium in infants and children increases their risk of hypertension later in life. However, there is sufficient biological plausibility for such an effect to encourage further research in this field.

References

1. Beauchamp GK, Cowart BJ, Mennella JA, Marsh RR. Infant salt taste: developmental, methodological, and contextual factors. Dev Psychobiol 1994;27:353-65.

2. Brown JJ, Lever AF, Robertson JIS, Schalekamp MA. Pathogenesis of essential hypertension. Lancet 1976;1:1217-9.

3. Cook NR, Gillman MW, Rosner BA, Taylor JO, Hennekens CH. Combining annual blood pressure measurements in childhood to improve prediction of young adult blood pressure. Stat Med 2000;19:2625-40.

4. Crystal SR, Bernstein IL. Infant salt preference and mother's morning sickness. Appetite 1998;30:297-307.

5. Geleijnse JM, Grobbee DE, Hofman A. Sodium and potassium intake and blood pressure change in childhood. BMJ 1990;300:899-902.

6. Geleijnse JM, Hofman A, Witteman JCM, Hazebroek AAJM, Valkenburg HA, Grobbee DE. Long-term effects of neonatal sodium restriction on blood pressure. Hypertension 1997;4:913-7.

7. Heino T, Kallio K, Jokinen E, Lagström H, Seppänen R, Vällimäki I, Viikari J, Rönnemaa T, Simell O. Sodium intake of 1 to 5-year-old children: the STRIP Project. Acta Paediatr 2000:89:406-10.

8. Hofman A, Hazebroek A, Valkenburg HA. A randomized trial of sodium intake and blood pressure in newborn infants. JAMA 1983;250:370-3.

9. Hooft IMS van, Grobbee DE, Derkx FHM, Leeuw PW de, Schalekamp MA, Hofman A. Renal hemodynamics and the renin-angiotensin-aldosterone system in normotensive subjects with hypertensive and normotensive parents. N Engl J Med 1991;324:1305-11.

10. Leshem M. Salt preference in adolescence is predicted by common prenatal and infantile mineralofluid loss. Physiol Behav 1998;63:699-704.

11. Lucas A, Morley R, Hudson GJ, Bamford MF, Boon A, Crowle P, Dossetor JF, Pearse R. Early sodium intake and later blood pressure in preterm infants. Arch Dis Child 1988;63:656-7.

12. Lurbe E, Redon J, Tacons J, Torro I, Alvarez V.Current and birth weights exert independent influences on nocturnal pressure-natriuresis relationships in normotensive children. Hypertension 1998;31:546-51.

13. Mackenzie HS, Brenner BM. Fewer nephrons at birth: a missing link in the etiology of essential hypertension? Am J Kidney Dis 1995;26:91-8.

14. McGarvey ST, Zinner SH, Willett WC, Rosner B. Maternal prenatal dietary potassium, calcium, magnesium, and infant blood pressure. Hypertension 1991;17:218-24.

15. Ray PE, Suga S, Liu XH, Huang X, Johnson RJ. Chronic potassium depletion induces renal injury, salt sensitivity, and hypertension in young rats. Kidney Int 2001;59:1850-8.

16. Sinaiko AR, Gomez-Marin O, Prineas RJ. Effect of low sodium diet or potassium supplementation on adolescent blood pressure. Hypertension 1993;21:989-94.

17. Singhal A, Cole TJ, Lucas A. Early nutrition in preterm infants and later blood pressure: two cohorts after randomised trials. Lancet 2001;357:413-9.

18. Stein LJ, Cowart BJ, Epstein AN, Pilot LJ, Laskin CR, Beauchamp GK. Increased liking for salty foods in adolescents exposed during infancy to a chloride-deficient feeding formula. Appetite 1996;27:65-77.

19. Whitten CF, Stewart RA. The effect of dietary sodium in infancy on blood pressure and related factors. Studies of infants fed salted and unsalted diets for five months at eight months and eight years of age. Acta Paediatr Scand Suppl 1980;279:1-17.

20. Yeung DL, Hall J, Leung M, Pennell MD. Sodium intakes of infants from 1 to 18 months of age. J Am Diet Assoc 1982;80:242-4.

21. Zhou L, Ambrosius WT, Newman SA, Wagner MA, Pratt JH. Heart rate as a predictor of future blood pressure in schoolchildren. Am J Hypertens 2000;13:1082-7.

De la salle

Le problème que vous soulevez me paraît particulièrement important. L'étude sur les adolescents menée aux Pays-Bas a été relatée. Il faut s'intéresser à cette période entre l'enfance et l'âge adulte. Il est parfois difficile de déceler les différences de pression artérielle chez les enfants, mais ne pensez-vous pas qu'il faudrait faire plus d'études sur les adolescents, dont la pression artérielle peut varier plus sensiblement ?

Johanna GELEIJNSE

Il faudrait faire plus de recherche sur l'enfance et l'adolescence. Les différences de pression artérielle peuvent être importantes et du même ordre que celles trouvées dans l'étude Intersalt, mais les intervalles de confiance ne permettent pas toujours d'assurer la crédibilité des données.

De la salle

A la fin des années 70, on a éliminé le sel des aliments pour les bébés, et certains d'entre eux ont développé le syndrome de Bartter. D'autres ont eu des retards de développement et d'acquisition des connaissances.

De la salle

Quelle est l'évolution de la croissance des bébés en fonction de l'apport en sodium ?

Johanna GELEIJNSE

Le sodium peut être un facteur de croissance *in utero*, mais je n'ai pas étudié les relations entre le sodium et le poids à la naissance ou le développement de l'enfant.

De la salle

Un faible apport en sodium peut avoir des effets sur les enfants en bas âge. J'aimerais savoir pourquoi les résultats de A. Lucas ne sont pas les mêmes que les vôtres. Quelles étaient les différences de procédure ?

Johanna GELEIJNSE

A. Lucas n'a pas pratiqué d'essai randomisé, mais cela n'explique pas les résultats obtenus. Par ailleurs, je ne sais pas s'il a suivi des enfants nés à terme ou des enfants prématurés.

De la salle

L'étude de A. Lucas n'est pas très précise, car les réductions de l'apport en sel n'ont été effectuées que sur quelques jours.

Par ailleurs, nous avons mesuré l'excrétion urinaire du sodium chez des enfants de quatre ans pendant plusieurs jours. En 1980, les enfants de quatre ans absorbaient en moyenne 5 grammes de sodium par jour, ce qui s'explique par le fait qu'ils consomment une nourriture de type snack, qui contient beaucoup de sel. A l'heure actuelle, les enfants de 4 ans absorbent 9 à 10 grammes de sel par jour, ce qui correspond à 40 grammes chez un adulte.

En Finlande, il semblerait que l'absorption de sel soit d'environ 5 grammes par jour.

Apport en sel et maladies cardiovasculaires

Salt intake and cardiovascular diseases

Session 3

animée par M. Jean-Louis IMBS,
Faculté de médecine, Strasbourg, France,

et Mme Marie-Christine DE VERNEJOUL,
Hôpital Lariboisière / INSERM, Paris, France

Cette session a réuni :
Malcom R. Law, Queen Mary's School of Medecine, Londres, Royaume-Uni
Paul K. Whelton, Tulane University Health Sciences Center, La Nouvelle Orléans, Etats-Unis
Jaakko Tuomilehto, National Public Health Institute, Helsinki, Finlande
Michael H. Alderman, Albert Einstein College of Medecine, New York, Etats-Unis
Hugh E. de Wardener, Charing Cross Hospital, Londres, Royaume-Uni
Albert Mimran, Hôpital La Peyronie, Montpellier, France

Introduction par Mme Marie-Christine de Vernejoul et M. Jean-Louis Imbs

Marie-Christine De VERNEJOUL

Cette session sera présidée par le Pr. Imbs, professeur de pharmacologie à la Faculté de Médecine de Strasbourg, et par moi-même. Je suis rhumatologue et professeur de biologie cellulaire. Une communication sera présentée cet après-midi afin de vous expliquer que les excrétions urinaires du calcium et du sodium sont liées.

Jean-Louis IMBS

En effet, l'évolution de l'excrétion urinaire du calcium en fonction de l'apport sodé est l'un des points majeurs qui sera évoqué lors nos échanges.

Les présentations de la matinée d'aujourd'hui porteront sur l'épidémiologie géographique. Des informations, portant sur le monde entier et concernant la relation entre la consommation de sel et la morbidité cardiovasculaire, vous seront communiquées. Nous entendrons ainsi des collègues venant du Royaume-Uni, des Etats-Unis et de Finlande.

Salt, blood pressure, cardiovascular disease and taste

Malcolm R. LAW
Queen Mary's School of Medicine, London, United Kingdom

The average Western daily diet contains about 10g of salt. About 7.5g of this 10g salt is added to manufactured foods by the food industry. Much unwarranted controversy and debate has surrounded the modest proposal that it is in the public health interest that this 7.5g of added salt be steadily reduced over the next 1 or 2 years to about 5g, with a view to further reduction in the longer term. There is everything to gain in implementing this and nothing to lose.

In Western countries average blood pressure levels increase with age, from about 115 mm Hg systolic at age 15 to about 145 mm Hg at age 65. While often considered "normal" this increase in blood pressure with age does not occur in hunter-gatherer societies unexposed to Western lifestyle. Blood pressure in such communities remains at about 115 mmHg systolic throughout life, but increases to levels characteristic of Western societies on migration to urban environments. Mortality from ischaemic heart disease, stroke, and other cardiovascular disease increases continuously with blood pressure. The high average blood pressure levels in Western countries is a major determinant of the high cardiovascular mortality, and a small reduction in average blood pressure levels would prevent many deaths.

Salt is an important determinant of this high average blood pressure for three reasons – its effects on blood pressure is large (about a third of the difference between the Western and hunter-gatherer societies), dietary intake in Western populations is high so a large reduction could be obtained, and, with the cooperation of the food industry, lowering dietary salt could be easy and straightforward.

Once certain complexities in the relationship between salt and blood pressure are understood, the evidence is consistent. First, the relationship cannot be quantified by a single summary estimate effect that applies in all circumstances; it depends on a person's age and the existing level of blood pressure. Second, the effect of a reduction in dietary salt on blood pressure is not instantaneous, it takes about a month to achieve the full effect; short term trials of salt reduction therefore underestimate the effect on blood pressure. Third, the day to day variation in a person's salt intake is large, much larger than the true variation in average salt intake between persons in a population. This means that cross-sectional studies of salt and blood pressure, and cohort studies of salt intake and cardiovascular disease, greatly underestimate the relationship.

In 1991 we published quantative estimates of the relationship that took these factors into account. Randomised trials of dietary salt reduction published subsequently fit our published model well and confirm these estimates. We estimate that a reduction in daily sodium intake of 50 mmol (3g of salt) would lower blood pressure by 5 mm Hg systolic on average at the age of 60. This in turn would reduce mortality from stroke by an estimated 22% and mortality from ischaemic heart disease by 16%. This is a realistic reduction in dietary salt. Trials have shown that lowering the salt content of manufactured foods does not result in a loss of palatability. A concerted plan by the food industry to gradually reduce the amount of salt added to manufactured food should be devised. People would either prefer or not notice the change in taste, and the health benefit would be great.

Population based studies of sodium and blood pressure in the United States and China
Experience in the Yi Migrant Study, TONE, TOHP and NHANES I Study

Paul K. WHELTON, MD, MSc[2]
Tulane University Health Sciences Center, New-Orleans, USA

Jiang HE, MD, PhD;

and Paul MUNTNER, PhD

Abstract

Evidence relating dietary sodium intake to level of blood pressure (BP) and cardiovascular disease complications comes from a variety of sources, including observational epidemiologic studies and population-based clinical trials. In this presentation observational epidemiologic experience from the Yi Migrant Study and NHANES I Follow-up Study, and population-based clinical trial experience from the TONE and TOHP trials will be reviewed.

In the context of a low BP environment, pooled multi-variate analysis of observational experience in 313 Yi farmers, 265 Yi migrants and 253 urban Han residents with an average systolic BP of 106.7, 114.8, and 118.2 mm Hg, respectively, identified urinary sodium excretion as being significantly (p=.003) and positively associated with systolic BP, even after adjustment for age, body mass index, alcohol consumption, community of residence, and urinary excretion of potassium, calcium and magnesium. The lower level of systolic BP in Yi farmers compared to YI migrants and Han residents was significantly associated with a lower level of urinary sodium excretion, even after adjustment for age, body mass index, alcohol intake, and urinary excretion of potassium, calcium and magnesium.

In the Trial of Nonpharmacologic Interventions in the Elderly (TONE), counseling in sodium reduction in 681 adults, aged 60-80 years, with well controlled hypertension on a single BP lowering medication resulted in an additional 4.3 mm Hg decrease in systolic BP and in a 32% reduction in need for recurrent drug treatment or cardiovascular complications following subsequent withdrawal of antihypertensive medication. In Phase I of the Trials of Hypertension Prevention (TOHP), 744 normotensive adults, aged 35-54 years, were randomly assigned to a sodium reduction intervention (n=327) or to usual care (n=417). Compared to usual care counseling in sodium reduction produced a 2.1 mm Hg reduction in systolic BP (95% CI, -3.3 to -0.8 mm Hg) and a 24% reduction in incidence of hypertension (95% CI -51% to +18%). In Phase II of TOHP, counseling in sodium reduction (n=594) compared to usual care (n=596) produced a 2.9 mm Hg (p<.00l) reduction in systolic BP at 36 months and a 1.2 mm Hg (p=.02) at 36 months, with corresponding reductions in the incidence of hypertension of 39% (p=.04) and 12% (p=0.9), respectively.

Among 2688 overweight participants in the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study with an average energy intake of 7452 kJ, a 100 mmol higher consumption of sodium was associated with a 32 % (95% CI, 7 to 64%)

[2] Speaker of the conference

increase in stroke incidence and 89% (95% CI, 31 to 174%) increase in stroke mortality 44% (95% CI, 14 to 81%) increase in coronary heart disease mortality, a 61% (95% CI, 32 to 96%) increase in cardiovascular disease mortality, and a 39% (95% CI, 23 to 58%) increase in mortality from all causes.

The Yi Migrant, TONE, TOHP, and NHANES I Follow-up studies suggest that a higher intake of dietary intake of sodium increases the risk of developing hypertension and cardiovascular disease and that reduction in sodium consumption provides an effective means of treating and preventing hypertension.

Introduction

Estimates suggest that stroke and coronary heart disease (CHD) account for almost 14.5 million deaths per year, on a world-wide basis (1). The optimal approach to reducing this burden of illness includes a combination of treating established disease using best known practices while concurrently treating and preventing major, modifiable risk factors for cardiovascular disease (2). High blood pressure is one of the most prevalent and important risk factors for cardiovascular disease in economically developing as well as economically developed countries (3). Application of diagnostic criteria recommended by the Joint National Committee for Detection, Evaluation and Treatment of High Blood Pressure (4) to results from Phase I of the 1988-91 Third National Health and Nutrition Examination Survey (NHANES III) suggests that approximately one-quarter of all US adults and two-thirds of those between 60-80 years have hypertension (5). The corresponding prevalence for adults aged 65 years or older in the People's Republic of China is almost 50%(6).

Increased attention to dietary factors and physical activity provides a potential mechanism to prevent as well as enhance the control of established hypertension. In this context, even a small shift in the population distribution of blood pressure is likely to yield a substantial reduction in the burden of illness in the community. Cook et al. estimated that as little as a 2 mm Hg downward shift in the population distribution of diastolic blood pressure would reduce the prevalence of hypertension by 17%, and the annual incidence of stroke and CHD by 14% and 6%, respectively (7). Further, they estimated that this blood pressure reduction would prevent 93% of the number of strokes and transient ischemic attacks, as well as an equal number of incident coronary heart disease events that could be averted by treatment of all hypertensive patients with antihypertensive drug therapy. These results underscore the potential value of complementing traditional hypertension detection and treatment approaches with public health interventions aimed at achieving a slight downward shift in the blood pressure of the general population (4,8). In 1960 Dahl described a linear relationship between average sodium intake and prevalence of hypertension across five-population groups (9). Since then, a large body of evidence suggesting a causal association between dietary sodium intake and high blood pressure has emerged from animal experiments, observational epidemiologic studies and randomized controlled clinical trials. In this manuscript, the relationship between sodium and blood pressure and cardiovascular disease in the Yi Migrant Study, the Trial of Nonpharmacologic Intervention in the Elderly (TONE), the Trials of Hypertension Prevention (TOHP), and the First National Health and Nutrition Examination Survey (NHANES 1) Follow-up Study will be reviewed.

Yi Migrant Study

Results from more than 30 populations with a lower average blood pressure that is customary in westernized societies and in whom blood pressure rises little if any with age and hypertension is virtually absent, have been described in the scientific literature. It has been suggested that much of the difference between the blood pressure patterns in these and populations with a higher average level of blood pressure can be explained by social and cultural differences, including dietary intake of sodium. In the Yi Migrant Study we examined the effect of local migration on blood pressure in 8,852 men and 6,653 women living in Southwestern China (10). Blood pressure rose very little with age after puberty in the Yi farmers. In contrast, Yi migrants and Han people living in local townships experienced a much greater increase in blood pressure with progressive aging. In a random sample of the 8,852 men, urine samples were obtained to estimate the contribution of cation excretion to differences in blood pressure in 313 Yi farmers living in their native environment, 265 Yi who had migrated into the local townships, and 253 Han living in the same towns (11). Characteristics of the three populations are presented in table 1.

Table 1. Characteristics of 313 Yi farmers and 265 Yi migrants and 253 Han people living in local townships.

	Yi Farmers	Yi Migrants	Han People
Number studied	313	265	253
Age, years	31.3	37.5	45.2
Systolic BP, mm Hg	106.7	114.8	118.2
Change in SBP/year, mmHg	0.1	0.45	0.56
Urinary Na mEq/24 hr.	105	172	183
Urinary Na/K	2.3	6.4	8
BMI, kg/m2	20.7	21.5	21.7
Alcohol, % (g/day)	72 (33.8)	69 (47.8)	47(38.9)

Modifief from data presented in Klag MJ et al. (11); with permission.

Differences in systolic blood pressure between the Yi farmers and the Yi migrants and Han were significantly (p<.00l) related to concurrent differences in urinary sodium excretion, even after adjustment for age, body mass index and excretion of other urinary cations. In a pooled analysis of experience in all 831 men, systolic blood pressure was significantly (p=.003) and positively related to urinary sodium excretion, independent of age, body mass index, alcohol consumption, excretion of other urinary cations, and community of residence. The relationship between urinary sodium excretion and blood pressure was modified by both age and bodyweight, with the age-blood pressure slope being steepest for those who were older and heavier (figure 1).

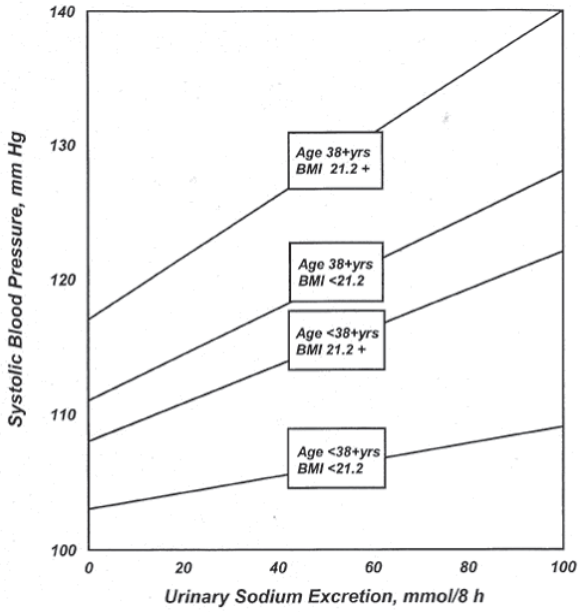


Figure 1. Systolic blood pressure, adjusted for daily alcohol consumption and community of residence, according to level of overnight urinary sodium excretion in a pooled analysis of experience for 831 Yi farmers, Yi migrants and Han people. Modified from Klag MJ et al. (11).

These findings suggest that changes in lifestyle, including an increased intake of dietary sodium, lead to a higher level of blood pressure and that the effect is most pronounced in those who are older and overweight.

Trial of Nonpharmacologic Interventions in the Elderly (TONE)

Randomized controlled trials provide the best opportunity to recognize a causal relationship between dietary sodium and blood pressure. During the past 30 years, more than 80 randomized controlled trials have been conducted to explore the efficacy and effectiveness of changes in sodium consumption on blood pressure and incidence of hypertension (12). The Trial of Nonpharmacologic Interventions in the Elderly (TONE) and Trials of Hypertension Prevention (TOHP) have been the largest and most prolonged such trials. TONE was a randomized controlled trial designed to determine whether weight loss and a reduction in dietary sodium intake, alone or in combination, enhance blood pressure control with antihypertensive medication and reduce the need for antihypertensive drug therapy in community dwelling older persons with hypertension. The trial was conducted in 975 hypertensives, aged 60-80 years, with a baseline systolic blood pressure <145 mm Hg and diastolic blood pressure <85 mm Hg on one antihypertensive medication (13). Using a factorial design, those meeting the National Center for Health Statistics criteria for overweight (body mass index ≥ 27.8 kg/m^2 in men and ≥ 27.3 kg/m^2 in women) were randomly assigned to either counseling aimed at a reduction in sodium consumption, weight loss, combined sodium reduction and weight loss, or usual care. Those who were in the normal weight category were randomly assigned to either counseling aimed at sodium reduction or usual care. Those assigned to usual care received counseling in health related topics remote to the goals of the trial but had the same investigator contact schedule as their counterparts who were assigned to the sodium reduction and/or weight loss counseling intervention arms. Mean 24-hour urinary sodium excretion was reduced by an average of 47, 49 and 40 mmol following 9, 18 and 36 months of intervention, respectively in those assigned versus not assigned to counseling in sodium reduction. Prior to attempting tapering or withdrawal of antihypertensive medication a significant reduction in blood pressure was noted in those assigned to the active intervention groups compared to their counterparts in the usual care group. For example, average systolic blood pressure in those assigned to counseling in sodium reduction alone was further

reduced by 3.4 mm Hg compared to the corresponding value in the usual care group (figure 2).

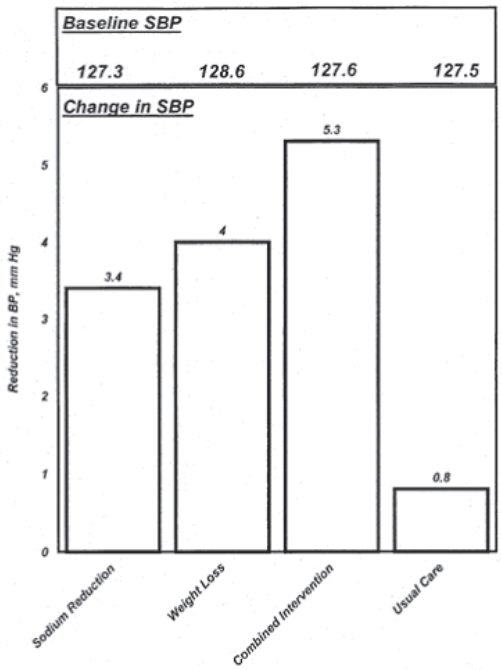


Figure 2. Baseline systolic blood pressure and change in systolic blood pressure from baseline to the last visit prior to attempted withdrawal of antihypertensive medication in 953 TONE participants. Modified from Whelton PK et al. (13); with permission.

For those assigned to the combination of sodium reduction and weight loss average systolic blood pressure was further reduced by 5.3 mm Hg. The percentage of trial participants remaining free of trial endpoints (high blood pressure at a TONE follow-up visit, continued use or resumption of antihypertensive medication, or a cardiovascular disease event) remained significantly higher in those assigned versus not assigned to sodium reduction throughout follow-up (figure 3).

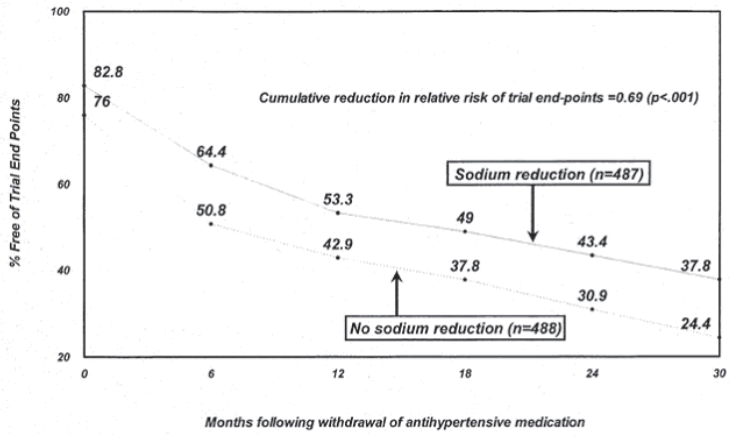


Figure 3. Percent of TONE participants remaining free of trial endpoints. Factorial analysis of participants assigned and not assigned to receive counseling in dietary sodium reduction. Modified from Whelton PK et al. (13); with permission.

Over the entire period of follow-up, the hazard ratio for trial endpoints was only .69 (95% CI, .59 to .81) in those assigned versus not assigned to sodium reduction (p<.001). After 30 months, the percent of participants who were free of trial endpoints was significantly higher in those assigned versus not assigned to counseling in sodium reduction (38% versus 24%). Throughout follow-up the percentage of overweight

participants who remained free of trial endpoints was significantly higher in those assigned to an active intervention (figure 4).

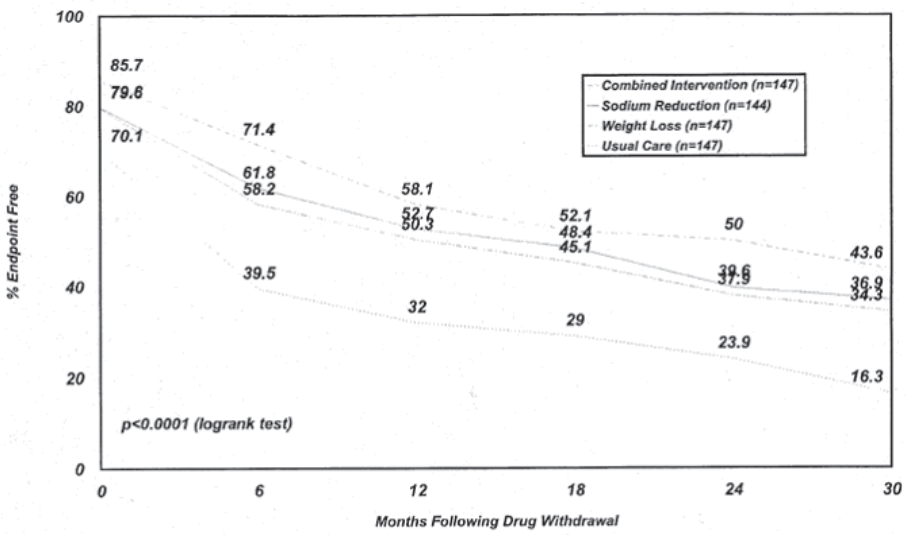


Figure 4. Percent of TONE participants in overweight group remaining free of trial endpoints (high blood pressure, use of antihypertensive medication, cardiovascular disease complications) following withdrawal of antihypertensive medication. Results are based on experience in 585 participants assigned to lifestyle modification (sodium reduction, weight loss, combined sodium reduction and weight loss) or an active control group that had a similar pattern of contact but did not receive counseling aimed at modification of their lifestyle. Modified from Whelton PK et al. (13); with permission.

Those assigned to sodium reduction and the combination of sodium reduction and weight loss had an incidence rate of trial endpoints that was 60% and 47% that experienced by their counterparts who were assigned to usual care. Blood pressure remained well controlled in the 328 participants who were still off antihypertensive medication at their final study visit (table 2).

	SBP	DBP	<140/90 mm Hg
Na Reduction (n=127)	133	75	71%
Weight Loss (n=52)	133	75	63%
Combined (n=66)	130	73	73%
Usual Care (n=83)	134	75	65%

Table 2. Blood pressure and percent of participants with a blood pressure <140/90 mm Hg at their final study visit. Experience in 328 TONE participants who remained off antihypertensive medication at their final study visit. Modified from Whelton PK et al., (13); with permission.

There was no significant difference in the rate of cardiovascular disease events, including myocardial infarction, in those assigned versus not assigned to sodium reduction (12.9 and 16.9 cardiovascular disease events/100 participants for those assigned to sodium reduction and usual care, respectively) but the number of events was relatively small (44 and 57 cardiovascular disease events for sodium reduction and usual care, respectively). Likewise, there was no apparent adverse effect on other nutrients in those assigned to sodium reduction.

Trials of Hypertension Prevention (TOHP)

TOHP was conducted as a series of randomized controlled clinical trials to test the feasibility and efficacy of different approaches to prevent hypertension in adults with a high-normal blood pressure. In a first phase, the efficacy of three lifestyle (sodium reduction, weight loss, stress management) and four nutrition supplements (calcium, magnesium, potassium, fish oil) was tested over 18 and 6 months, respectively, in 2,182 community-dwelling adults, aged 30-54 years, with an initial diastolic blood pressure 80-89 mm Hg (14). At 6 and 12 months, sodium reduction and weight loss were well tolerated and produced significant declines in blood pressure (figure 5).

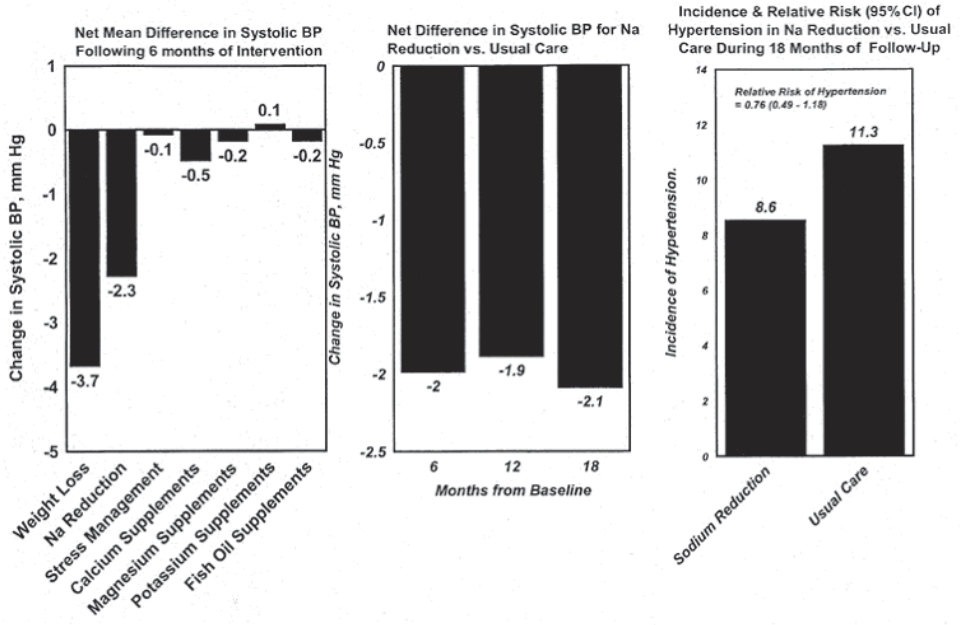


Figure 5. Experience in the Trials of Hypertension Prevention, Phase I (n=2183). Modified from TOHP Collaborative Research Group (14) and Whelton PK et al., (15); with permission.

The net difference in 24-hour urinary sodium excretion for those assigned to sodium reduction compared to usual care was 56, 52 and 47 mmol at 6, 12 and 18 months, respectively. The corresponding difference (95% CI) in systolic blood pressure was -2 (-3.3, -0.8), -1.9 (-3.0, -0.8), and -2.1 (-3.3, -0.8) (15). There was a strong association between the corresponding net differences in reduction of 24-hour sodium excretion and blood pressure, the net change in systolic blood pressure by quintile of 24-hour urinary sodium (<65, 65-98, 99-130, 131-178, >178 mmol) being -5.5, -5.1, -3.8, -2.3, and -2.7, respectively (16). Phase I was not designed to provide sufficient statistical power for a test of the efficacy of sodium reduction in reducing incidence of hypertension but the relative risk (95% CI) of hypertension during follow-up was 0.76 (0.49,1.18). In a 7 year follow-up of 181 Phase I participants at the Baltimore Clinical Center (87% of the original cohort), the incidence of hypertension was 22.4% in the sodium reduction group (n=58) and 32.9% in the corresponding usual care control group (n=70), yielding a relative risk (95% CI) of 0.65 (0.25, 1.69) (17).

In a second phase, the efficacy of sodium reduction and weight loss, alone and in combination, in reducing blood pressure and preventing hypertension was tested over 36-48 months of follow-up in 2,382 community-dwelling adults, aged 30-54 years, with an average diastolic blood pressure 83-89 mm Hg, systolic blood pressure <140 mm Hg, and body mass index 110-165% of desirable body weight (18). The net difference in 24-hour urinary sodium excretion for those assigned to sodium reduction compared to usual care was 50, 43 and 40 mmol at 6, 18 and 36 months, respectively. The corresponding

difference in systolic blood pressure was -2.9 (p<.00l), -2.0 (p<.00l), and -1.2 (p=.02) mm Hg (figure 6).

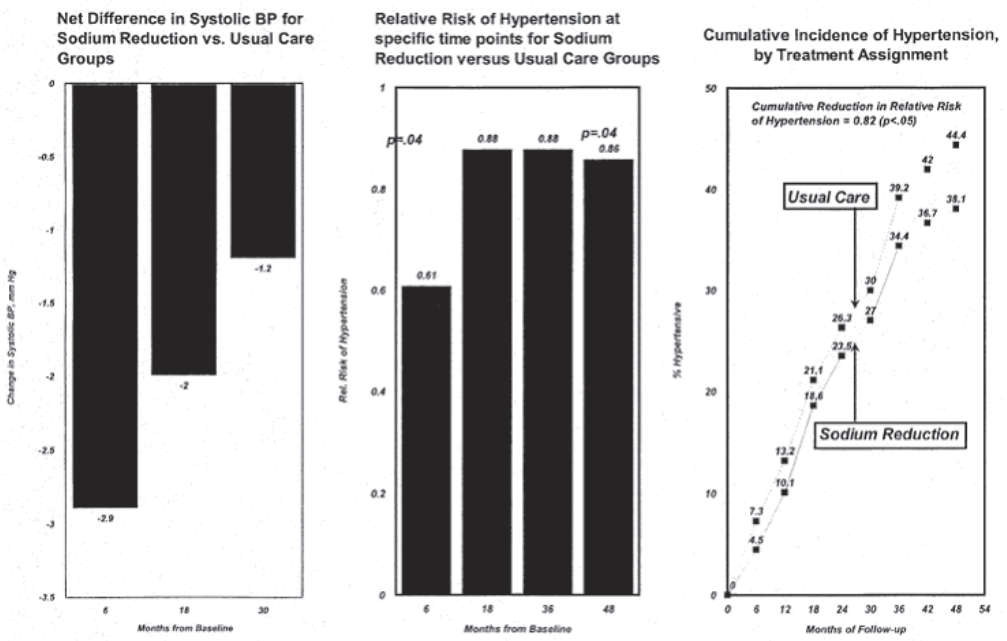


Figure 6. Experience in the Trials of Hypertension Prevention, Phase II (n=2,382). Modified from Trials of Hypertension Prevention Collaborative Research Group (18); with permission.

The relative risk of hypertension for those assigned to sodium reduction versus usual care at 6 and 48 months was 0.61 (p=.04), and 0.86 (p=.04), and was 0.85 (p<0.05) over the entire duration of follow-up. To test whether an allele within the angiotensinogen gene is related to risk of hypertension and blood pressure response to sodium reduction, 1509 white male and female participants in phase II of TOHP were genotyped at the angiotensinogen locus. In the usual care group, those with the AA genotype at nucleotide position -6 had a somewhat higher relative risk (95% CI) of hypertension of 1.4 (0.87, 2.34) compared to their counterparts with the GG genotype (19). However, the efficacy of sodium reduction in reducing the relative risk (95% CI) of incident hypertension compared to usual care was 0.57 (0.34, 0.98) in those with the AA genotype versus 1.2 (0.79, 1.81) in their counterparts with the GG genotype. A similar trend was noted for the relationship between genotype and change in blood pressure.

In aggregate, the two phases of TOHP demonstrated the capacity of a life-style change to reduce sodium consumption, blood pressure, and the incidence of hypertension during prolonged follow-up of middle-aged adults in the community. In contrast to the long-term success of a behavioural intervention aimed at reducing sodium consumption in the TONE participants, who were older and hypertensive, it was more challenging to maintain intervention success in the younger, normotensive participants enrolled in TOHP. Phenotyping and genotyping may provide an opportunity to identify those who are most likely to benefit from life-style modification. However, greater reliance needs to be placed on environmental interventions which yield a reduction in dietary sodium content without conscious effort by the individual. Much of this would be dependent on changes in food processing and marketing aimed at more natural foods which are lower in sodium and higher in potassium content.

Salt intake and the Risk of Cardiovascular Disease

We took advantage of the large sample size (14,407 adults, aged 25-74 years), nutrition data base and prolonged follow-up of participants (average of 19 years in our analysis) in

the National Health and Nutrition Examination Survey I (NHANES 1) Epidemiologic Follow-up Study to examine the relationship between baseline dietary sodium intake and risk of cardiovascular disease (20). Exclusion of those with no record of baseline dietary sodium intake (n=3,061), a self-reported history of cardiovascular disease or treatment (n=1,133) or consumption of a low-salt diet (n=337) at baseline, or loss to follow-up (n=391), yielded a total of 9,485 participants (113,467 person-years of follow-up) of whom 2,688 were overweight. We identified a consistent and highly significant positive relationship between baseline dietary intake of sodium and risk of stroke, cardiovascular disease and total mortality in those who were overweight (figure 7).

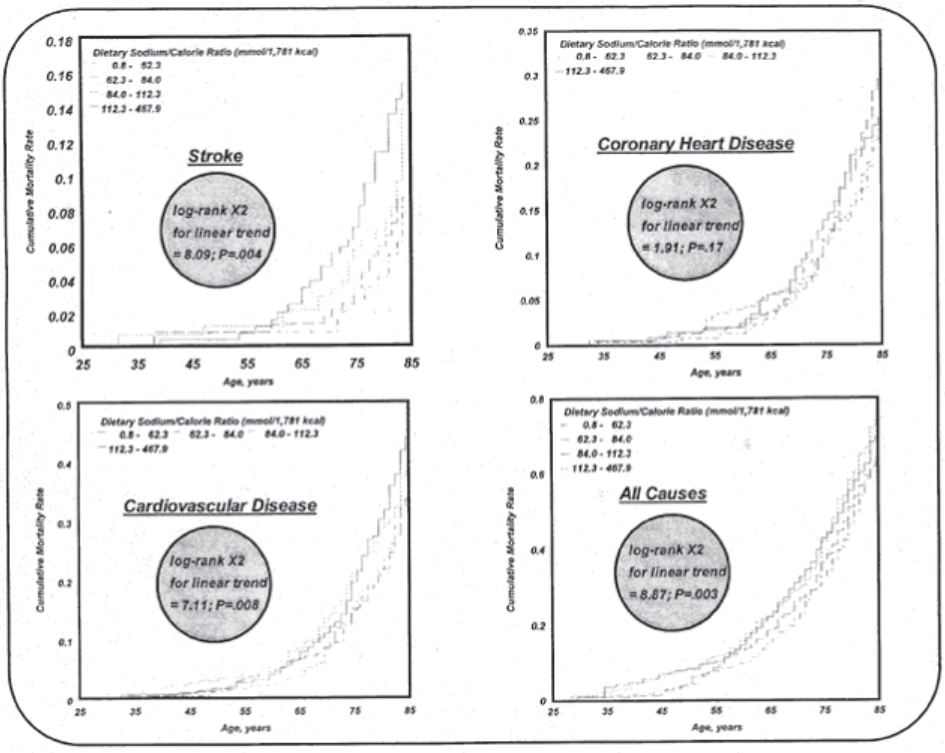


Figure 7. Cumulative mortality by quartile of sodium-to-energy Intake in 2,688 overweight NHANES I Follow-up Study Participants with a cumulative follow-up experience of 43,788 person-years, during which 87 deaths from stroke, 214 deaths from coronary heart disease, 329 deaths from cardiovascular disease, and 810 deaths from all causes were observed. Modified from He J et al. (20): with permission.

For an average caloric intake, a 100 mmol higher sodium intake was associated with an increased risk (95% CI) of 32% (7%, 64%) for stroke incidence, 89% (31%, 74%) for stroke mortality, 44% (14%, 81%) for coronary heart disease mortality, 61% (32%, 96%) for cardiovascular disease mortality, and 39% (23%, 58%) for mortality from all causes. Dietary sodium intake was not significantly associated with non-fatal coronary heart disease in overweight participants or with risk of cardiovascular disease in participants with normal weight.

Conclusion

In aggregate, experience in the Yi Migrant Study, TONE and TOHP trials, and the NHANES I Follow-up Study suggest that 1) dietary sodium influences the individual level of blood pressure and the risk of hypertension, 2) reduced intake of dietary sodium lowers blood pressure and the risk of hypertension, and 3) the level of dietary sodium predicts the risk of cardiovascular disease, independent of blood pressure and other major cardiovascular disease risk factors. These findings are consistent with the vast majority of the information emanating from animal experiments, observational studies, and randomized controlled trials (12).

References

1. Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997;349:1269-1276.
2. Whelton PK. Epidemiology of hypertension. Lancet 1994;344:101-106.
3. Whelton Pk, Brancati FL, Appel Lj, Klag MJ. The challenge of hypertension and atherosclerotic cardiovascular disease in economically developing countries. High Blood Pressure 1995;4:1-10.
4. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). Arch lntern Med 1997; 157:2413-2446.
5. Burt VL, Whelton PK, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991.
6. Gu D, He J, Wu X, Duan X, Muntner P, Huang G, Reynolds K, Chen J, Reynolds RF, Su S, Whelton PK for the InterASIA Collaborative Group. Prevalence, Awareness, Treatment, and Control of Hypertension in China: The International Collaborative Study of Cardiovascular Disease in ASIA (InterASiA). Abstract, American Heart Association 42nd Annual Conference on Cardiovascular Disease Epidemiology and Prevention, 2002.
7. Cook NR, Cohen J, Hebert P, Taylor J, Hennekens C: implications of small reductions in diastolic blood pressure for primary prevention. Arch lntern Med 1995;155:701—709.
8. Working Group on Primary Prevention of Hypertension. Report of the National High Blood Pressure Education Program Working Group on Primary Prevention of Hypertension. Arch Intern Med 1993;153:186-208.
9. Dahl LK. Possible role of sait intake in the development of essential hypertension, in Collier P Bock KD (eds): Essential Hypertension — An International Symposium. Berlin, Springer-Verlag, 1960, pp 53—65.
10. He J, Klag MJ, Whelton PK, Chen JY, Mo JP, Qian MC, Mo PS, He GQ. Migration, blood pressure pattern and hypertension: The Yi Migrant Study. Am J Epidemiol 1991 ;134:1085-1101.
11. Klag MJ, He J, Coresh J, Whelton PK, Chen J-Y, Mo J-P, Qian M-C, Mo P-S, and He G-Q. The contribution of urinary cations to the blood pressure differences associated with migration. Am J Epidemiol 1995;142:295-303.
12. He J, Whelton Pk. Salt intake, hypertension, and risk of cardiovascular disease: an important public health challenge. int J Epidemiol (in press).
13. Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger WH, Kostis JB, Kumanyika S, Lacy CR, Johnson KC, Folmar S, Cutler JA for TONE Collaborative Research Group. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). JAMA 1 998;279:839—846.
14. The Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. JAMA 1992;267:1213-1220.
15. Whelton PK, Kumanyika 5K, Cook NR, Cutler JA, Borhani NO, Hennekens CH, Kuller LH, Langford H, Jones DW, Satterfield S, Lasser N and Cohen JD for the Trials of Hypertension Prevention Collaborative Research Group. Efficacy of nonpharmacologic interventions in adults with high-normal blood pressure: results from phase 1 of the Trials of Hypertension Prevention. Am J Clin Nutr l997;65:652S-6605.
16. Kumanyika SK, Hebert PR, Cutler JA, Lasser VI, Sugars CP, Steffen-Batey L, Brewer AA, Cameron M, Shepek LD, and Cook NR. Feasibility and efficacy of sodium reduction in the Trials of Hypertension Prevention, phase I. Trials of Hypertension Prevention Collaborative Research Group. Hypertension 1993;22:502-512.
17. He J, Whelton PK, Appel LJ, Charleston J, Klag MJ. Long-term effects of weight loss and dietary sodium reduction on incidence of hypertension. Hypertension 2000;35:544-549.
18. The Triais of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, Phase II. Arch intern Med 1997;157:657-667.
19. Hunt SC, Cook NR, Oberman A, Cutler JA, Hennekens CH, Allender PS, Walker WG, Whelton PK, Williams RR. Angiotensinogen genotype, sodium reduction, weight loss, and prevention of Hypertension. Hypertension 1998;32:393—401.
20. He J, Ogden LG, Vupputuri S, Bazzano LA, Loria C, Whelton PK. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. JAMA l999;282:2027—2034.

High sodium intake is associated with increased mortality and the risk of cardiovascular disease

Jaakko TUOMILEHTO
Department of Epidemiology and Health Promotion, National Public Health Institute and Department of Public Health, University of Helsinki, Helsinki, Finland

---

Background: The evidence that high salt intake increases the risk of cardiovascular disease has been challenged previously even though experimental evidence has provided unequivocal evidence for harmful cardiovascular effects of sodium. The main reason for this debate has been the lack of adequate prospective data on health effects of high sodium intake.

We aimed to find out whether sodium intake measured by the 24-hour urinary sodium and potassium excretion, is an independent risk factor for cardiovascular disease and all-cause mortality.

Methods: This prospective study followed 1,173 men and 1,263 Finnish women aged 25-64 years with complete data on 24-hour urinary sodium and potassium excretion and cardiovascular risk factors. The end-points were an incident coronary and stroke event, and death from coronary heart disease, cardiovascular disease and any cause. Each of the end-points was analysed separately using the Cox proportional hazards models.

Findings: The hazard ratios for coronary heart disease, cardiovascular disease and all cause mortality, associated with a 100 mmol increase in 24-hour urinary sodium excretion, were 1.51 (95% CI 1.14 – 2.00), 1.45 (95% CI 1.14 – 1.84) and 1.26 (95% CI 1.06 – 1.50), respectively, in both genders combined. Also the incidence of acute coronary events, but not acute stroke events, increased significantly by increasing sodium excretion. When the analyses was done separately for each gender, the risk ratios were statistically significant in men. The effects of sodium intake remained almost unchanged after adjusting for other known cardiovascular risk factors. There was a significant interaction between the sodium excretion and body-mass index for cardiovascular and total mortality; the sodium was a stronger predictor of mortality among overweight than normal weight subjects. In normal weight subjects there was also a 23% increase in cardiovascular mortality, but it did reach the level of statistical significance. Correction for the regression dilution bias increased the hazard ratios markedly, suggesting that the true effect of sodium intake is larger than that observed in our study with a single sodium intake measurement at baseline. There was no association between potassium intake and mortality or cardiovascular risk.

Interpretation: High sodium intake predicted mortality and the risk of coronary heart disease, independent of other cardiovascular risk factors including blood pressure. These results provide direct evidence of the harmful effects of high salt intake in the middle-aged population. Lowering sodium intake is needed for the effective prevention of cardiovascular disease.

De la salle

J'ai noté que pour le groupe des personnes en surpoids dans l'étude NHANES I, aucun lien n'a été établi entre l'excrétion de sodium et les maladies coronariennes. En revanche, dans l'étude finlandaise portant sur une population plus large, un lien étroit a pu être établi entre l'excrétion de sodium et les maladies coronariennes, mais non avec les cas d'accidents vasculaires cérébraux. Comment interpréter ces différences de résultats ?

Paul K. WHELTON

Dans certains cas, aucune relation n'a effectivement été établie entre l'excrétion de sodium et les maladies coronariennes. Dans l'étude NHANES I, il est tout à fait remarquable que nous n'ayons pas identifié une telle relation.

Jaakko TUOMILEHTO

Dans le cadre de notre étude, nous avons obtenu des résultats relativement fiables. Je tiens à souligner que la Finlande présente une fréquence des maladies coronariennes particulièrement élevée. Il se peut que cette situation puisse avoir un effet sur la relation entre l'excrétion de sodium et les maladies cardiaques coronaires.

De la salle

Pourriez-vous nous rappeler pourquoi le niveau de consommation de potassium est si élevé dans votre étude ?

Jaakko TUOMILEHTO

Deux facteurs expliquent cette situation. Le premier est lié au fait que les aliments riches en sodium sont généralement riches en potassium. Lors de la première journée de ce colloque, nous avons ainsi entendu dire que le pain constituait l'une des principales sources de sodium et de potassium. Or la consommation de pain est importante en Finlande. Le second facteur concerne le café. La consommation de café en Finlande est l'une des plus élevées du monde. Or cette boisson est particulièrement riche en potassium.

Salt, hypertension, and human health

Michael H. ALDERMAN
Albert Einstein College of Medecine, New York, USA

The positive relationship of sodium intake and blood pressure is well established by ecological, epidemiological, and experimental human studies. Equally well established is the association of increasing blood pressure and cardiovascular morbidity and mortality. Indeed, the pharmacological capacity to reduce blood pressure has been associated with one of the great public health accomplishments of the 20th Century.

These two facts - the positive relation of blood pressure to strokes and heart attacks, and the positive association of sodium intake to blood pressure - underlay the hypothesis that a reduction in sodium intake, by virtue of its hypotensive effect, might prevent strokes and heart attacks. Moreover, even if the effect on blood pressure were in the range of a 1-2 mmHg fall in blood pressure for every 75-100 mmols difference in sodium intake, the impact of such a change, applied to the whole population, would be of great importance.

The practical issue for the public, patients, and physicians is, of course, whether the potential hemodynamic benefits of changing sodium intake outweigh other, less desirable effects associated with alterations in dietary sodium.

Blood pressure modestly, but significantly reduces blood pressure in the aggregate, but this is characterized by enormous individual variation in response. In addition to its blood pressure effects, sodium restriction is also known to increase insulin resistance, activate the renin-angiotensin system, and stimulate sympathetic nerve activity. In short, modification of sodium intake has multiple effects. For patients and physicians, as well as for the general population, the important question is how these multiple effects impact on human health.

Unfortunately, only a modest body of even observational data links sodium intake to health outcomes, and, what is available, is inconsistent. Moreover, there is no controlled trial testing the effect of reduced sodium intake on the length or quality of life in either the general population or among hypertensive patients. Absent this critical information, that no single universal prescription for sodium intake can be scientifically justified.

Salt, Surrogate Effects, and Human Health

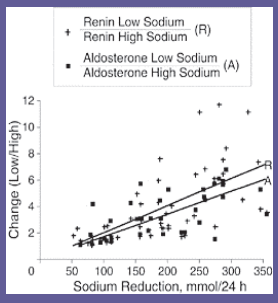
Michael Alderman

Paris, January 12, 2002

Consequences of Variation in Sodium Intake

1. Physiological effects and surrogate endpoints
2. Health Effects in the General Population
3. Role in the Treatment of Hypertension

Effects of Sodium Restriction on Renin and Aldosterone



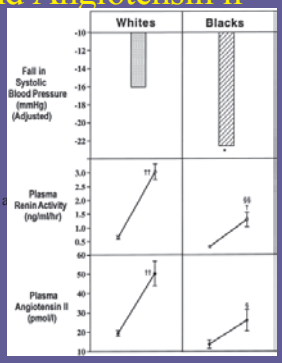
The relation between sodium reduction and change in plasma renin (R) (r_Z=0.43, and P<.001) and change in plasma aldosterone (A) (r_Z=0.41, and P<.001).

.

Graudal NA et al. JAMA. 1998;279:1383-1391

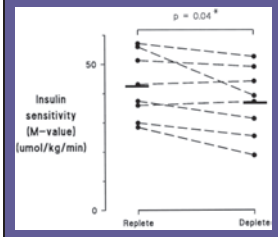
Sodium, BP, and Angiotensin II

- Changes in systolic blood pressure, PRA, and Ang II from the high to the low salt diet in black and white hypertensive patients. *P<0.05 blacks vs whites adjusted for age and systolic blood pressure on the normal diet; P<0.01, P<0.001 compared with the high salt diet; §P<0.05, §§P<0.001 blacks vs whites for the rises in PRA or Ang II from the high to the low salt diet adjusted for age.

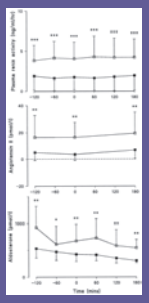


He, Hyp. 1998;32:820

Dietary Sodium Restriction Impairs Insulin Sensitivity in Noninsulin-Dependent Diabetes Mellitus



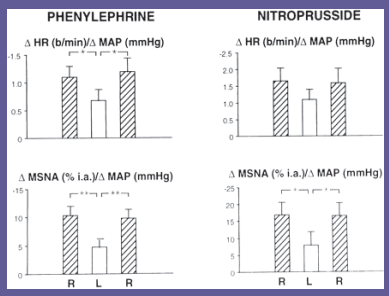
M-value (μmol glucose/kg·min) on sodium replete (160) and sodium deplete (40 mmol)diets. *, P < 0.05.



Mean ± SD PRA, ANGII, and aldosterone, sodium replete vs. deplete; P < 0.05; **, P < 0.01; ***, P < 0.001

PETRIE JR JCEM, 1998;83:1552-1557

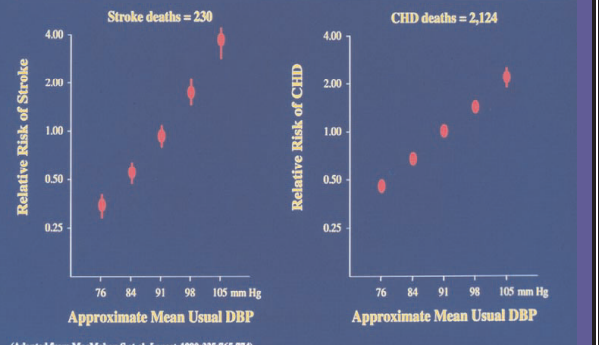
Baroreflex Impairment by Low Sodium Diet in Mild or Moderate Essential Hypertension



Sensitivity of the baroreceptor–(HR) and muscle sympathetic nerve Activity (MSNA) reflex for regular (R), low (L), and regular (R) sodium diets. accompanying changes in mean arterial pressure (MAP) induced by phenylephrine and nitroprusside. Data are from 9 subjects. *P<.05, **P<.01

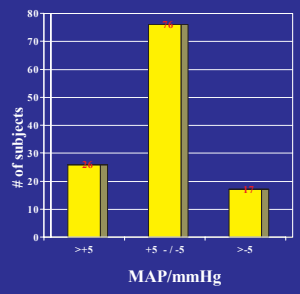
Grassi, G(*Hypertension.* 1997;29:802-807

Relative Risks of Death From Stroke and Coronary Heart Disease



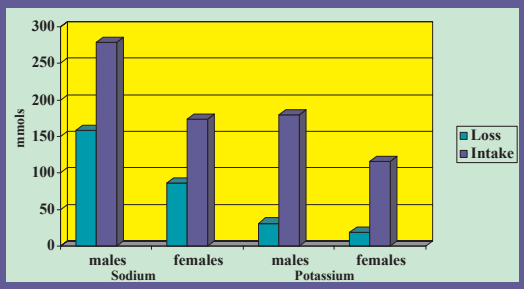
(Adapted from MacMahon S et al. *Lancet.* 1990;335:765-774)

HETEROGENEITY OF BLOOD PRESSURE RESPONSE IN 119 MILD HYPERTENSIVE SUBJECTS



LONGWORTH,CLIN PHARM THER:1980,MacGREGOR,LANCET:1982 AND WATT,BM□J:1983

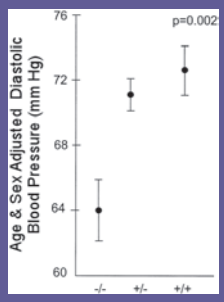
SODIUM BALANCE DURING TENNIS IN HEALTHY YOUNG ADULTS



Bergeron MF. 1995;5:180-93

Mutations in the Na-Cl Cotransporter Reduce Blood Pressure in Humans

Gitelman's Syndrome



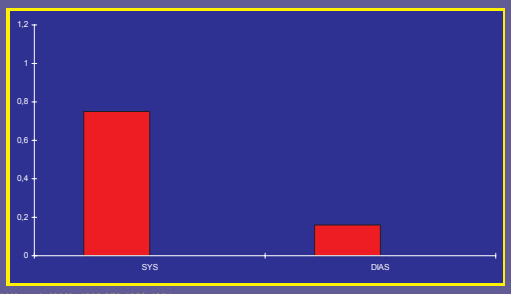
UNa/Cr was 13, 20, 23mmol/mmol (p=.001) in individuals normal(60), heterozygous (113), and homozygous (26) for ***NCCT*** mutations

Individuals homozygous for ***NCCT*** mutations have significantly lower blood pressure than normal relatives. The effect of genotype on systolic blood pressure was also significant and quantitatively similar (*P*=0.038).

Cruz D. Hypertension. 2001;37:1458

Effect of 100 mmols Sodium Reduction on Blood Pressure in Normotensive Subjects

A Meta-analysis of 56 trials



Graudal NA et al. JAMA. 1998;279:1383-1391

SUMMARY

- Multiple physiological effects
- Heterogeneity of effects, determined by genetics, environment, and behavior
- Individual surrogates uncertain predictors of health outcome
- Health impact sum of multiple individual effects

HOW DOES SODIUM INTAKE IMPACT ON HUMAN HEALTH?

ANSWER CAN BE BASED UPON:

AUTHORITY
ECOLOGICAL DATA
OBSERVATIONAL DATA
(5 STUDIES)

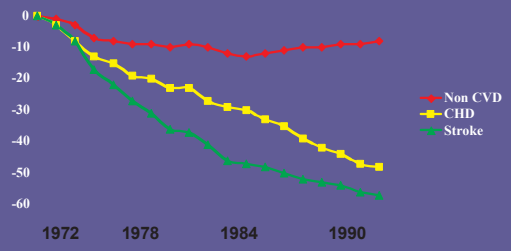
Effects of Sodium Restriction

A Meta-analysis of 56 trials in normotensive subjects.

" These results do not support a general recommendation to reduce sodium intake. .. Further long-term studies of the effects of high reduction of sodium intake on blood pressure and metabolic variables may clarify the disagreements as to the role of reduced sodium intake, but ideally trials with hard end points such as morbidity and survival should end the controversy."

Graudal NA et al. JAMA. 1998;279:1383-1391

% Decline in Age-adjusted Mortality



NCHS data calculated by *NHLBI*

Observational Studies of Sodium Intake and Morbidity/Mortality in the General population

- Scottish Heart Study. BMJ 1997;315:722-29.
- NHANES I. Total Population. Lancet 1998;351:781-85.
- MRFIT. Presented 1/29/99, NIH Conference, Bethesda, MD.
- NHANES I. Obese Subsample. JAMA 1999;282:2027-34.
- Finish Study. Lancet 2001;357:848-51.

SCOTTISH HEART HEALTH STUDY

THE IMPACT OF 27 FACTORS ON DEATH, REVASCULARIZATION, AND MYOCARDIAL INFARCTION IN 11,629, 40-59 YEAR OLD SUBJECTS FOLLOWED FOR 7.6 YEARS WITH MORE THAN 6000 EVENTS

"Sodium excretion did not predict coronary heart disease in men and showed a borderline negative gradient for all deaths, whereas in women it was just positive for all coronary heart disease."

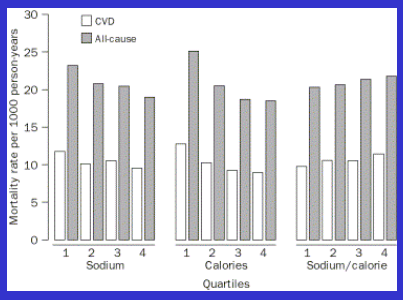
TUNSALL-PEDOE ET AL, BMJ 1997;315:722-729.

NHANES I SODIUM AND MORTALITY: OBESITY SUBSTUDY

	Full Analysis	Obese Subset
Subjects	11,346	9,475
Obese		2,688
Deaths	3,923	1,673
CVD Deaths	1,740	566
Exclusions	None	Hx CVD,Low Na, Mortality

JAMA,1999:282,2027

Dietary sodium intake and mortality: the National Health and Nutrition Examination Survey (NHANES I)



All-cause and CVD mortality rates per 1000 person-years according to quartile of daily sodium intake, total calorie intake, and sodium per calorie intake (adjusted for age and sex)

ALDERMAN et al,LANCET,1998:351;781-785

NHANES 1:OBESE SUBSET

Table 3. Multivariate Relative Risk (95% CI) of Cardiovascular Disease and Total Mortality Associated With a 100-mmol Increase in Dietary Sodium Intake Among Nonoverweight and Overweight Participants*

	Nonoverweight (n = 6797)	Overweight (n = 2688)	*P* Value†
Sodium-to-Energy Ratio (100 mmol/7452 kJ)			
Stroke incidence	0.98 (0.83-1.16)	1.32 (1.07-1.64)	.03
Stroke mortality	0.90 (0.63-1.28)	1.89 (1.31-2.74)	<.001
Coronary heart disease incidence	0.95 (0.83-1.10)	1.06 (0.88-1.29)	.39
Coronary heart disease mortality	1.07 (0.87-1.31)	1.44 (1.14-1.81)	.07
Cardiovascular disease mortality	1.02 (0.85-1.22)	1.61 (1.32-1.96)	.003
Mortality from all causes	1.00 (0.90-1.11)	1.39 (1.23-1.58)	<.001
Dietary Sodium Intake (100 mmol/d)			
Stroke incidence	0.99 (0.81-1.21)	1.39 (1.09-1.77)	.02
Stroke mortality	0.82 (0.55-1.22)	1.98 (1.25-3.14)	.003
Coronary heart disease incidence	0.96 (0.86-1.08)	0.94 (0.76-1.17)	.87
Coronary heart disease mortality	1.07 (0.89-1.28)	1.29 (1.01-1.64)	.22
Cardiovascular disease mortality	1.00 (0.84-1.19)	1.45 (1.20-1.75)	.006
Mortality from all causes	0.98 (0.88-1.09)	1.32 (1.16-1.50)	.002

*Data are stratified by birth cohort and adjusted for age, sex, race, systolic blood pressure, serum cholesterol level, body mass index, history of diabetes, diuretic use, physical activity, level of education, regular alcohol consumption, current cigarette smoking, and total energy intake. CI indicates confidence interval.
†*P* value for interaction between sodium intake and body weight (nonoverweight vs overweight).

He, JAMA,1999:282:2027

Sodium Intake and Morality: The Finnish Study

Cause of death	Hazard ratio (95%CI)*
Normal weight (n=659)	
Cardiovascular (n=29)	1 · 23 (0 · 76–1 · 98)
All causes (n=60)	0 · 98 (0 · 70–1 · 36)
Overweight (n=514)	
Cardiovascular (n=43)	1 · 44 (1 · 02–2 · 04)
All causes (n=76)	1 · 56 (1 · 21–2 · 00)

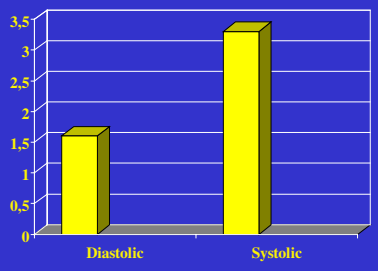
Tuomilehto,Lancet 2001:357:848-51

What are the facts upon which to base a general recommendation regarding dietary sodium?

- **MULTIPLE PHYSIOLOGICAL EFFECTS**
- **THESE DIFFER ACCORDING TO GENETICS, BEHAVIOR, & ENVIRONMENT**
- **ECOLOGICAL DATA DOES NOT ENCOURAGE LOW SODIUM**
- **OBSERVATION DATA INCONSISTANT**
- **EFFECT OF CHANGING SODIUM ON QUALITY AND DURATION OF LIFE UNKNOWN**

THE ROLE OF SODIUM REDUCTION IN HYPERTENSIVE PATIENTS

A meta-analysis of 58 trials



Graudal NA et al. JAMA. 1998;279:1383-1391

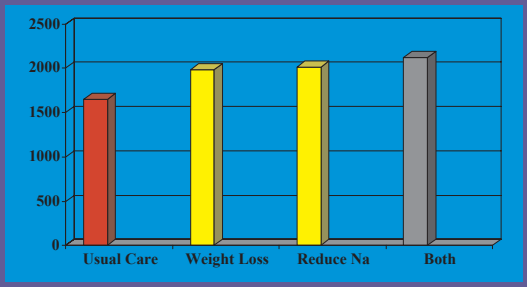
Therapy of Hypertension
Non-Pharmacological v. H˚ CTZ:
(-43 mmols NA, 1.5%Body fat)

	Baseline mmHg	Final mmHg	LVMI
Non-Pharm (16)	141/96	136/92	127 –119
HCTZ (20)	138/95	122/83*	132 - 124

*P<0.05

Cheung,AJH;14:141A

The Cost of TONE



Elliot, AJH 2001:14;141A

THE ROLE OF REDUCED SODIUM INTAKE IN THE TREATMENT OF HYPERTENSION

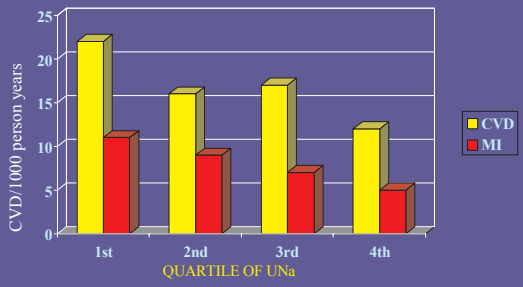
"The goal of .. management of Hypertension is to reduce morbidity and mortality …." JNC VI

"While there is no direct randomized evidence that reducing BP through lifestyle measures reduces the risk of CVD, this seems likely…"
1999 WHO_ISH Guidelines

The Single Observational Study of Sodium Intake and Morbidity/Mortality in Hypertensive Patients

- NYC Hypertensive Subjects.
  Hyp 1995;25:1144-52.

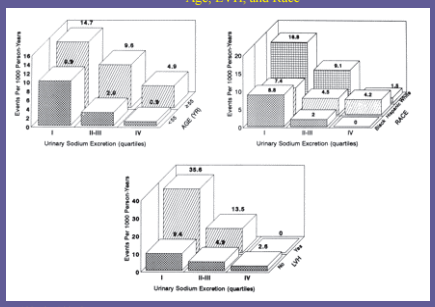
WORKSITE HYPERTENSION STUDY CARDIOVASCULAR EVENTS BY UNa



ALDERMAN, HYPERTENSION, 1995:12;428

Sodium Intake and Myocardial Infarction: The Worksite Study

Age, LVH, and Race



Alderman, Hyp. 1995:25:144-52

STUDIES DEMONSTRATING THAT LOW (OR LOWER) SODIUM INTAKE IS ASSOCIATED WITH IMPROVED HEALTH OUTCOMES IN HYPERTENSIVE SUBJECTS

NONE

SODIUM INTAKE IN TREATMENT OF HYPERTENSION: SUMMARY

1. Less effective than other therapies
2. More costly than other therapies
3. Other therapies proven to reduce morbidity and mortality
3. No evidence that low (or reduced) sodium intake reduces morbidity or mortality

CONCLUSION

1. SODIUM INTAKE HAS **MULTIPLE** AND **HETEROGENEOUS** EFFECTS, INFLUENCED BY **GENETICS**, **BEHAVIOR**, & **ENVIRONMENT**

2. THE **HEALTH IMPACT** OF THESE EFFECTS IS **UNCERTAIN**, BUT PROBABLY **VARIES**

3. IN **ANTIHYPERTENSIVE TREATMENT**, **SODIUM REDUCTION** MAY BE CONSIDERED **IF CONVENTIONAL CARE** IS **INADEQUATE** OR **UNACCEPTABLE**

Une réduction modérée des apports sodés est-elle dangereuse ?

Hugh E. de WARDENER
Charing Cross Hospital, Londres, Royaume-Uni

En toute logique, réduire l'apport en sel à 6 g/jour doit être bénéfique. Durant des millions d'années notre ration quotidienne a été inférieure à 1 g/j (1). Il n'y a que depuis 5 000 a 10 000 ans que les humains ajoutent du sel à la nourriture. En termes d'évolution, nous sommes programmés pour ingérer beaucoup moins de 6 g. Diminuer la ration de sel est donc physiologique. Le chimpanzé, génétiquement notre plus proche parent, presque aussi lourd d'un homme adulte, prospère avec moins de 1 g par jour de sel et ne devient pas hypertendu avec l'âge; il peut vivre jusqu'à 50 ans (2). Et si on leur donne du sel, ils deviennent hypertendus. Rien de surprenant donc, que, chez l'homme, le danger d'un régime n'apportant que 6 g de sel par jour n'ait pas été prouvé. Soutenir le contraire ne repose que sur des faits inexistants ou des interprétations non fondées.

Commençons par les faits inexistants. Muntzel et Drüeke prétendent qu'une réduction modeste de la ration de sel *élève* la pression artérielle d'une fraction significative de la population (3). Une telle conclusion méconnaît la logique des essais cliniques. Examinons avec soin les résultats d'une des expériences sur lesquelles repose ce postulat de Muntzel et Drüeke (4) (Fig. 1).

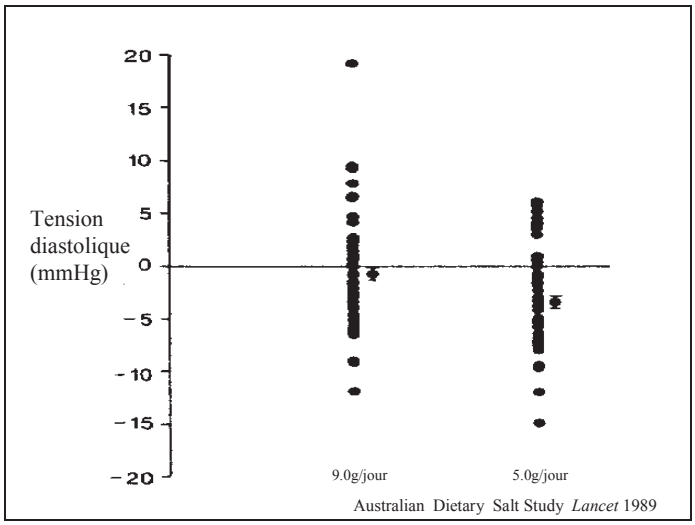
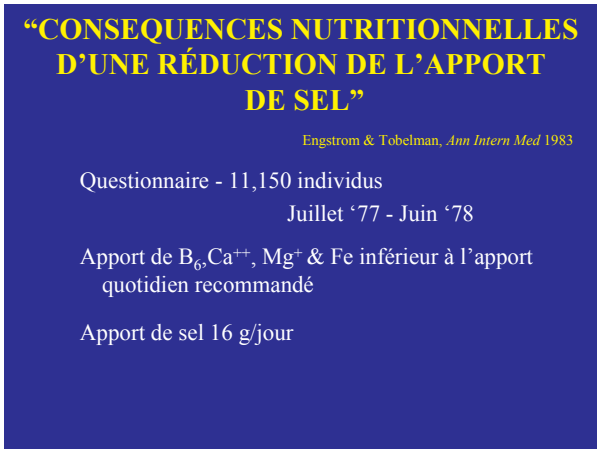


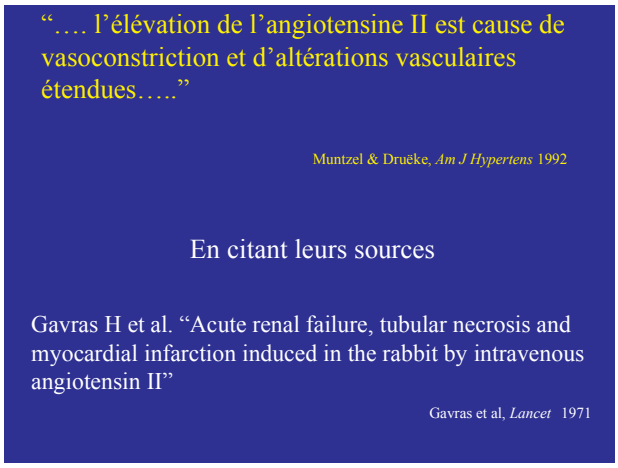
Figure 1. : Altération de la tension diastolique de sujets hypertendus soumis à un apport de sel de 9g ou 5g pendant huit semaines. Australian Dietary Salt Study *Lancet* 1989;399

Ils reproduisent les pressions diastoliques de deux groupes d'hypertendus, d'une part, un groupe témoin soumis pendant 8 semaines à un apport sodé contrôlé de 9 g de sel par jour, et d'autre part un groupe expérimental où l'apport sodé est réduit à 5 g de sel par jour. La pression diminue significativement sous restriction saline mais dans les deux groupes, certains sujets voient leur pression artérielle augmenter. Ces chercheurs semblent ignorer que la pression artérielle fluctue, ce que montrent des mesures répétées. Une pression décalée vers le haut chez quelques sujets en restriction saline, ne suffit pas à créer un lien de causalité alors que la réponse courante est un abaissement significatif. En outre si, selon Muntzel et Drüeke, ces élévations de la pression artérielle sont dues à une ration sodée réduite, quelle serait alors la cause de son augmentation, hors de toute restriction saline, chez les témoins?

Un autre fait est avancé, tout aussi inexistant : une réduction saline modérée aurait un effet pathogène en créant un déséquilibre nutritif. L'argument ne supporte pas la critique, les preuves avancées étant plutôt des contre-arguments (5). Cette étude nutritionnelle repose sur un questionnaire soumis à 11 000 sujets. Un soit-disant déficit en vitamine B6, calcium, fer et magnésium aurait été ainsi révélé. Mais que penser d'un travail sur les conséquences d'une réduction saline quand l'apport en chlorure de sodium est de 16 g/j ? Néanmoins, dans le titre et lors de la discussion, les auteurs rattachent ces modestes anomalies métaboliques à une restriction saline, qui n'existe pas.



Parmi les facteurs incriminés par Muntzel et Drüeke pour expliquer l'effet pathogène supposé du régime hyposodé se trouve la libération de rénine qu'il induit. Ils postulent que l'élévation de la concentration plasmatique d'angiotensine II est à l'origine de vasoconstriction et d'altérations vasculaires étendues. Certes, Gavras et son équipe ont provoqué chez le lapin, par injection intraveineuse de quantités considérables d'angiotensine II, des insuffisances rénales aiguës, des nécroses tubulaires et des infarctus du myocarde (6). Mais cette référence n'a manifestement pas sa place ici, des différences majeures opposant les régimes hyposodés chez l'homme (ou la rénine circulante augmente peu) et l'injection au lapin de doses massives d'angiotensine par voie intraveineuse.



Passons aux études cliniques. Alderman et son équipe ont comparé la fréquence des infarctus du myocarde et la mortalité cardio vasculaire chez des hypertendus, selon la teneur en sodium du régime. Leurs interprétations ne sont pas plus fondées que celles des experimentateurs précédents. Deux études ont été publiées, la première en 1995 (7). Dans un groupe de 3000 hypertendus les auteurs observent une relation inverse entre la fréquence des infarctus du myocarde ou d'autres manifestations cardiaques, et l'excrétion urinaire de sodium des 24 h. Donc ils incriminent la faible consommation habituelle de sel.

Deux biais méthodologiques font rejeter cette conclusion. Le premier est que l'urine des 24 heures a été recueillie après modification du régime, des instructions ayant été données de supprimer les aliments riches en sel dans les jours précédant sa collecte. Voici ce qui figure dans la section *Methods* de l'article : "Il était demandé aux patients, de suivre leur régime habituel, tout en évitant les aliments riches en sel, pendant les 4-5 jours précédent le recueil de leurs urines des 24 heures" (7). Cet extrait nous dispense de commenter les chiffres supposés évaluer l'apport sodé habituel de ces patients.

Alderman MH, Madhavan S, Cohen H, Sealey JR & Laragh JH

"Une faible excrétion urinaire de sodium est associée avec un plus grand risque d'infarctus du myocarde chez les hommes hypertendus sous traitement"

Alderman et al, *Hypertension* 1995

"Il était demandé aux patients de suivre leur régime habituel tout en évitant les aliments riches en sel pendant les 4-5 jours précédant le recueil de leurs urines de 24h"

Alderman et al *Hypertension* 1995

Le second biais méthodologique tient à la difficulté d'obtenir un recueil exact des urines de 24h. Les auteurs regroupent les patients selon leur natriurèse des 24h en quartiles. Le premier groupe des hommes hypertendus, excrètent moins de 3.8 g de sel par jour.

HYPERTENDUS (Hommes)

Quartile	476	466	462	472
Débit de sel urinaire g/jour	3.8	6.25	8.7	12.8

N'est-il pas paradoxal que ce chiffre de 3.8 g soit grossièrement la moitié de la ration aujourd'hui recommandée? Pour réduire à ce point le sodium urinaire, tout aliment préparé de façon industrielle doit être écarté, y compris, et surtout, le pain, et cela par la seule volonté du patient : ceci n'est pas croyable. Un autre facteur intervient donc. Le plus courant dans les études métaboliques est le recueil des urines de 24h, rarement exact même chez les patients alités à l'hôpital. C'est d'ailleurs ce que suggère les chiffres de la clairance de la créatinine, car ils sont parallèles (dans tous les quartiles) à ceux de l'excrétion urinaire de sodium. Le soupçon est devenu certitude quand ultérieurement ont été connus les chiffres de la créatininurie des 24 heures (Tableaux ci-après). Il fut alors avéré que le débit urinaire de créatinine était parallèle à la clairance de le créatinine, ce qui démontre que la récolte imparfaite des urines était à l'origine des variations de la clairance de la créatinine. La créatininurie des 24 heures devrait être constante.

HYPERTENDUS (Hommes)

Quartile	476	466	462	472
Débit de sel urinaire g/jour	3.8	6.25	8.7	12.8
Clairance de la créatinine ml/min	77	88	95	108

HYPERTENDUS (Hommes)

Quartile	476	466	462	472
Débit de sel urinaire g/jour	3.8	6.25	8.7	12.8
Clairance de la créatinine ml/min	77	88	95	108
Créatininurie mg/24h	1267	1414	1563	1760

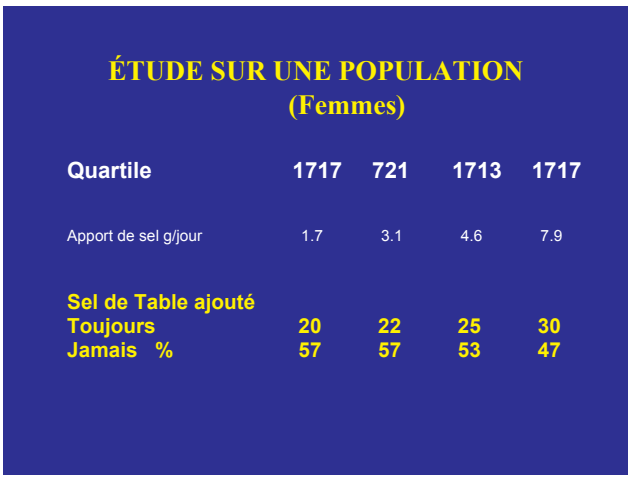
Ce travail ne peut être pris en considération car la répartition en quartiles de la population d'hypertendus, selon le débit urinaire de sodium par 24 heures, souffre d'erreurs fondamentales. L'une est que la quantité de sodium excrétée le jour de l'épreuve n'est pas celle ingérée habituellement, certains aliments riches en sels ayant été écartés. L'autre est que le recueil de l'urine des 24 heures est manifestement inexact. Si bien qu'il est illusoire d'utiliser la natriurèse des 24 heures pour espérer mesurer la teneur habituelle du régime en ce cation. Donc les quartiles sur lesquels repose cette première étude ne permettent pas d'avancer qu'il existe chez les hypertendus une relation inverse entre l'apport de sodium et la fréquence des infarctus du myocarde.

En 1998, M. Alderman et son équipe ont publié un autre article reposant cette fois sur une seule donnée, un seul rappel de l'alimentation courante des 24 heures. Ils voulaient ainsi mesurer la valeur calorique et la teneur en chlorure de sodium habituelles du régime de 11 348 patients, entre 1971 et 1975, suivis cliniquement 20 ans plus tard (8). La méthode était pleine d'embûches. Comme on pouvait le prévoir, les sujets avaient gardé une idée floue de leur alimentation d'alors. Les résultats furent classés selon la natriurèse des 24 heures en quatre groupes. Les tableaux ci-après montrent les résultats obtenus chez les femmes.

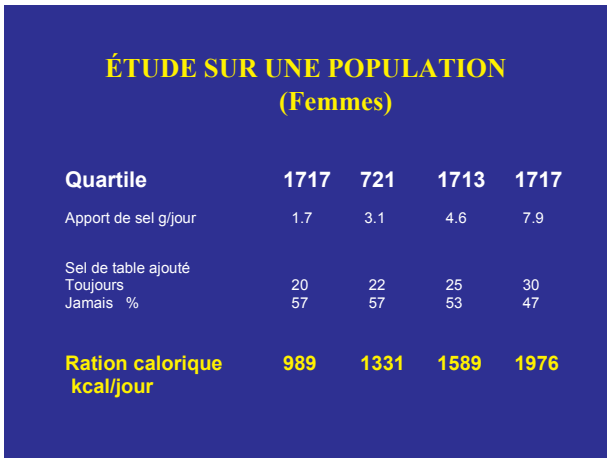
ÉTUDE SUR UNE POPULATION (Femmes)

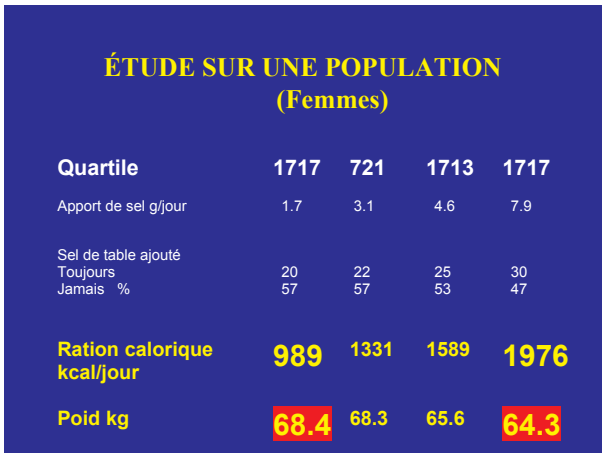
Quartile	1717	721	1713	1717
Apport de sel g/jour	1.7	3.1	4.6	7.9

Ces chiffres sont encore moins crédibles que ceux de la publication précédente. La moitié des sujets étudiés parait n'avoir consommé qu'au plus 3 g de sel par jour et un quart des sujets aurait consommé moins de 2 g/j, ce qui n'est pas crédible. Il est vrai que ces chiffres ne tiennent pas compte du sel ajouté à la nourriture qui, dans les années 70, représentait jusqu'à 50% des apports totaux. La seule information sur le sel ajouté est "toujours" ou "jamais". La moitié des femmes indiquaient ne pas ajouter de sel de table. Si tel est le cas, 1414 femmes avaient une alimentation comportant moins de 3 g de sel par jour. Cela est si peu vraisemblable qu'il n'est pas logique d'en tenir compte.



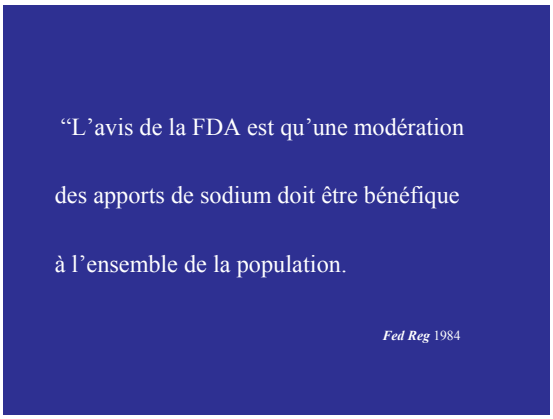
Maintenant passons à la ration calorique : les chiffres suivent ceux relatifs à l'apport de chlorure de sodium et suscitent des remarques identiques. Avec bon sens et humour, Engelman (9) et Karppanen et Mervaala (10) s'étonnent de tant de femmes du premier groupe survivant 20 ans à une ration calorique inférieure à 1000 calories. Et, il est véritablement stupéfiant de noter que les mêmes femmes de ce groupe pèsent 4 kg de plus en moyenne que celles du quatrième groupe dont la ration calorique est la plus élevée (presque 2000 calories par jour). On peut conclure qu'il est impossible de faire confiance aux donnés recueillies.

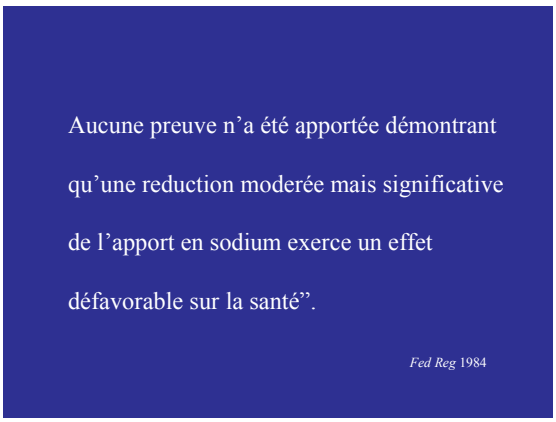




Pour conclure ces deux analyses critiques, il convient d'indiquer que le prétendu danger de la diminution modérée de l'apport alimentaire en sodium (en particulier en terme d'évènements cardiovasculaires) est une illusion, fruit d'une méthodologie très défectueuse, due avant tout à un recueil inexact des urines des 24 heures ou à des données anamnestiques, impossibles à vérifier, donc sans valeur scientifique.

On peut donc affirmer que les deux conclusions de la « Food and Drug Administration » (FDA) des États Unis, formulées en 1984, sont toujours de mise : "L'avis de la FDA est que des apports de sodium modérés doivent être bénéfiques à l'ensemble de la population. Aucune preuve n'a été apportée montrant qu'une réduction modérée mais significative de l'apport en sodium exerce un effet défavorable sur la santé" (11).





References

1. Eaton SB & Konner M. Paleolithic nutrition. *N Eng J Med* 1985;312:283-288.

2. Denton O, Weisinger R, Mundy NI et al. The effect of increase salt intake on blood pressure of chimpanzees. *Nature Med* 1995; 1:1009-1 QI 6.

3. Muntzel M & Druëke TA. A comprehensive review of the salt and blood pressure relationship. *Arn J Hypertens* 1992;5:IS-42S.

4. Australian National Health and Medical Research Council Dietary Salt Study Management Committee. Fail in blood pressure with modest reduction in dietary salt intake n mild hypertension. *Lancet* 1989;1:399402.

5. Engstrom AM & Tobelmann R. Nutritional consequences of reducing salt intake. Ann *Intern Med* 98:870-872.

6. Gavras H, Brown JJ, Lever AF et al. Acute renal failure, tubular necrosis and myocardial infarction induced in the rabbit by intravenous angiotensin II. *Lancet* 1971 ;ii:19-22.

7. Alderman MH, Madhaven S, Cohen H. et al. Low urinary sodium is associated with greater risk 0f myocardial infarction among treated hypertensive men. *Hypertension* I 995;25:1 144-1152.

8. Alderman MH, Cohen H, Madhaven S. Dietary sodium intake and mortality. The National Health and Nutrition Examination survey (NHANES 1). *Lancet* I 998;351 :781-785.

9. Engelman K. Sodium intake and mortality (Letter). *Lancet* 1998;351:1509.

10. Karppanen H & Mervaala E. Sodium intake and mortality. (Letter). *Lancet* 1998;351 :1509.

11. Food and Drug Administration: Food labelling: declaration of sodium content of foods and label claims for foods on the basis of sodium content: final rule. *Fed Reg* I 984;49(76):51 0-535.

Sel et traitement anti-hypertenseurs

Albert MIMRAN
Hôpital La Peyronie, Montpellier, France

Tous les traitements hypertenseurs ont été accusés d'induire une expansion du volume extracellulaire qui peut être mesurée par le poids. En répondant aux questions qui me sont adressées par mes patients, je m'aperçois que beaucoup d'entre eux ne savent pas que le sodium peut être mesuré dans les urines. Tout traitement hypertenseur est susceptible d'induire une rétention de sodium. Il est donc nécessaire de veiller à réduire l'apport de sodium.

Les traitements anti-hypertenseurs en monothérapie permettent de réduire la pression systolique d'environ 6 mm Hg.

Il a été montré que l'addition d'hydrochlorothiazide (HCTZ) ou la réduction de l'apport de sodium de 200 à 80 mmol auraient un effet identique sur la pression artérielle chez les patients hypertendus traités par un inhibiteur de l'enzyme de conversion.

Une réduction drastique de l'apport du sodium combinée à la prescription d'agents hypertenseurs se traduit souvent par à la fois une modification excessive de la pression artérielle de repos et la détérioration de la fonction rénale.

Les traitements anti-hypertenseurs visent à réduire la pression artérielle. Cette réduction permet de protéger les organes cibles, et donc de réduire la mortalité. Au-delà des modifications de pression, le traitement peut avoir un effet protecteur.

Les médicaments ayant l'effet le plus marqué sur la masse ventriculaire gauche sont les inhibiteurs du système rénine-angiotensine. Lors d'une étude que nous avons récemment réalisée dans le sud de la France, nous avons pu observer que 40 % des hommes excrètent plus de 172 mmol par 24 heures et que 40 % des femmes excrètent plus de 130 mmol par 24 heures.

Concernant le ventricule gauche, nous avons observé une augmentation de la pente de la relation entre la pression systolique et l'indice de masse ventriculaire gauche. Ce résultat signifie que le sodium alimentaire amplifie la réponse de l'organe cible à une élévation de pression. Il en va de même pour la micro-albuminurie.

Lorsque des hypertendus sont traités avec des médicaments contenant un inhibiteur du système rénine-angiotensine, un certain nombre d'entre eux voient leur pression artérielle diminuer alors que la masse ventriculaire gauche reste inchangée.

Nous avons identifié deux groupes de 17 patients traités par une thérapie contenant un inhibiteur de l'hypertension. Le suivi de ce groupe s'est déroulé sur une période de 30 mois. Le premier groupe présente une réponse appropriée puisque les sujets ont vu leur pression artérielle systolique diminuer et la masse de leur ventricule gauche s'est réduite de plus de 10 %. Le second groupe présentait une réponse inappropriée puisque la pression systolique des sujets observés a diminué également de plus de 10 % mais la masse du ventricule gauche est restée inchangée.

Nous avons observé chez les sujets à réponse appropriée une réduction de 70 mmol de l'apport de sodium, alors que nous n'avions donné aucune consigne particulière. Cette

réduction correspond à une diminution de 25 % de l'apport de sodium. Une telle diminution correspond généralement à la quantité de sel que les personnes ajoutent avant de goûter leur nourriture. Il est donc possible que les patients suivis aient supprimé cette habitude.

La réduction de l'apport sodé chez les patients hypertendus me paraît importante. Par ailleurs, le sodium constitue non seulement un facteur d'élévation de la pression artérielle systolique, mais également un facteur de modulation de l'interaction entre la pression artérielle et les organes cibles. Enfin, dans des conditions particulières, l'effet favorable obtenu chez ces patients est souvent lié à la médication et à la réduction de l'apport de sodium.

De la salle

Je suis néphrologue et je suis très intéressé par les questions relatives aux collectes de l'urine des 24 heures. Le Dr. De Wardener a mis l'accent sur la collecte incomplète des urines. Je tiens à dire que la collecte excessive est également problématique. Il est donc important de prendre en compte ces deux travers. Par ailleurs, le Dr. De Wardener a fait référence à l'article d'Engstrom. Il me semble qu'il a fait un calcul erroné en ce qui concerne la consommation de sodium. En effet, j'ai procédé à un calcul identique qui m'a permis d'aboutir à un résultat correspondant à la moitié du chiffre avancé.

Hugh E. De WARDENER

Si la consommation de sodium n'est pas correctement mesurée, il n'est pas possible de faire d'hypothèses correctes. Concernant votre deuxième point, il me semble que les auteurs de l'étude ont commis quelques erreurs.

De la salle

Je souhaiterais revenir sur l'intervention du Dr. Alderman, et plus particulièrement sur ce qui concerne l'activation sympathique. Lors d'une rencontre organisée à Milan sur le thème de l'hypertension, le Pr. Grassi a fait une présentation au cours de laquelle il a montré que si la durée de l'étude était prolongée d'une à trois semaines, l'activation sympathique était beaucoup moins importante. Ces résultats ont peu de liens avec les recommandations de réduction de l'apport en sel destinées à la population générale. En effet, cette réduction doit être à la fois modérée et durable. Aucune preuve n'a été apportée sur le fait que ce type de réduction se traduirait par une activation sympathique. Certains essais chez les animaux ont même montré qu'une réduction de l'activation sympathique était possible.

Michael H. ALDERMAN

Je ne connaissais pas ces données. Elles sont intéressantes. Elles n'ont effectivement aucun lien avec les recommandations de santé publique. Il s'agit en réalité de résultats intermédiaires qui ne doivent en aucun cas être généralisés.

Par ailleurs, je tiens à revenir sur la critique formulée par le Pr. De Wardener à l'encontre de notre étude portant sur la consommation de sodium chez les patients hypertendus. Il a notamment précisé que, compte tenu du fait que les patients devaient éviter la consommation d'aliments riches en sel avant la collecte des urines des 24 heures, il ne fallait pas tenir compte des résultats obtenus. Je pense qu'il a voulu dire que cette recommandation introduisait un biais. Selon moi, nos consignes auraient pu, dans une certaine mesure, biaiser les résultats si plus de patients avaient réduit plus significativement leur consommation de sel. Il est à noter que nos études ont montré que les personnes ayant respecté au mieux nos consignes sont celles qui ont obtenu les meilleurs résultats.

Je pense que le point de vue du Pr. De Wardener est différent. Il me semble en effet qu'il suggérait que les patients devant avoir une crise cardiaque le savaient. Ils faisaient donc

en sorte que la teneur en sel de leur alimentation soit la plus faible possible. Comme il existe une relation inverse entre le taux de sodium et la probabilité d'occurrence d'une crise cardiaque, ces patients devaient agir de manière très précise afin d'obtenir les résultats inverses. Dans un monde de conspiration, une telle situation est possible, mais demeure fort peu probable. En revanche, la réalité a été plus probable puisque notre avis a eu peu d'impacts. Ainsi les collectes des urines des 24 heures chez des individus à Chicago et New York ont été identiques – la valeur de l'écart-type était la même. De 1981 à 1988, nous avons cessé de demander aux patients de limiter leur consommation de sel avant la collecte. Une hausse de la prise de sodium de 8 % a alors été observée.

Les études d'observations sont limitées en nombre et souffrent d'un certain nombre de défauts. Toutefois, plus les études sont nombreuses, plus les résultats sont significatifs. La question n'est donc pas de savoir si notre étude apporte la bonne réponse. Le point important est plutôt que davantage de données soient disponibles.

De la salle

Ma question s'adresse au Pr. Alderman. Je me demande si vous vous souvenez avoir signé une pétition rédigée par l'Institut du Sel (Etats-Unis) qui a été adressée il y a quelques années à la FDA. Cette pétition a été signée par plusieurs autres personnes présentes aujourd'hui à ce colloque. Dans ce document, il était indiqué que la réduction de la consommation de sel pouvait entraîner des crises cardiaques. Partagez-vous toujours cet avis ?

Michael H. ALDERMAN

Je n'ai jamais partagé un tel avis.

De la salle

Je souhaiterais revenir sur les remarques faites à propos des collectes des urines des 24 heures. Il est clair que ces collectes peuvent être incomplètes ou excessives. Pour ce type de mesure, il convient de mesurer la créatinine. Si vous établissez une corrélation entre le sodium urinaire et la pression artérielle systolique, tout en tenant compte de la créatinine, les résultats obtenus sont parfaitement corrigés.

Albert MIMRAN

Il faut savoir que la créatinine est plus faible chez les femmes que chez les hommes.

De la salle

Dans ce cas, il convient de séparer les hommes et les femmes.

Albert MIMRAN

Nous avons effectivement procédé à des essais séparés. Toutefois les résultats obtenus sont très différents de ceux que je vous ai montrés.

De la salle

Je voudrais apporter un point de vue de physiologiste aux débats portant notamment sur la clairance. De nombreux chercheurs s'accordent pour dire que davantage de données sont nécessaires. C'est pourquoi je voudrais vous encourager à indiquer dans vos articles les mesures relatives à l'excrétion du sodium et au volume de fluides, en particulier des urines. Je vous demanderais également d'indiquer la valeur de l'excrétion de l'urée, qui permet de connaître le niveau d'apport de protéines. L'urine est hyper-osmotique par rapport au plasma et l'urée est l'élément le plus concentré dans l'urine. La concentration de l'urée dans l'urine nécessite une certaine réabsorption du sodium au niveau rénal. J'espère que dans vos prochaines études, qu'elles soient conduites à petite ou à grande échelle, vous rapporterez les données relatives non seulement à l'excrétion urinaire de sodium, mais aussi celles concernant le débit urinaire et l'excrétion de l'urée.

Albert MIMRAN

Ces données figurent dans nos articles.

De la salle

Mon commentaire s'adresse au Dr. Alderman. Concernant l'étude écossaise relative aux maladies cardiovasculaires, je tiens à vous dire que nous avions invité le Dr. Tunsall-Pedoe, qui n'a pu venir. Toutefois il nous a fait part d'une information : chez les hypertendus et les obèses, un effet de la consommation de sel sur la morbidité et la mortalité cardiovasculaires a été mis en évidence. Cette information fera prochainement l'objet d'une publication.

Michael H. ALDERMAN

Cette information soutient mon propos : j'essayais justement de montrer qu'il existait une réelle hétérogénéité. Toutes les études publiées (il convient de se réjouir de leur nombre croissant) confirment cette hétérogénéité qui pose la question de la pertinence des recommandations universelles.

De la salle

Je souhaiterais apporter un complément de réponse à une question précédente : le Dr. Alderman ne se souvient sans doute pas d'avoir signé la pétition adressée à la FDA pour la simple raison qu'il ne l'a pas signée. Il a en revanche signé une autre pétition dont le contenu était différent de celle à laquelle il était fait référence. Cette autre pétition, qui a été publiée dans plusieurs revues de nutrition, visait à témoigner du fait que les acteurs de l'industrie, d'anciens présidents de grandes organisations internationales et des scientifiques étaient d'avis que l'intérêt d'une réduction générale de la consommation de sel n'avait été montré par aucune étude scientifique.

De la salle

Pour chaque recommandation de santé publique que nous formulons, il existe une hétérogénéité de réponses. Il semble toutefois que la réduction de la consommation de sel soit généralement bénéfique pour la population dans son ensemble.

Salt intake and the risk of CHD and stroke

Ivan J. PERRY[3]
University College, Cork, Ireland

Abstract

Diet is undoubtedly a major contributor to variation in the occurrence of hypertension and cardiovascular disease, including stroke, worldwide. We have substantial and compelling evidence from observational epidemiological studies, animal models, and randomised controlled trials in hypertensives and normotensives that dietary salt intake plays a critical role in blood pressure regulation. Thus, insofar as salt intake is a contributory factor in the development of essential hypertension, it also contributes to the burden of morbidity and mortality from CVD. However the question of whether high dietary salt intake increases risk of CVD, either indirectly via effects on blood pressure or indirectly via alternative mechanisms, has received less attention. There is accumulating evidence that high salt intake predicts left ventricular hypertrophy, independent of other variables including body mass index and blood pressure. Data are now available from nine different studies worldwide consistent with a significant independent effect of salt intake on left ventricular hypertrophy. It is suggested that impaired suppression of the renin-angiotensin II system in response to salt loading acts as a stimulus for myocardial hypertrophy in hypertensive patients. There is also evidence that a high salt intake enhances cardiac sympathetic activity, an additional factor in the development of left ventricular hypertrophy. There is also evidence from animal experiments and ecological studies of an independent association between salt intake and risk of stroke. However, data from prospective observational studies on the relation between sodium intake and cardiovascular endpoints (including stroke) are less consistent. To date this hypothesis has not been comprehensively addressed in studies with adequate power, i.e. with valid and reliable measurements of dietary salt exposure and a substantial number of stroke end-points. Alderman and colleagues have presented data from NHANES 1 suggesting that there may be a significant inverse association between urinary sodium excretion and risk of cardiovascular disease. These analyses have provoked considerable controversy. In a number of prospective studies no association between salt intake and cardiovascular disease end-points (including stroke) has been observed. However, in further analyses from the US NHANES follow-up study, there was evidence that high salt intake is strongly and significantly associated with risk of stroke, other cardiovascular disease and all cause mortality in overweight persons, but not in those of normal weight. In a recent prospective study based on a Finnish cohort, Tuomilehto and colleagues observed significantly increased hazard ratios for coronary heart disease, cardiovascular disease and all-cause mortality, associated with a 100 mmol increase in 24 h urinary sodium excretion in both men and women. These findings on salt intake and major CVD endpoints need to be replicated in other populations. In summary, current data on the association between salt intake, blood pressure, left ventricular hypertrophy and CVD events support public policy

[3] **Correspondence:**
Ivan J Perry, Professor of Public Health
Department of Epidemiology & Public Health,
Distillery House, University College Cork,
Republic of Ireland.
Phone: +353-21-904234
Fax: +353-21-904236
e-mail: i.perry@ucc.ie

recommendations on the need for a moderate reduction in dietary salt intake at the population level.

Introduction

Cardiovascular disease, including both coronary heart disease and stroke, are major causes of death in both developed and developing countries. Diet is a major contributor to variation in the occurrence of cardiovascular disease worldwide. There is a substantial body of work on the role of dietary salt intake and on the ratio of dietary sodium to potassium consumption in the development of essential hypertension. [1, 2] There is also evidence from observational epidemiological studies that increased dietary potassium intake reduces the risk of stroke. [3] By contrast, the possibility of a link (indirect or direct) between salt intake and major cardiovascular disease events, has received less attention. Essential hypertension is clearly a major risk factor for cardiovascular disease including coronary heart disease and stroke. [4] Thus, insofar as salt intake is a contributory factor in the development of essential hypertension it will also contribute to the burden of cardiovascular disease incidence and mortality. The evidence linking salt intake with essential hypertension will be considered briefly in this review, together with evidence linking salt to hypertensive target organ disease in the heart and brain, specifically, left ventricular hypertrophy, myocardial infarction and stroke.

Salt and blood pressure

The contribution of dietary factors such as salt to the rise in blood pressure with age and the development of essential hypertension has been difficult to elucidate due to the poor precision (or reliability) with which dietary exposures are measured in free living subjects and the limited range of dietary exposures in most populations. There is also the problem of multi-collinearity, i.e. the tendency for dietary elements such as sodium, potassium and fat to be inter-correlated at both the individual and population level. Despite these difficulties however, the evidence that salt intake plays a critical role in blood pressure regulation is now overwhelming. [2] The evidence from diverse sources, including observational epidemiological studies [15 6], animal models [7], and randomised controlled trials in hypertensives and normotensives, all points in the same direction. [8 9 10 11]

INTERSALT study

In the INTERSALT study, a study of over 10,000 subjects (men and women aged 20-59 years) in 52 different population groups in 32 countries, positive associations between urinary sodium excretion (a marker of salt intake) and blood pressure were observed within and between populations. [5 1] Within populations, individuals with higher sodium excretion tended to have higher blood pressure and in the across population, ecological analyses, populations with higher mean sodium excretion had higher mean blood pressures. In men and women at all ages it was estimated that a 100 mmol/day increase in sodium intake was associated with an average increase in systolic blood pressure of 3 mmHg adjusted for obesity and 6 mmHg unadjusted for obesity. [1] Estimates of association were larger for older people (40-59 years) than for younger people (20-39 years). A key finding from this study was a consistent and highly significant association of sodium excretion across populations with the slope or rise of blood pressure with age.

Animal and experimental data

In virtually all mammals, high blood pressure is caused or aggravated by a high salt intake. For example, it has been shown in chimpanzees that an increase in salt intake from 0.5 grams daily (their usual intake) to a level between 9 and 15 grams daily (our usual intake), leads to a substantial increases in blood pressure [7].

The best evidence for the role of salt in blood pressure comes from randomised control trials and from a classic community intervention trial in Portugal[11]. In a randomised control trial involving 500 newborn infants in the Netherlands, it was found that infants given formula milk and solids with reduced salt content had significantly lower blood pressure at six months of age relative to a control group on a standard infant diet [8]. Intriguingly, on re-examination of a subgroup of these children at age 15 years, there was evidence that the beneficial effects of early salt restriction on blood pressure persisted into adolescence.[12] Law and colleagues, in a meta-analysis of 78 trials of the effect of sodium intake on blood pressure, reported that the effect of sodium restriction of at least 5 weeks duration were consistent with the observational epidemiological data. [9] It was estimated that in people aged 50 – 59 years, a reduction in daily salt intake of about 3 grams, attainable by moderate dietary salt reduction, will lower systolic blood pressure by an average of 5 mmHg. An average reduction in blood pressure of this magnitude in the general population of most western countries would reduce the incidence of stroke by 25% and the incidence of ischaemic heart disease by 15%. Thus the potential clinical and public health impact of relatively modest salt restriction is substantial.

Reductions in salt intake may be of particular benefit in the elderly. Cappuccio and colleagues have shown that a reduction in salt intake from approximately 10 grams to 5 grams daily over one month in a group of men and women aged 60 – 78 years, is associated with an average fall in systolic blood pressure of 7 mmHg.[10] These effects, which were seen in normotensive and hypertensive subjects, translate into an estimated 36% reduction in stroke risk over a 5 year period in this age group. Given the high underlying incidence of stroke in the elderly, a reduction in stroke incidence of this magnitude (more than one third), would represent a public health triumph. In this, as in other similar studies, there was no evidence of a distinct subgroup of so called salt-sensitive subjects. The latter concept, much favoured by the food industry, that a well-defined minority of the population is salt-sensitive, with the rest relatively immune, has now been largely discredited. [2]

In the community intervention trial in Portugal, the salt intake of an entire village was reduced by reducing salt in cooking and in processed food, including bread. At the end of the observation period, blood pressure was significantly lower than in a control village. [11]

Problems with the salt -blood pressure hypothesis

In INTERSALT, the magnitude of the effect on blood pressure over a substantial range of sodium excretion (100 mmol/day, approximately 6 grams) was small and was further attenuated on adjustment for body mass index. The effect size estimate was also inflated by a controversial adjustment for “regression dilution bias” or imprecision in the measurement of salt intake and blood pressure. [1] Measurement imprecision affecting both exposure and outcome is undoubtedly a critical issue in observational studies of diet and blood pressure. However, the findings from INTERSALT, essentially a cross-sectional snapshot of the relation between salt and blood pressure, are supported by evidence from animal [7] and experimental studies. [9]

It is argued that the magnitude of effect of salt intake on blood pressure, an average increment of between 3 and 6 mm Hg per 100 mmol of sodium per day, is clinically trivial. From the population perspective however, small downwards shifts in mean blood pressure are associated with substantial reductions in both the proportion of hypertensives in the upper tail of the distribution and in hypertension related morbidity and mortality. As discussed above, it is estimated that a sustained reduction in mean systolic blood pressure of 5 mmHg in a typical western country would reduce the incidence of stroke by 25% and the incidence of ischemic heart disease by 15%. The substantial public health impact of relatively small decrements in population mean blood pressure reflects the fact that usual levels of blood pressure are directly and continuously related to the risks of both stroke and CHD across the entire distribution of blood pressure in the population.

It is also argued that the data from intervention studies (the Salt restriction trials) are based on short-term follow-up and we lack data on the effects of prolonged sodium restriction on blood pressure and CVD risk. [13] Given the consistency of the observational data in man and the animal experiments it seems biologically implausible that the effects of sodium restriction on blood pressure will be attenuated on long term follow-up. However, this is an important clinical and public health issue that should be addressed in future trials.

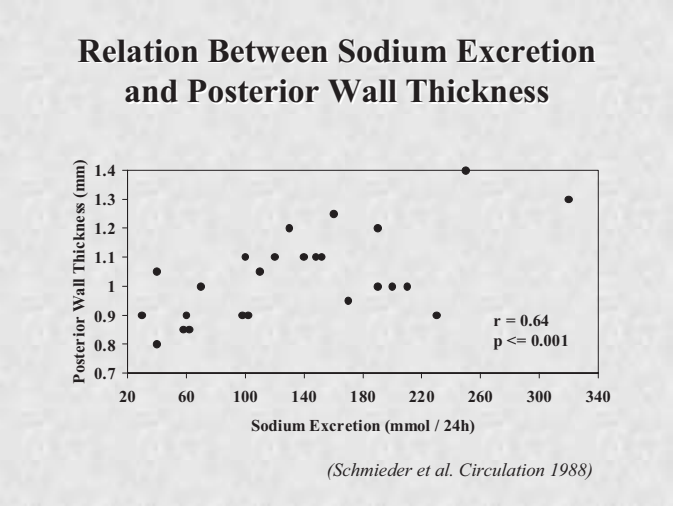
Salt and left ventricular hypertrophy

It is suggested that associations between sodium intake and blood pressure in cross-sectional studies are attenuated by measurement imprecision reflecting large intra-subject variation in both salt intake and blood pressure. One might expect therefore to find stronger associations between sodium intake and stable indices of hypertensive end-organ damage such as left ventricular hypertrophy. Consistent with this hypothesis, there is accumulating evidence that high salt intake predicts left ventricular hypertrophy [14].

Studies Showing a Correlation Between Dietary Sodium Intake and Left Ventricular Mass

		PWT		LVM or LVMI	
Source	Country	r	p	r	p
Schmieder et al, [13] 1988	United States	0.64	<.001	0.37	.01
du Cailar et al,[14] 1989	France	0.48	<.005	0.44	<.005
Schmieder et al,[15] 1990	Germany	0.30	.11	0.35	<.05
Daniels et al,[12] 1990	United States	....	....	0.39	<.001
du Cailar er al,[16] 1992	France	0.21	<.05	0.22	<.01
Liebson et al,[17] 1993	United States	....	<.001	....	.001
Kupari et al,[18] 1994	Finland	....	....	0.61	<.001
Gerdts et al,[19] 1996	Norway	....	....	0.49	<.01
Schmieder et al,[20] 1996	Germany	0.44	<.001	0.43	<.001

Schmieder and colleagues examined the relation between dietary salt intake, assessed by 24-hour urinary sodium excretion and indices of left ventricular structure in a group of 42 patients with mild essential hypertension. [15] 24-hour urinary sodium excretion was a strong independent determinant of posterior wall thickness ($r = 0.64$ $p<0.001$), relative wall thickness ($r = 0.67$ $p<0.001$) and left ventricular mass ($r = 0.37$ $p<0.05$).

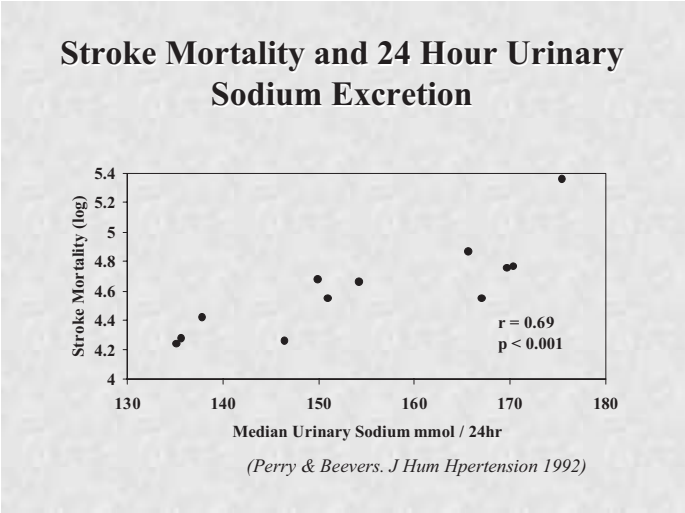


In this study a substantial range of potential predictors of left ventricular structure were examined including body mass index, systolic, diastolic, and mean arterial pressure, cardiac output, plasma catecholamines, renin, angiotensin and aldosterone concentrations. In univariate analyses, sodium excretion was the only variable that was significantly associated with all of the measured indices of left ventricular structure (septal, posterior and relative wall thickness and left ventricular mass. In multiple regression analysis sodium excretion emerged as the most powerful determinant of left ventricular wall thickness, independent of other variables including body mass index and blood pressure. [15] In subsequent work from the same group salt intake predicted left ventricular hypertrophy in analysis adjusted for 24-hour ambulatory blood pressure.[16] In this study, patients with high angiotensin II concentrations in relation to sodium excretion had a greater left ventricular mass, posterior wall thickness, and septal wall thickness than those with "relatively low" angiotensin II levels in relation to sodium excretion. This suggests that impaired suppression of the renin-angiotensin II system in response to salt loading acts as a stimulus for myocardial hypertrophy in hypertensive patients. There is also evidence that a high salt intake enhances cardiac sympathetic activity, an additional factor in the development of left ventricular hypertrophy. [14] Data are now available from nine different studies world-wide consistent with a significant independent effect of salt intake on left ventricular hypertrophy.[15-21 14] There is also evidence that dietary salt restriction is effective in reducing left ventricular mass. In the TOMHS study, changes in urinary sodium excretion together with changes in weight and blood pressure were positively and significantly related to changes in left ventricular mass.[22]

Salt intake, CHD and stroke

There is also evidence from animal experiments [23, 24] and ecological studies [25 26 27] of an independent association between salt intake and risk of stroke. Tobian and colleagues have described a significant increase in stroke (cerebral infarction) mortality in Dahl salt resistant rats placed on high salt diets compared with those maintained on lower salt diets despite similar blood pressure levels in the two groups.[23] Findings from ecological analyses have suggested that the association between salt intake and stroke may be stronger than that between salt and blood pressure. [25] Perry and Beevers studied the association between stroke mortality and sodium excretion in Western Europe, using WHO cerebrovascular disease mortality rates and data on 24-hour sodium excretion provided by the INTERSALT study. In these ecological analyses, national stroke mortality rates were highly correlated with median 24-hour sodium excretion. This association was independent of body mass index. The relationship between stroke mortality and systolic

blood pressure, though positive, was weaker than that between stroke mortality and sodium excretion and was not significant in these data. [25]



Despite these intriguing findings from animal experiments and ecological analyses, data from prospective observational studies on the relation between sodium intake and cardiovascular endpoints are sparse and inconsistent. Indeed much of the current data address the relation between salt intake and coronary heart disease events. In the Scottish Heart Health study baseline urinary sodium excretion was positively and significantly associated with the subsequent incidence of myocardial infarction in women but not in men.[28] No association with all cause mortality was observed. By contrast in this study, potassium excretion showed a highly significant protective gradient for all cause mortality in both sexes and a significant inverse relation with coronary heart disease mortality in men.[28] These findings echo the earlier findings from the Rancho Bernardo cohort in which potassium intake predicted the subsequent occurrence of stroke.[3] Salt intake did not predict stroke in the Rancho Bernardo cohort. [3] Similarly, in a longitudinal study involving 7895 men of Japanese ancestry living on the island of Oahu, aged between 45-68 years and followed for 10 years during which there were 238 strokes, no relation was found between salt intake and the incidence of stroke. [29] Given the extent of inter-correlation between dietary sodium and potassium (and other electrolytes including calcium and magnesium) and the problem of variable measurement precision for dietary exposures, it is clearly extremely difficult to isolate independent effects on disease end-points in observational epidemiological studies. There is therefore a need for caution in declaring "independent effects" in multivariate analyses.

Alderman and colleagues have reported a significant inverse association between urinary sodium excretion and incidence of myocardial infarction in a prospective study involving 2,937 drug-treated hypertensives enrolled in a work-site treatment programme.[30] This study has major methodological problems and the findings have generated considerable controversy. Urinary sodium excretion was measured after five days of dietary sodium restriction and is, therefore, unlikely to have provided a valid assessment of habitual salt intake. Participants in this study who were most successful at reducing their salt intake over the five day of dietary restriction may well have been at higher risk. In this context, detailed information on potential confounders such as smoking and alcohol intake was not provided. Similarly, data on drug therapy were lacking and the influence of drug therapy on measured sodium excretion in this study is unclear. [30] In a further controversial study based on twenty years follow-up of NHANES 1 (National Health and Nutritional Examination Survey) Alderman and colleagues supported a similar inverse association between reported sodium intake at baseline and all cause and cardiovascular disease mortality. [31] In this study, however, there was a positive association of mortality at twenty

years follow-up with sodium intake per 1,000 calories. The analysis and conclusions drawn from this study have also attracted criticism. In particular Alderman and colleagues did not exclude from their main analysis participants with baseline histories of cardiovascular disease. Clearly, individuals with established cardiovascular disease may well have had changed their dietary intake of sodium. In addition participants who had adopted a low salt diet at baseline were not excluded from the analyses. Additional concerns raised with regard to this study include the definition of cardiovascular disease outcomes, the use of several highly interrelated salt exposure variables in multivariate analyses and the inconsistency of the associations between the two major sodium intake indicators, i.e. sodium alone and the sodium to energy ratio.[31]

In a follow-up study from MRFIT, involving a group of 11,697 men who provided between three and five 24-hour dietary recalls no significant differences in CHD mortality were observed across the quintiles of sodium intake.[32] The findings were similar in a sub-group of over 6,000 hypertensive men. Unfortunately, data on urinary sodium excretion were not available. Given the age-group involved, 40 to 64 years, this study had limited power to examine the relation between sodium intake and risk of stroke.

Salt intake, obesity and stroke

In a recent paper He and colleagues have revisited the relation between salt intake and cardiovascular disease (CHD events and stroke) in the NHANES 1 data. [33] The focus in these analyses, was on the relation between dietary sodium intake and subsequent risk of cardiovascular disease in obese persons, reflecting clinical and epidemiological evidence that obesity may be associated with increased sensitivity to the effects of sodium on blood pressure. Participants consuming low salt diets because of health concerns and those with a history of established cardiovascular disease were excluded. For overweight and non-overweight per persons, during an average of nineteen years follow-up, there were 680 stroke events, 1727 coronary heart disease events, 895 cardiovascular disease deaths and 2486 deaths from all causes. Among overweight persons, defined on the basis of standard criteria (i.e. > 27.8 kg/m^2 in men and 27.3 kg/m^2 in women, a 100 mmol higher sodium intake (based on a single 24-hour recall) was associated with a 32% increase risk in stroke incidence (RR,1.32; 95% C.I. 1.07 to1.64, an 89% increase in stroke mortality, (RR,1.89; 95% C.I. 1.31 to 2.74). A 100 mmol higher sodium intake was associated with a 44% increase in coronary heart disease mortality, a 61% increase in CVD mortality and a 39% increase in mortality from all causes. Dietary sodium intake was not significantly associated with cardiovascular disease risk in non-overweight persons. [33] In a recent study Tuomilheto and colleagues prospectively followed 1173 Finnish men and 1263 women aged 25-64 years with data on 24 h urinary sodium excretion and cardiovascular risk factors and major CVD endpoints. [34] The hazard ratios for coronary heart disease, cardiovascular disease and all-cause mortality associated with a 100 mmol increase in 24 h urinary sodium excretion, were 1.51 (95% CI 1.14-2.00), 1.45 (1.14-1.84), and 1.26 (1.06-1.50), respectively in both men and women. As in the analysis from NHANES 1, there was evidence of an interaction between sodium excretion and body mass index for cardiovascular disease and total mortality, with a stronger association between sodium excretion and events in overweight men relative to those of normal weight. The findings from these two studies on sodium excretion and major CVD events are consistent with the effects of sodium intake on blood pressure and left ventricular hypertrophy. The proposed interaction with obesity is of particular interest. Obesity is associated with activation of both the sympathetic nervous system and the renin-angiotensin systems and with insulin resistance. These metabolic changes have all been implicated in enhanced renal sodium reabsorption and sodium retention. [35] Thus the findings from these two studies have considerable biological plausibility. However, associations between dietary exposures and

cardiovascular disease endpoints in specific sub-groups of the populations such as the obese must be regarded as tentative until extensively replicated.

Salt and CVD End-Points

Observational Studies

Kagan	Stroke 1985	Stroke Incidence	Negative
Khaw	NEMJ 1987	Stroke Incidence	Negative
Yamori	Health Rep. 1994	Stroke/CHD Mortality	Positive
Alderman	Hypertension 1995	CHD Incidence	Negative
Tunstall-Pedoe	BMJ 1997	CHD Incidence	Negative
Alderman	Lancet 1998	CVD Mortality	Negative
Cohen	Circulation 1999	CVD Mortality	Negative
He	JAMA 1999	Stroke/CHD Incidence	Positive
Tuomilehto	Lancet 2001	Stroke/CHD Incidence	Positive

Summary and conclusions

The evidence linking dietary salt intake to hypertension and left ventricular hypertrophy is strong and consistent. It is therefore highly plausible that salt intake makes a substantial contribution to the burden of cardiovascular disease in the population, in particular to the burden of stroke. We lack, however, good data from either observational studies or randomised control trials that measures taken to reduce dietary salt intake from the current high levels seen in Western populations will lead to a reduction in risk of cardiovascular disease. Population studies on the relation between dietary salt intake and both cardiovascular disease and non-CVD outcomes (such as osteoporosis[36]) is currently a high priority. Observational studies in the elderly, based on rigorous dietary exposure measurements including multiple 24-hour urinary collections, are likely to yield useful and relevant data in the short-term.

Despite the dearth of data on salt intake and disease endpoints, current data on sodium intake and blood pressure have clear implications for both clinical practice and public health policy. Patients with diagnosed hypertension or those with high normal blood pressure can be advised, on the basis of good evidence, to reduce their salt intake. At the population level, we also need to reduce salt intake from the current high levels seen in Western societies. The achievement of population wide reductions in salt intake is difficult and ultimately will depend on public pressure and political action. Most salt in our diet is hidden in processed foods such as bread, biscuits and breakfast cereals. Indeed, the salt concentration of many processed foods approaches or exceeds that of sea water. Unfortunately, the food industry is keen on salt as it enhances the palatability and extends the shelf life of food. Salt also enhances food water retention, thereby increasing the weight of food products. However, the sensitivity of the salt taste receptors depends on an individual's habitual intake and once salt intake has been reduced for a month or more, highly salted food becomes distasteful. Thus, the case for gradually reducing the salt content of processed food, particularly bread, which is the single largest source of salt in our diet, is strong.

We should also consider work on salt, blood pressure and CVD end-points in a broader healthy public policy context. Ultimately, substantial progress in the control of blood pressure and hypertensive complications in the population will depend on developments in public policy across a range of inter-related issues. Thus in addition to the accumulating evidence in support of at least modest salt restriction, there is substantial evidence that

public policies aimed at reducing the prevalence of obesity in children and adults, promoting fruit and vegetable consumption, reducing the extent of heavy alcohol consumption and promoting regular exercise will make a substantial contribution to the control of blood pressure and prevention of stroke and other manifestations of cardiovascular disease in the population.

References

1. Elliott P, Stamler J, Nichols R, et al. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. Intersalt Cooperative Research Group [see comments] [published erratum appears in BMJ 1997 Aug 23;315(7106):458]. Bmj 1996; 312:1249-53.

2. Kuller LH. Salt and blood pressure: population and individual perspectives. Am J Hypertens 1997; 10:29S-36S.

3. Khaw KT, Barrett-Connor E. Dietary potassium and stroke-associated mortality. A 12-year prospective population study. N Engl J Med 1987; 316:235-40.

4. Warlow CP. Epidemiology of stroke. Lancet 1998;352:SIII1-4.

5. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. Bmj 1988; 297:319-28.

6. Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? I-- Analysis of observational data among populations. Bmj 1991; 302:811-5.

7. Denton D, Weisinger R, Mundy NI, et al. The effect of increased salt intake on blood pressure of chimpanzees [see comments]. Nat Med 1995; 1:1009-16.

8. Hofman A, Hazebroek A, Valkenburg HA. A randomized trial of sodium intake and blood pressure in newborn infants. Jama 1983; 250:370-3.

9. Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? III-- Analysis of data from trials of salt reduction [published erratum appears in BMJ 1991 Apr 20;302(6782):939]. Bmj 1991; 302:819-24.

10. Cappuccio FP, Markandu ND, Carney C, Sagnella GA, MacGregor GA. Double-blind randomised trial of modest salt restriction in older people [see comments]. Lancet 1997; 350:850-4.

11. Forte JG, Miguel JM, Miguel MJ, de Padua F, Rose G. Salt and blood pressure: a community trial. J Hum Hypertens 1989; 3:179-84.

12. Geleijnse JM, Hofman A, Witteman JC, Hazebroek AA, Valkenburg HA, Grobbee DE. Long-term effects of neonatal sodium restriction on blood pressure [published erratum appears in Hypertension 1997 May;29(5):1211]. Hypertension 1997; 29:913-7.

13. Ebrahim S, Smith GD. Lowering blood pressure: a systematic review of sustained effects of non-pharmacological interventions [In Process Citation]. J Public Health Med 1998; 20:441-8.

14. Messerli FH, Schmieder RE, Weir MR. Salt. A perpetrator of hypertensive target organ disease? [see comments]. Arch Intern Med 1997; 157:2449-52.

15. Schmieder RE, Messerli FH, Garavaglia GE, Nunez BD. Dietary salt intake. A determinant of cardiac involvement in essential hypertension. Circulation 1988; 78:951-6.

16. Schmieder RE, Langenfeld MR, Friedrich A, Schobel HP, Gatzka CD, Weihprecht H. Angiotensin II related to sodium excretion modulates left ventricular structure in human essential hypertension. Circulation 1996; 94:1304-9.

17. Schmieder RE, Grube E, Impelmann V, Ruddel H, Schulte W. [Determinants for myocardial hypertrophy in mild essential hypertension. The effect of sodium chloride on left-ventricular hypertrophy]. Z Kardiol 1990; 79:557-64.

18. du Cailar G, Ribstein J, Grolleau R, Mimran A. Influence of sodium intake on left ventricular structure in untreated essential hypertensives. J Hypertens Suppl 1989; 7:S258-9.

19. Du Cailar G, Ribstein J, Daures JP, Mimran A. Sodium and left ventricular mass in untreated hypertensive and normotensive subjects. Am J Physiol 1992; 263:H177-81.

20. Kupari M, Koskinen P, Virolainen J. Correlates of left ventricular mass in a population sample aged 36 to 37 years. Focus on lifestyle and salt intake. Circulation 1994; 89:1041-50.

21. Liebson PR, Grandits G, Prineas R, et al. Echocardiographic correlates of left ventricular structure among 844 mildly hypertensive men and women in the Treatment of Mild Hypertension Study (TOMHS). Circulation 1993; 87:476-86.

22. Liebson PR, Grandits GA, Dianzumba S, et al. Comparison of five antihypertensive monotherapies and placebo for change in left ventricular mass in patients receiving nutritional-hygienic therapy in the Treatment of Mild Hypertension Study (TOMHS). Circulation 1995; 91:698-706.

23. Tobian L, Hanlon S. High sodium chloride diets injure arteries and raise mortality without changing blood pressure. Hypertension 1990; 15:900-3.

24. Tobian L. Salt and hypertension. Lessons from animal models that relate to human hypertension. Hypertension 1991; 17:I52-8.

25. Perry IJ, Beevers DG. Salt intake and stroke: a possible direct effect. J Hum Hypertens 1992; 6:23-5.

26. Xie JX, Sasaki S, Joossens JV, Kesteloot H. The relationship between urinary cations obtained from the INTERSALT study and cerebrovascular mortality. J Hum Hypertens 1992; 6:17-21.

27. Sasaki S, Zhang XH, Kesteloot H. Dietary sodium, potassium, saturated fat, alcohol, and stroke mortality. Stroke 1995; 26:783-9.

28. Tunstall-Pedoe H, Woodward M, Tavendale R, A'Brook R, McCluskey MK. Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish Heart Health Study: cohort study [published erratum appears in BMJ 1998 Jun 20;316(7148):1881]. Bmj 1997; 315:722-9.

29. Kagan A, Popper JS, Rhoads GG, Yano K. Dietary and other risk factors for stroke in Hawaiian Japanese men. Stroke 1985; 16:390-6.

30. Alderman MH, Madhavan S, Cohen H, Sealey JE, Laragh JH. Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men [see comments]. Hypertension 1995; 25:1144-52.

31. Alderman MH, Cohen H, Madhavan S. Dietary sodium intake and mortality: the National Health and Nutrition Examination Survey (NHANES I) [see comments]. Lancet 1998; 351:781-5.

32. Chobanian AV, Hill M. National Heart, Lung, and Blood Institute Workshop on Sodium and Blood Pressure : a critical review of current scientific evidence. Hypertension 2000; 35:858-63.

33. He J, Ogden LG, Vupputuri S, Bazzano LA, Loria C, Whelton PK. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults [see comments]. Jama 1999; 282:2027-34.

34. Tuomilehto J, Jousilahti P, Rastenyte D, et al. Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. Lancet 2001;357:848-851

35. Hall JE. Mechanisms of abnormal renal sodium handling in obesity hypertension. Am J Hypertens 1997; 10:49S-55S.

36. Devine A, Criddle RA, Dick IM, Kerr DA, Prince RL. A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women [see comments]. Am J Clin Nutr 1995; 62:740-5.

Does salt have a detrimental effect on the cardiovascular system that is not mediated by blood pressure?

Franz H. MESSERLI, M.D.
Oschner Clinic Foundation, New Orleans, Louisiana, USA

Numerous studies have documented that high salt intake increases blood pressure and, conversely, that a low salt diet leads to a fall in blood pressure. High blood pressure is a well documented risk factor for cardiovascular morbidity and mortality, i.e., heart attacks, strokes, and renal failure. Recent evidence suggests that not all effects of sodium on cardiovascular disease are directly mediated by blood pressure. Sodium, by itself, has been identified in numerous studies as a powerful pressure-independent risk factor for hypertensive heart disease, specifically left ventricular hypertrophy. Left ventricular hypertrophy is a well-known blood pressure-independent, powerful risk factor for cardiovascular events. Similarly, particularly in overweight subjects dietary sodium intake has been shown to directly affect stroke incidence, stroke mortality, and coronary heart disease mortality. Recent data also demonstrate a closer association between dietary sodium and cerebrovascular disease than between dietary sodium and blood pressure. Dietary sodium has been shown to directly affect progression of renal disease and progression of vascular disease independently of changes in blood pressure. Finally, in patients with congestive heart failure an excessive sodium intake can accelerate progression of disease. The effects of sodium on the heart, the brain, the kidney and the vascular tree are at least additive, but possibly even synergistic to the effects of blood pressure.

Salt and left ventricular hypertrophy

Pr. Dr. Roland E. SCHMIEDER
Department of Medicine IV/4, Erlangen-Nürnberg University, Germany

Increased dietary salt intake profoundly influences the cardiovascular system. It has been repeatedly documented that an increase in dietary salt intake leads to an increase in arterial pressure, at least in saltsensitive patients. Whether increased salt intake also impacts cardiac structural adaptation due to increased afterload in essential hypertension - independently of the impact of dietary salt intake on the level of blood pressure – has been questioned for a long time.

Nowadays, abundance of epidemiological studies clearly indicate that there is a blood pressure independent relation between dietary salt intake and left ventricular mass. This has been found in particular in patients with essential hypertension. In two cross-sectional studies we documented this blood pressure independent effect of dietary salt intake on left ventricular mass, even after taking 24 hour blood pressure measurements (as the most accurate parameter for the increased afterload) into account. Conversely, in the TOMHS-study reduction of dietary salt intake emerged as a blood pressure independent effect for the decrease in left ventricular mass.

The observation of a significant association between dietary salt intake and the degree of left ventricular hypertrophy does not *a priori* indicate a causal relationship between the two parameters. Experimental studies, however, have established such a causal relationship between increase in dietary salt intake and degree of left ventricular hypertrophy in hypertensive patients. In spontaneously hypertensive rats an increase of sodium concentration in the drinking water led to an increase in left ventricular weight whereas other confounding factors known to influence the pathogenesis of left ventricular hypertrophy (in particular arterial pressure) remained stable. Thus, experimental data and the above-mentioned TOMHS-study provide very solid evidence that dietary salt intake affects cardiac structural adaptive processes in patients with essential hypertension independently from blood pressure.

Although the pathogenetic mechanism for such a causal relationship remains yet to be elucidated, the interaction with the renin angiotensin aldosterone system is evident. Whereas in the systemic circulation an increase in dietary salt intake leads to a decrease of serum aldosterone concentrations, the local aldosterone system is upregulated by an increase in dietary salt intake thereby accelerating fibrotic and hypertrophic processes. Similarly, in a sub-group of hypertensive patients an increase in dietary salt intake does not lead to an appropriate fall in angiotensin II concentrations thereby leading to an inadequate suppression of the renin angiotensin aldosterone system. Angiotensin II is now well established to be a hypertrophic and pro-fibrotic mediator. Finally, although not precisely known, an increase in sodium concentration *per se* elicits an upregulation of hypertrophic and pro-fibrotic genes.

In summary, clinical and experimental evidence exists that increased dietary sodium intake leads to an increase in left ventricular mass, particular in hypertensive patients. This relationship appears to be causal and at least in part mediated by the interaction with the renin angiotensin aldosterone system. Conversely, reduction of dietary salt intake appears to be an effective measure to reduce left ventricular hypertrophy in essential hypertension.

De la salle

Tout le monde se réfère aux effets délétères du sodium. Personne ne parle cependant du potassium. Il est pourtant impossible d'expliquer les effets du sodium en faisant abstraction des effets du potassium.

Roland E. SCHMIEDER

Nous avons effectivement étudié les rapports entre le sodium et le potassium, mais aucune relation directe ne nous est apparue.

De la salle

La concentration du sodium cellulaire augmente. En revanche, il est avéré que la concentration cellulaire de potassium est trop faible. Par conséquent, la cellule ne peut pas expulser le sodium grâce au potassium. Le potassium me paraît par conséquent très important.

De la salle

Je crois également que le potassium est tout aussi important que le sodium dans l'hémostase cardiovasculaire. Nous avons d'ailleurs organisé un symposium sur le potassium, il y a deux ans, à Paris.

De la salle

J'ai beaucoup apprécié l'étude du Dr. Schmieder consacrée au contrôle de la pression artérielle sur 24 heures afin de montrer l'effet indépendant qu'exerce sur elle le sel. Elle me conduit à poser la question suivante : que pensez-vous des données récentes montrant que les diurétiques favorisent plus efficacement la baisse de l'hypertrophie du ventricule gauche. Il est possible que le manque de suivi de la pression artérielle pendant 24 heures ait favorisé les effets plus durables de l'indapamide sur la pression artérielle, à la différence d'autres produits, dont les effets durent moins longtemps, pour une dose de 20 milligrammes par jour.

Roland E. SCHMIEDER

Cette étude est plus difficile à interpréter, puisque même ceux qui ont mené l'étude à laquelle vous faites référence ne disposent toujours pas d'une réponse définitive. Il est certain que l'indapamide est loin d'être un diurétique simple à analyser. Les expériences ont montré que la sensibilité à l'indapamide était elle aussi mitigée dans ce cas de figure. Il est possible qu'un blocage de l'angiotensine intervienne également et contribue à modifier les résultats des études.

De la salle

Existe-il des preuves montrant que l'hypertrophie du ventricule gauche a une incidence sur l'hypertension artérielle ?

Roland E. SCHMIEDER

A ma connaissance, quatre ou cinq études prospectives ont montré que la réduction de la masse ventriculaire gauche est indépendante du pronostic cardiovasculaire. La publication la plus récente sur ce point est italienne et confirme également cette hypothèse.

Sel et ostéoporose

Salt and osteoporosis

Francesco P CAPPUCCIO, MD MSc FRCP MFPHM[4]
St George's Hospital Medical School, London, Uinted Kingdom

Low Bone Mineral Density and Osteoporosis: definition, frequency and consequences.

Osteoporosis is characterised by low bone mass and deterioration of bone tissue, with a consequent increase in bone fragility and fracture [1]. Bone mineral density (BMD) declines with age, and twice as fast in women than in men [2]. By the age of 50 the lifetime risk of an osteoporotic fractures is around 40% in women and 13% in men. The incidence of osteoporotic fractures rises sharply with age in women [3], but also in men [4]. (Figure 1). In the US there are about 1.5 million fractures per year and in England they are more that 100,000 per year [5; 6]. These figures will increase sharply with the increase in the elderly population of the Western world. Given the high public health impact of osteoporosis the main aim of intervention in osteoporosis in prevention of fractures.

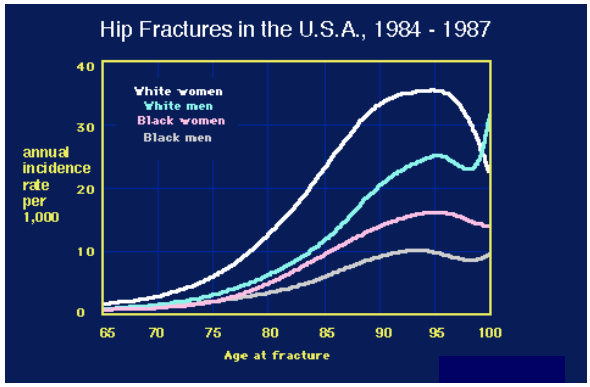


Figure 1. Incidence rate of hip fractures in the United States 1984-1987

Low BMD is an independent risk factor for fractures in both women and men [7], so that the gender difference in the incidence of hip fractures can be entirely explained by differences in BMD. Risk factors for low BMD are therefore risk factors for fracture. The two crucial elements that influence the development of osteoporosis are (a) peak bone mass attained in the first 30 years of life and (b) the rate at which bone mass is lost later in life (Figure 2). In both cases, an important determinant of bone mass is the amount of calcium available

[4] Correspondence to:
Prof. FP Cappuccio
Professor of Primary Care Research & Development
Department of General Practice & Primary Care, St George's Hospital Medical School
Cranmer Terrace, London SW17 0RE
Tel +44-20-8725 3329
Fax +44-20-8725 2234
E-mail: f.cappuccio@sghms.ac.uk

for bone formation, which is the net result of the amount effectively absorbed by the gut and the amount lost with the urine. Ideally this should be zero, but in the elderly or in some physio-pathological conditions this balance can be negative, so that more calcium is lost than is absorbed, resulting in low BMD.

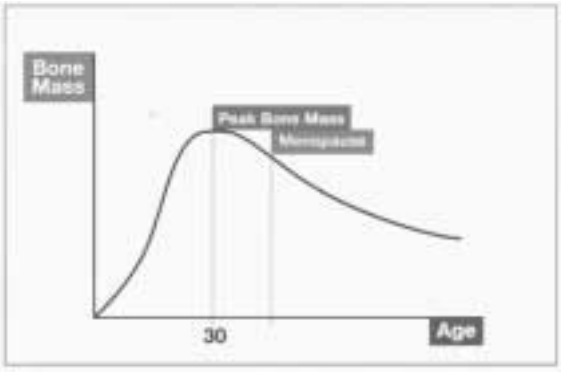


Figure 2. Bone mass over a life-time. The two crucial elements that influence the development of osteoporosis are (a) peak bone mass attained in the first 30 years of life and (b) the rate at which bone mass is lost later in life

Salt intake and bone metabolism

Salt (sodium) intake is the major determinant of urinary calcium excretion. The higher the urinary sodium (marker of salt intake) the higher the calcium excretion, within populations of young and old, men and women, and also within an individual on different days [8-10]. This association is causative, as it has been shown in intervention trials (Figure 3)**.** There would be a 1 mmol (40 mg) extra loss of calcium per day in the urine for every 100 mmol higher sodium excretion (~5g higher salt intake). It is therefore conceivable that, over a life-time, a high salt intake could lead to a negative calcium balance, lower BMD and a worsening of osteoporosis. The evidence comes from epidemiological and clinical studies in humans. A high salt intake, at least in the short-term, leads to a reduction in bone formation and an increase in bone re-sorption, via secondary activation of PTH (see [9] for review) (Figure 4). It is associated with reduced peak bone mass in young girls [11] and with higher rate of BMD loss in postmenopausal women [12]. There is also a negative correlation between urinary sodium excretion and both BMD and BMD loss over time. The evidence so far points to an important role that salt intake plays in contributing to bone mineral loss and, hence, osteoporosis. A reduction in salt intake at the population level, by reducing urinary calcium losses, should encourage a positive calcium balance and a reduction in the risk of osteoporosis and bone fractures, similar to the effect of thiazide diuretics [13-15].

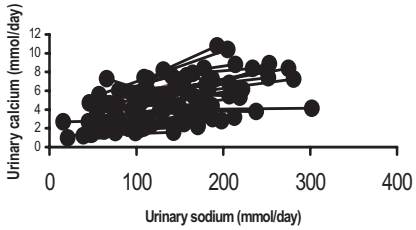


Figure 3. Relationship between urinary sodium and calcium excretion during changes in salt intake in 47 men and women over the age of 60 years during a randomised double-blind cross-over trial. An average reduction in sodium intake of 83 mmol/day caused and average reduction in urinary calcium excretion of 1.13 mmol/day. The association between sodium and calcium was strong both on the low (r=0.47;p<0.001) and the high (r=0.59;p<0.001) sodium intake. It was estimated that a change in 100 mmol/day of sodium excretion would predict a 1.19 (0.28 SD) mmol/day change in urinary calcium excretion.

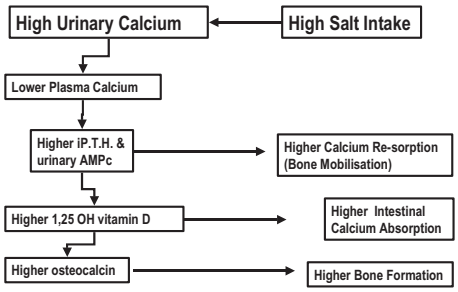


Figure 4. Metabolic features of salt-induced increase in urinary calcium excretion

Bone metabolism and cardiovascular disease

Low BMD is also associated with high blood pressure both in women and in men [16; 17], and the loss of BMD with age is faster in those with higher blood pressure [18]. Furthermore, low bone density has been found to be inversely related to both stroke incidence [19]and cardiovascular mortality [20]. A reduction in salt intake could reduce both the occurrence of osteoporosis and associated complications and the population blood pressure levels with a possible reduction in cardiovascular complications [21].

Implications for prevention and public health

The rate of decline in bone mineral density varies from site to site and between men and women. For the neck of femur in post-menopausal women the expected rate of bone mineral density loss may average 1% per year, meaning a 10% bone mineral loss per decade [22]. A 100-mmol per day reduction in sodium excretion (equivalent to approximately 5g of salt reduction in the diet) would cause a 1 mmol per day reduction in urinary calcium losses. Over decades, this reduction in calcium loss, particularly in elderly women, may be expected to reduce the rate of bone mineral loss by half (Figure 5). The implications may be very significant at a population levels as relatively small increases in bone mineral density may result in disproportionately large decreases in fracture rates [2](Figure 6). For example, for the average 80-year-old woman, a 14% increase in mean bone mineral density would decrease the risk of hip fracture by 50%.

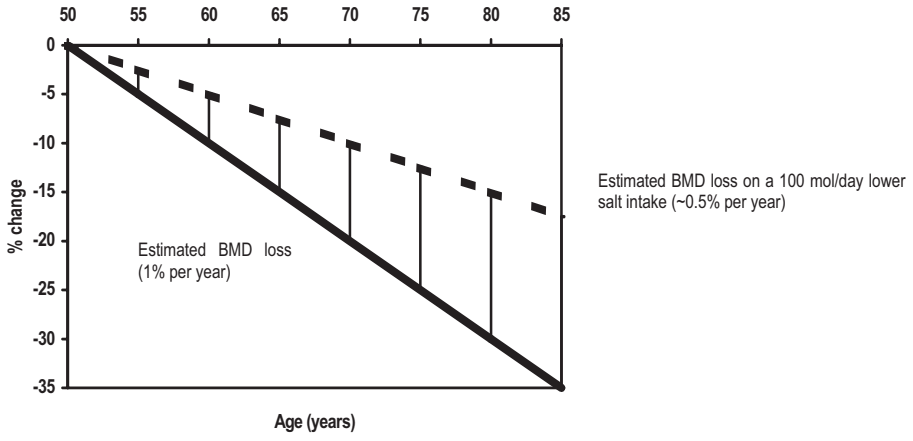


Figure 5. Estimated effect of a reduced salt intake on yearly changes in femoral neck bone mineral density.

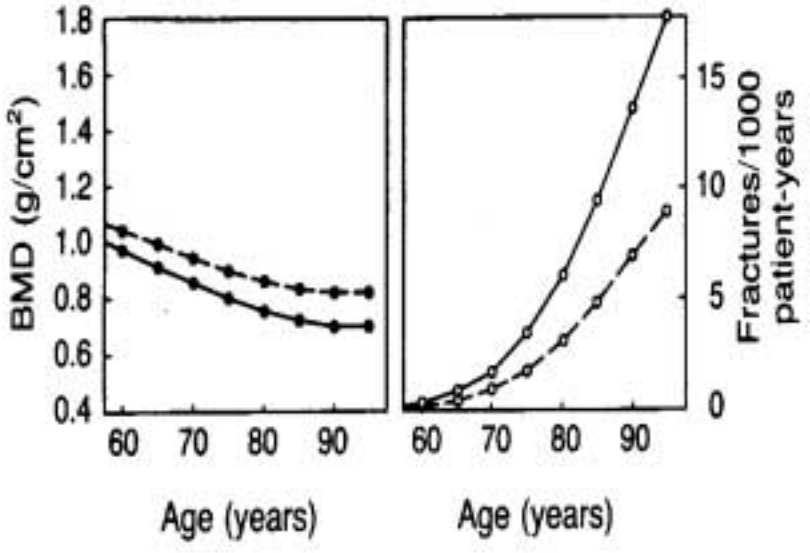


Figure 6. Relation between the bone mineral density (BMD) of the femoral neck and the rate of hip fracture. (Adapted from ref. 2)

To conclude, a moderate reduction in salt intake at the population level may exert large benefits, especially - but not exclusively - to the elderly. The absolute risk reduction is likely to be large and, therefore, highly cost-effective. No harmful effect can be envisaged.

References

1. NIH Consensus Development Panel on osteoporosis prevention dat. Osteoporosis prevention, diagnosis and therapy. *JAMA* 2001;285:785-795.

2. Melton LJ III, Kan SH, Wahner HW, Riggs BL. Lifetime fracture risk: an approach to hip fracture risk assessmente based on bone mineral density and age. *J Clin Epidemiol* 1988;41:985-994.

3. Melton LJ III. Epidemiology of hip fractures: implications of the exponential increase with age. *Bone* 1996;18 (suppl 3):121-125.

4. de Laet CEDH, van Hout BA, Burger H, Hofman A, Pols HAP. Bone density and risk of hip fracture in men and women: cross sectional analysis. *Br Med J* 1997;315:221-225.

5. Riggs BL, Melton LJ III. The prevention and treatment of osteoporosis. *N Engl J Med* 1992;327:620-627.

6. Donaldson LJ, Cook A, Thomson RG. Incidence of fractures in a geographically defined population. *J Epidemiol Comm Health* 1990;44:241-245.

7. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *Br Med J* 1996;312:1254-1259.

8. MacGregor GA, Cappuccio FP. The kidney and essential hypertension: a link to osteoporosis? *J Hypertens* 1993;11:781-785.

9. Cappuccio FP, Kalaitzidis RG, Duneclift S, Eastwood JB. Unravelling the links between calcium excretion, salt intake, hypertension, kidney stones and bone metabolism. *J Nephrol* 2000;13:169-177.

10. Blackwood AM, Sagnella GA, Cook DG, Cappuccio FP. Urinary calcium excretion, sodium intake and blood pressure in a multi-ethnic population: results of the Wandsworth Heart and Stroke Study. *J Hum Hypert* 2001;15:229-237.

11. Matkovic V, Ilich JZ, Andon MB, et al. Urinary calcium, sodium, and bone mass of young females. *Am J Clin Nutr* 1995;62:417-425.

12. Devine A, Criddle RA, Dick IM, Kerr DA, Prince RL. A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. *Am J Clin Nutr* 1995;62:740-745.

13. Wasnich R, Davis J, Ross P, Vogel J. Effect of thiazide on rates of bone mineral loss: a longitudinal study. *Br Med J* 1990;301:1303-1305.

14. Wasnich RD, Benfante RJ, Yano K, Heilbrum L, Vogel JM. Thiazide effect on the mineral content of bone. *N Engl J Med* 1983;309:344-347.

15. LaCroix AZ, Wienpai J, White LR, et al. Thiazide diuretic agents and the incidence of hip fracture. *N Engl J Med* 1990;322:286-290.

16. Grobbee DE, Burger H, Hofman A, Pols HAP. Blood pressure and bone density are inversely related in the elderly. *J Hypertens* 1996;14:S35 (Abstract)

17. Tsuda J, Nishio I, Masuyama Y. Is hypertension a risk factor for osteoporosis? Dual energy X-ray absorptiometric investigation. *J Hypertens* 1998;16 [suppl.2]:S209 (Abstract)

18. Cappuccio FP, Meilahn E, Zmuda JM, Cauley JA. High blood pressure and bone-mineral loss in elderly white women: a prospective study. *Lancet* 1999;354:971-975.

19. Browner WS, Pressman AR, Nevitt MC, Cauley JA, Cummings SR. Association between low bone density and stroke in elderly women. The Study of Osteoporotic Fractures. *Stroke* 1993; 24:940-946.

20. von der Recke P, Hansen MA, Hassager C. The association between low bone mass at the menopause and cardiovascular mortality. *Am J Med* 1999;106:273-278.

21. Cappuccio FP. Salt and blood pressure. Issues for population-based prevention and public health strategies. *Public Health Medicine* 2000;2:57-61.

22. Nordin BEC, Need AG, Steurer T, Morris HA, Chatterton BE, Horowitz M. Nutrition, osteoporosis and aging. *Ann NY Acad Sci* 1998;336-351.

De la salle

Pourquoi pensez-vous qu'il faille réduire l'apport de sel tout au long de la vie pour obtenir un effet bénéfique sur le plan de l'ostéoporose ? Des études ont pourtant montré que deux années suffisaient pour que des différences significatives apparaissent.

Francesco CAPPUCCIO

Il n'était pas question, dans mes propos, de parler des personnes souffrant d'une ostéoporose aiguë, caractérisée par une densité osseuse très faible. Seule une posologie puissante me paraît adaptée au cas de ces patients. Mon approche concerne au contraire la population dans son ensemble, puisque en tout état de cause, l'ostéoporose est un phénomène naturel. Il est néanmoins possible de modifier son incidence. Sept à onze ans d'études et d'observation sont nécessaires pour parvenir à réellement déceler une réduction des fractures osseuses.

De la salle

Il est évident que la diminution de la perte minérale est essentielle dès lors qu'il s'agit d'agir sur l'ostéoporose. Des études très intéressantes ont été publiées sur ce point. Elles ont notamment concerné l'effet du sodium. Il n'existe aucune preuve concernant les effets réels des diurétiques sur la perte aiguë de sodium. Aucune évolution du taux de sodium ne peut réellement être démontrée en l'espace de quelques mois. Il est certain que les minéraux sont importants. Nous savons par ailleurs que l'effet des diurétiques s'atténue au cours du temps.

Sel et politique de santé publique

Salt and public health policies

Session 5

animée par M. Joël MENARD
Faculté de médecine Broussais, Hôtel Dieu, Paris, France

Cette session a réuni :
Jozef V. JOOSENS, UZ Saint Raphaël, Louvain, Belgique
Heikki KARPANNEN, Institute of Biomedecine, University of Helsinki, Helsinki, Finland
Lisa JACKSON, Foods Standards Agency, Londres, Royaume-Uni
Martha HILL, John Hopkins University School of Nursing, Baltimore, Etats-Unis
Serge HERCBERG, INSERM / CNAM, Paris, France
Jean-Luc VOLATIER, OCA, Afssa, Maisons-Alfort, France

Introduction par M. Joël MENARD

Je vous propose de procéder à la présentation par les experts des différentes politiques de santé publique actuellement mises en place dans différents pays. Ces experts procéderont à leur présentation en tant que membres des agences chargés de ces politiques ou bien plus simplement en tant que scientifiques originaires du pays en question et participant à des comités de recommandation ou responsables d'un travail de recherche consacré à cette question, travail pouvant être d'ailleurs comparable à celui effectué par l'Afssa sous la responsabilité du Dr. S. Hercberg. Je précise qu'avant de diriger un groupe de travail consacré au sel mis en place par l'Afssa au début de l'année 2001, M. Hercberg a été responsable de l'orientation de la politique nutritionnelle globale menée en France. Depuis 1998, en collaboration avec différents experts, il a émis plusieurs rapports, dont un rapport du Haut Comité de Santé Publique. Le travail réalisé par M. Hercberg au sein du groupe de travail de l'Afssa s'intègre au Programme National Nutrition-Santé (PNNS), présenté par le Ministre de la Santé.

Salt intake and public health in Belgium

Jozef V. JOOSSENS
UZ Saint Raphaël, Leuven, Belgium

Around 1968 a mass campaign was launched by researchers from four Belgian universities in order to reduce salt and saturated fat intake and to increase n-6 polyunsaturated fat intake. This was supported by television, radio and press. The anti-salt campaign gradually came to a standstill in the mid-eighties. The main reasons were increased efforts of the salt lobby, lack of funding and lack of interest of the government. Seven surveys on 24h urinary excretion were performed in Belgium on 14,506 subjects between 1966 and 1987. None was realized after 1987.

A royal decree in 1976 gradually reduced the maximum level of salt in bread from 3% (18 g kg/fresh bread) to 2% (12 g) over a 3 year period. Since then a further decrease in salt content in bread was refused by the government against an advice from the Belgian High Council of Public Health (1995) and from the Belgian Academies of Medicine in 2000. The levels of salt in fresh bread (g/kg) in the Leuven area and Belgium are given up to 1992 in fig. 1 (1, 4). In 1998 the mean salt content of fresh bread was 11.6 g ± 1.9 g.

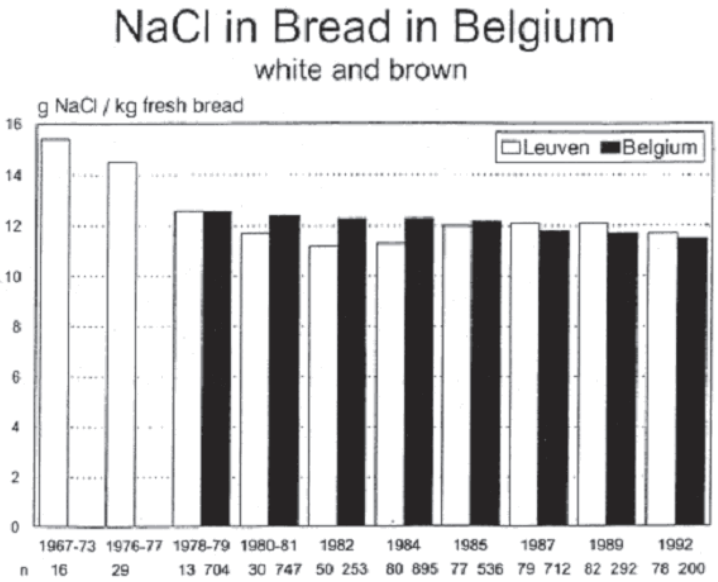


Fig. 1. Salt in g/kg fresh bread in Belgium and the Leuven area. Average of white and brown bread values, 1970-1992. The effect of the Royal Decree of 1976 on salt in bread is clearly seen in the Leuven area.
n = number of loaves examined.
Courtesy of Elsevier (2000), ref. 4.

Before ± 1950, the period when refrigeration of foods was only available for the rich, salt intake in Belgium was high (around 30 g/d). The salt came from pork and vegetables kept in brine, from salted dried fish (codfish) and from a high intake of lard, bread and potatoes. All these food items were cheap and the main source of energy intake.

After 1950 the gradual mass introduction of refrigerators made salting for conservation of food no longer necessary. This contributed to a gradual decrease in salt intake, which was not noticed as such by the consumers.

In the following figures and tables the remarkable increase of systolic blood pressure (SBP) with age is first shown in Norway in 1953 (fig. 2, ref. 2). The increase is already somewhat smaller in Sweden in 1965 (fig. 3, ref. 3). The increase in SBP with age is much smaller in Belgium in 1982 (fig. 4, BIRNH data, ref. 4). In all studies the increase in SBP with age is higher in women than in men (fig. 2-4, ref. 4, 5*).* The significant relationship between 24h Na excretion and the increase in SBP between ages 25 and 55, i.e. $\triangle SBP_{5525}$, is shown in 52 worldwide centers of Intersalt (fig. 5*,* 1988, ref. 5*).*

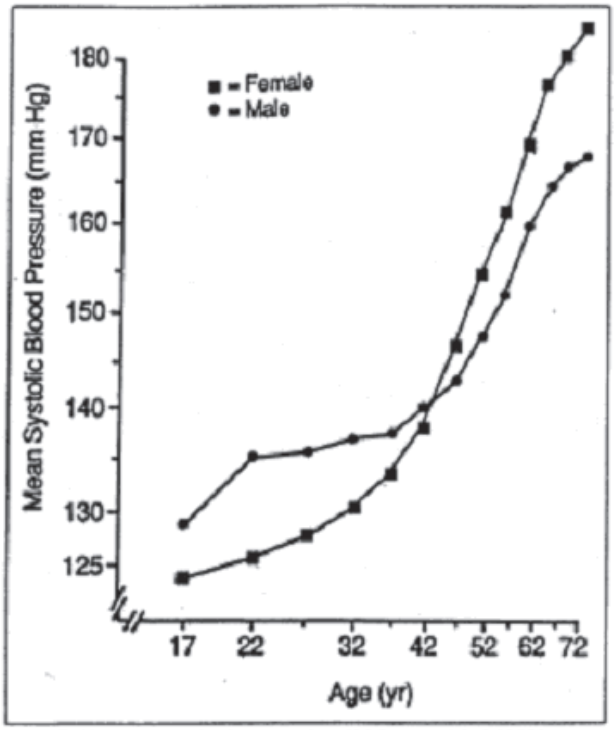


Figure 1. Mean systolic blood pressure (mm Hg) from a total of 44,182 patients, by age and sex in Norway, on a double-log scale. •=male; ▪=female. Data from Bøe *et al* [9]. Reprinted with permission of the publisher from Acta Med Scand. (1953)

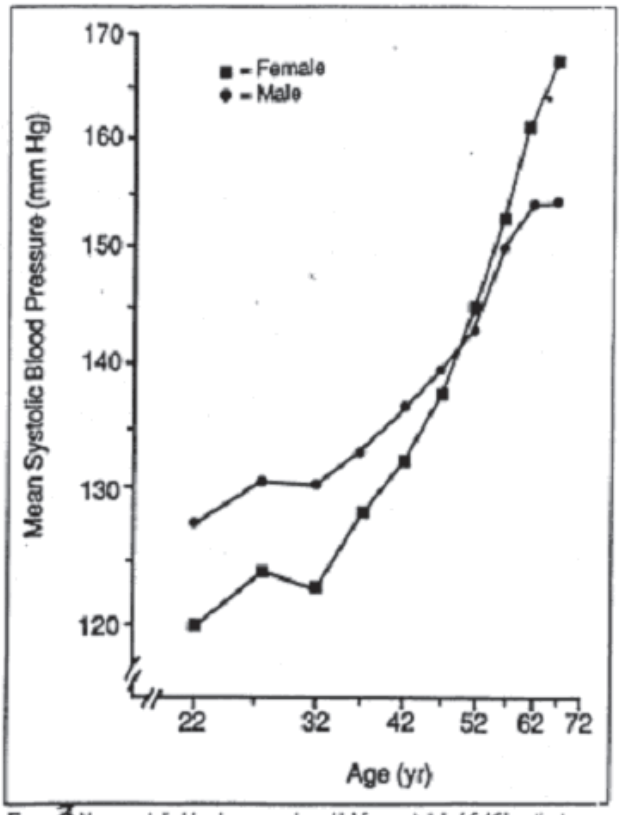


Figure 2. Mean systolic blood pressure (mm Hg) from a total of 6,461 patients, by age and sex in Sweden, on a double-log scale. •=male; ▪=female. Data from Carlson *et al* [10]. Reprinted with permission of the publisher from Acta Med Scand. (1965)

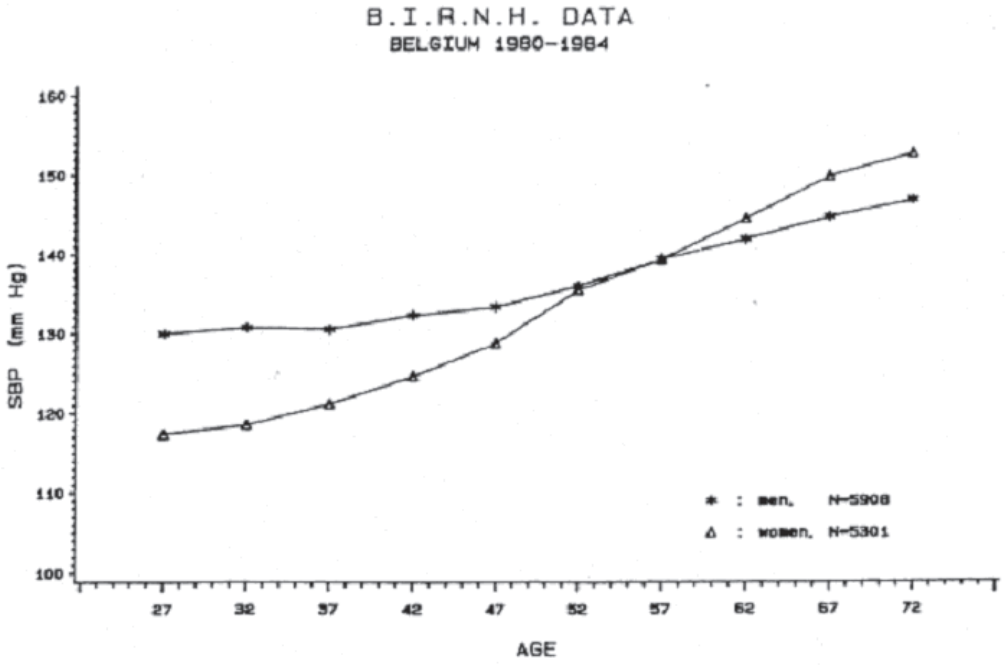


Fig. 4. SBP plotted against age for men and women in Belgium 1982. BIRNH Study (19). Courtesy of M. Kornitzer, L. Bara and *Acta Cardiologica*.

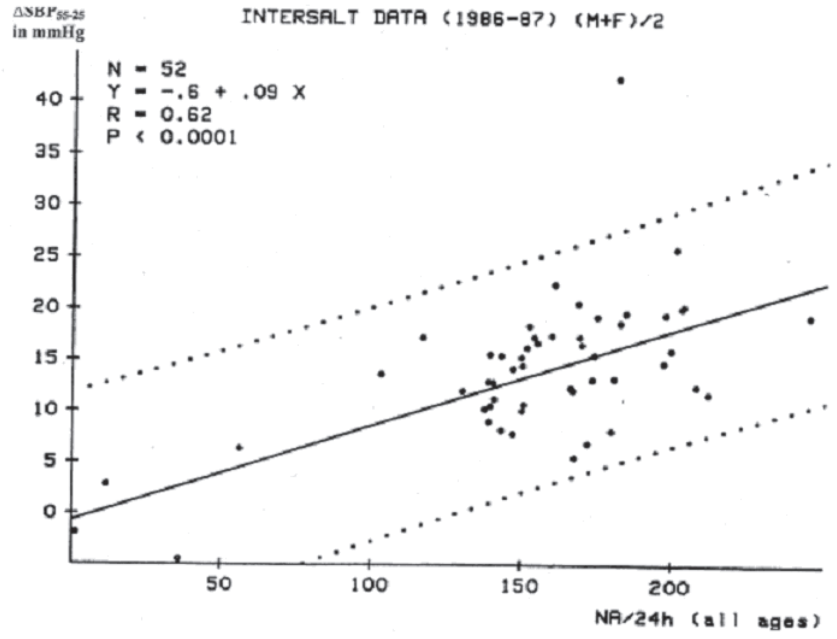


Fig. 5. ΔSBP_{55-25} plotted against mmol/24h Na. Source of data: INTERSALT 1986-1987. Courtesy of Elsevier (2000), ref. 4.

The prevalence of systolic hypertension and severe systolic hypertension in elderly from 1967 to 1986 is given for Belgium in table 1. The data of table 2 relate $\triangle SBP_{5525}$ versus 24h Na in Belgium from 1966 to 1987 (4). Table 3 gives the same information for several other countries (4). Table 3 gives the same information for several other countries.

Table 1. Prevalence of Systolic Hypertension (≥ 160 mmHg) and Severe Systolic Hypertension (> 220 mmHg) in Elderly subjects in Belgium

	1967	1972	1975	1982	1983	1986
	(n=510)	(n=366)	(n=143)	(n=1803)	(n=344)	(n=162)
Mean age (years)	*71*	*76*	*70*	*70*	*71*	*81*
Systolic hypertension (%)						
Men	51	50	32	23	16	21
Women	66	70	36	32	19	22
Severe systolic hypertension (%)						
Men	2.0	2.9	0	0	0	0
Women	6.5	2.6	0	0.4	0	0

Compiled data from Joossens and Kesteloot. Courtesy of Elsevier (2000), ref. 4.

Table 2 : △ SBP 55-25 and 24h sodium in Belgium. 1966-1987
(Men + Women)/2

Year	N	△ SBP 55-25 mmHg	mmol Na/24h
1966	216	-	203
1968	1538	22	179
1972	300 *	15	169
1975	6548	15	-
1982	6867	14	142
1983	5181	12	146
1983	1510	11	158
1987	357	10	144

* Ten 24h urine collections in each person Courtesy of Elsevier (2000), ref. 4.

Table 3 : △SBP 55-25 in different countries and different years

Country	Year	N	△SBP 55-25 * (mmHg)	Na/24h (mmol)
Norway	1953	44182	25	-
US	1954	594	21	-
	1987	581	12	135
Japan	1958	9408	21	356
	1987	591	8	187
Sweden	1965	6461	23	-
East Germany	1968	2908	20	-
	1987	198	14	148
Portugal	1972	229	35**	205
	1987	198	42	182

* Except Portugal 1972: △SBP 60-30

** Value adjusted to the saime urinary creatinine amount as in 1987. Courtesy of Elsevier (2000), ref. 4.

In general it shows that $\triangle SBP_{5525}$ is strongly similarly associated over the years and between countries to the level of 24h Na excretion.

Preventing the rise of $\triangle SBP_{5525}$ at the population level through a lower salt intake is therefore more important than reducing existing SBP levels.

Final remarks

1. Average salt intake is decreasing worldwide since many decades in conjunction with, among others, the mass introduction of refrigerators and deepfreezers. On the other hand there are huge differences in 24h Na excretion between populations, going from milligrams in the jungle of the Amazones to 14.5g in Tianjin (PR of China) (Intersalt, 5*).*

All those populations enjoyed their food, whatever their previous and actual level of salt intake. This makes it likely that the taste of salt adapts itself to the changing situation, on condition that any decrease in salt intake is spread over a long period of time. This was clinically proved in Australia.

2. Refrigerators, salt intake, stroke and stomach cancer mortality.

Mass introduction of refrigerators started around 1925 in the U.S. after the synthesis of freon by Dupont in 1920.

In Europe most countries did the same after World war II, except Portugal where this occurred in the seventies. Japan had only 9% of the households with a refrigerator in 1960, but 91% in 1970.

This resulted in a decreasing salt intake and was associated with a continued decrease in stroke mortality. In the US the decrease in stroke mortality started around 1930, long before any treatment of hypertension was available. Stomach cancer mortality also started

to decline in the US at the same time. In Europe this occurred since ± 1950 (Portugal ± 1975*)* and Japan since 1960.

A social gradient existed for refrigerators in Belgium, combined with nutritional differences. This was associated in 1968 (total n=1538) with a 2 g lower salt intake (from 24h urine) in the highest social quintile versus the lowest one (6).

The highly significant relation between stomach cancer and stroke mortality was found in 1965. The first international presentation occurred in Paris in 1968 (7).

The yearly changes in mortality from stroke and stomach cancer since 1980 are significantly correlated in the EU (fig. 6, ref. 4).

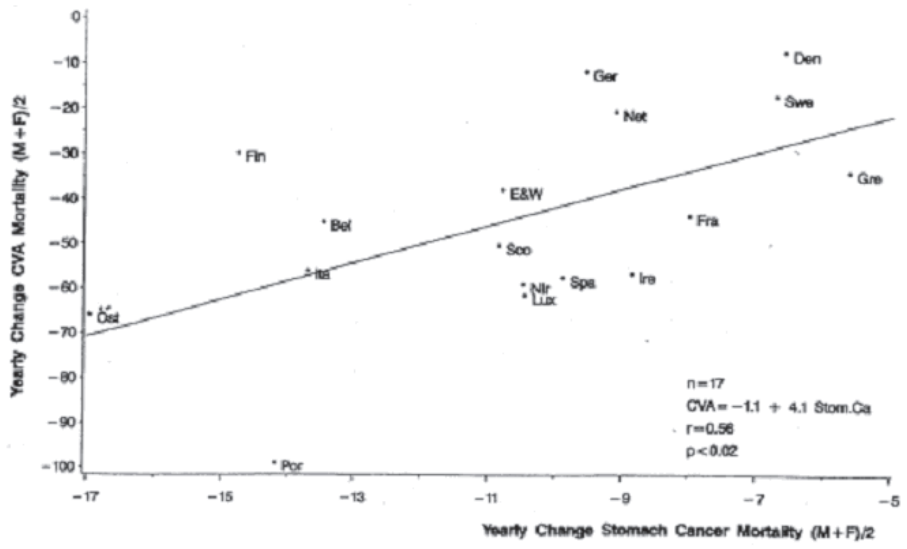


Fig. 6. Yearly change in number of deaths per million in the EU, obtained by linear regression of CVA and stomach cancer mortality with years. From 1980 or first available to 1994 or last available. Mean of both sexes.
Age adjusted 45-74 years.
Courtesy of Elsevier (2000), ref. 4.

The same is similarly true for the relationship between populations worldwide (4) and the relations within a country, e.g. Belgium, France, UK (fig. 7, 8, 9). Quantitatively, either between or within countries, the slopes of these correlations are of the same order of magnitude. This makes a spurious association unlikely.

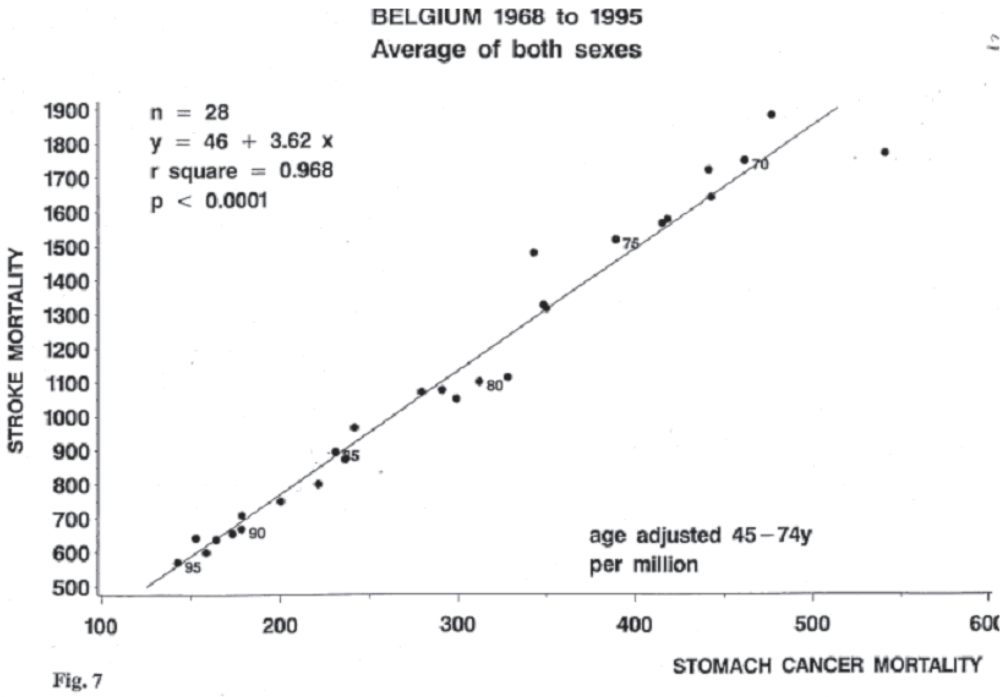


Fig. 7

Courtesy Elsevier, ref.4 (2000). Updated to 1995

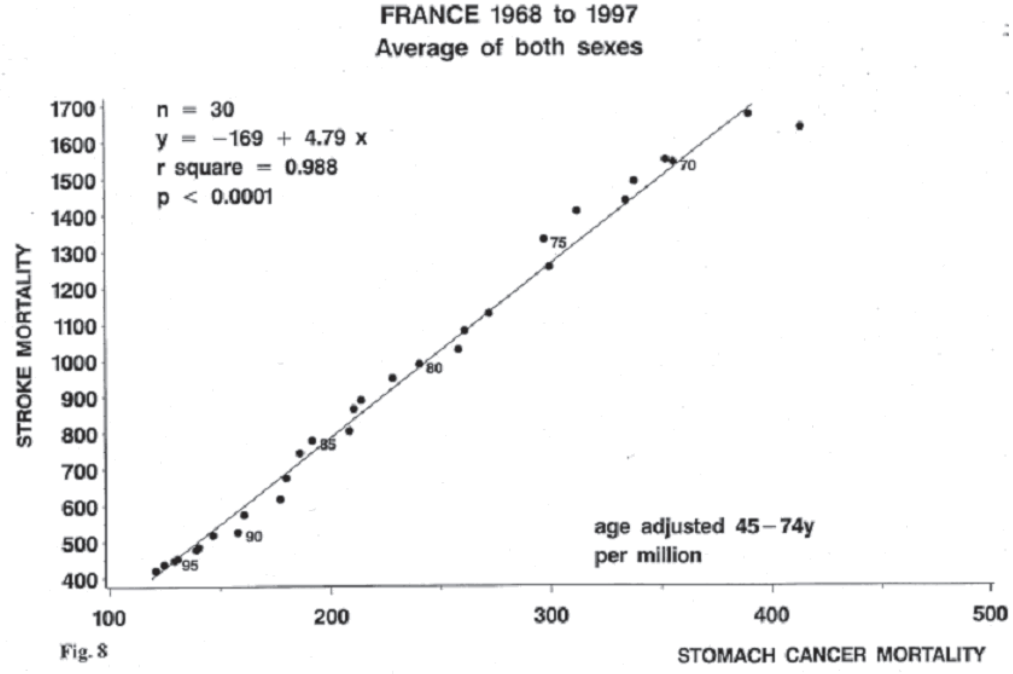


Fig. 8

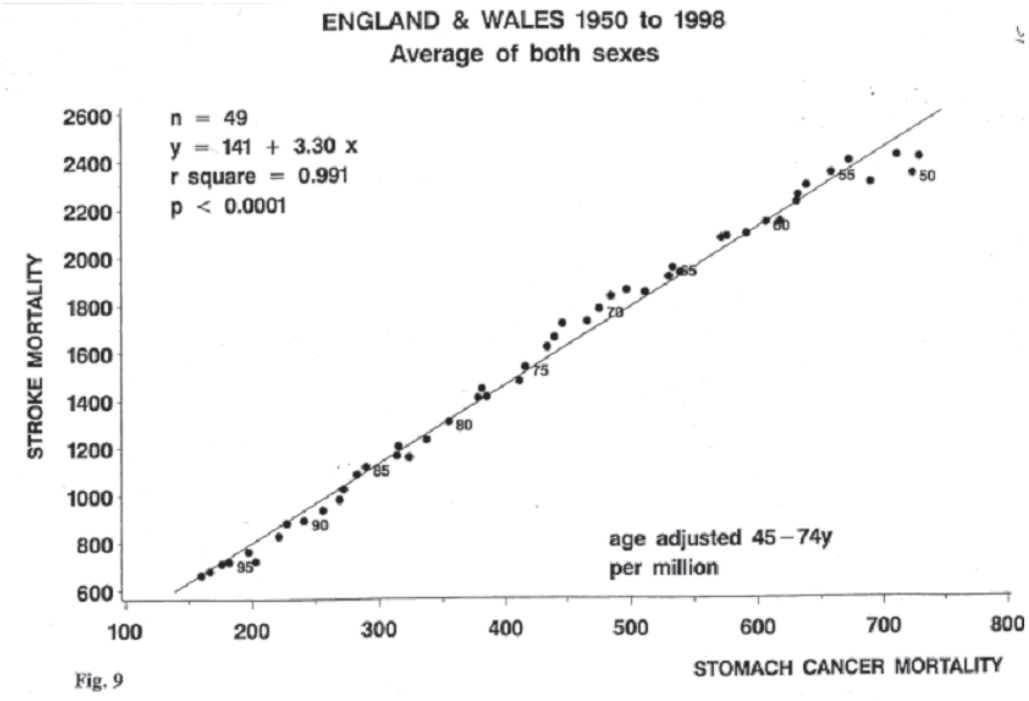


Fig. 9

Courtesy of Elsevier, ref. 4 (2000). Updated to 1998

Salt intake is likely an important linking factor between stroke and stomach cancer mortality (8, 9).

In conclusion a further gradual decrease in salt intake will be important for improving public health at the population level.

References

1. Joossens JV, Sasaki S, Kesteloot H. Bread as a source of salt: an international comparison. J Am Coll Nutr 1994; 13: 179-183.

2. Boe J, Humerfeit S, Wedervang FR. The blood pressure in a population. Acta Med Scand 1957*;* (suppl 32): 1-336.

3. Carlson LA, Lindstedt S. The Stockholm prospective study. I. The initial values for plasma lipids. Acta Med Scand 1969; (suppl 493): *1-635.*

4. Joossens JV. Community control of hypertension in Belgium. In: "Handbook of Hypertension, Vol. 20. Epidemiology of Hypertension". C.J. Bulpitt, ed. Amsterdam, Elsevier 2000, pp. 645-660.

5. INTERSALT Cooperative Research Group. Sodium, potassium, body mass, alcohol and blood pressure: the INTERSALT study. J Hypertens 1988; 6(suppl 4): S584-S586.

6. Joossens JV, Claessens J, Geboers J, Claes JH. Electrolytes and creatinine in multiple 24-hour urine collections (1970-1974). In: "Epidemiology of Arterial Blood Pressure". H. Kesteloot, J.V. Joossens, eds. The Hague-Boston-London, Martinus Nijhoff Publishers, 1980, pp. 45-63.

7. Joossens JV. Relation entre l'épidémiologie des accidents cérébro-vasculaires et celle du cancer de l'estomac. Evolution Médicale 1968; 12: 381-385.

8. Joossens JV, Hill MJ, Elliott P, et al. Dietary salt, nitrate and stomach cancer mortality in 24 countries. It J Epidemiol 1996; *25:* 494-504.

9. Joossens JV, Kesteloot H. Nutrition in relation to stomach cancer and stroke mortality. In: "Current Perspectives on Nutrition and Health". K.K. Carroll, ed. London, Ontario, Canada, McGill-Queen's University Press, 1998, pp. 227-236.

Regulations and Health Policies on Salt in Finland

Heikki KARPPANEN[a, 5]
Institute of Biomedicine, University of Helsinki, Helsinki, Finland

Eero MERVAALA[a]
Institute of Biomedicine, University of Helsinki, Helsinki, Finland

and Erkki PIHKALA[b]
Helsinki School of Economics and Business Administration, Helsinki, Finland

Intake of salt has decreased, and life expectancy increased in Finland

Comprehensive activities aiming at a considerable reduction in the average intake of salt in the whole population began in Finland in January 1978. Thereafter the decrease in the use of salt at home has been remarkable (Figure 1). From the average level of approximately 6.6 g per person a day the use decreased to 5.5 g within the first four years of the intervention (-17%), to 4.4 g within eight years (-33%), to 3.3 within 13 years (-50%), to 2 g within 18 years (-70%), and further to approximately 1.8 g a day within 20 years (-73%). Moreover, there has also been a dramatic change in the type of salt added at home. The sodium-reduced, potassium-, magnesium- and lysine-enriched “Pansalt” has replaced approximately 30% of the use of common salt, hence also contributing to an increased intake of potassium in Finland.

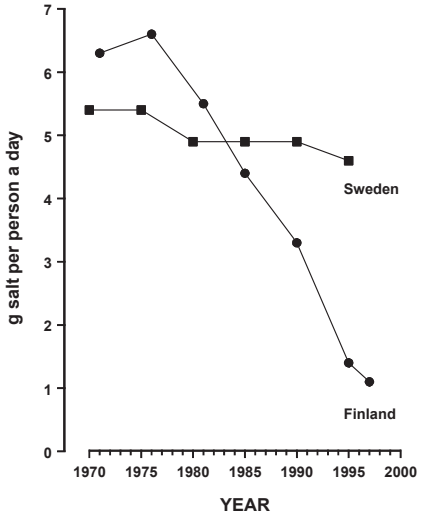


Figure 1 : Salt home use in Finland and Sweden

The intake of salt decreased even before the beginning of the salt intervention (Figure 2). The increase in refrigerators and later also in freezers, decreasing the need for high concentrations of salt in the preservation of meat, fish, and other food items, may mainly

[5]Speaker of the conference
[a]University of Helsinki, Institute of Biomedicine, POB 63, FIN 00014 University of Helsinki, Finland, and [b]Helsinki School of Economics and Business Administration, FIN 00100 Helsinki, Finland.

explain the decrease in salt use in the late 1960s and in 1970s. However, the decrease in the 1980s and 1990s is very likely due to other factors. This assumption is supported by data from Sweden. In our neighbouring country the prevalence of refrigerators increased and reached 100% saturation several years earlier than in Finland. However, after 1980s when all families even in Finland have had a refrigerator, the rapid decrease in the use of salt has continued in Finland, but the decrease in Sweden has been small (Figure 1).

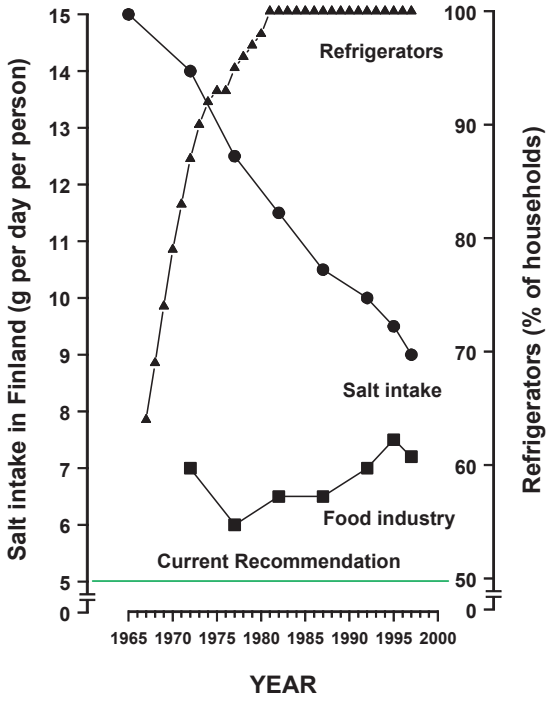


Figure 2 : Salt intake and refrigerators in Finland

During the 20-year salt intervention period from 1978 to 1997 the average total intake of salt in the population of Finland has decreased from 12.5 g to approximately 9 g a day per person (-28%). Taking into consideration the fact that the figures represent the average change in the whole population, the decrease in the salt use, which has been achieved so far, can be considered a great success.

The content of salt even in industrially manufactured food items has gradually decreased in Finland as seen, for example, in the salt level of sausages (Figure 3). The reduction in the total intake of salt is the result of the decrease in the average salt concentration of both homemade and industrially manufactured foods.

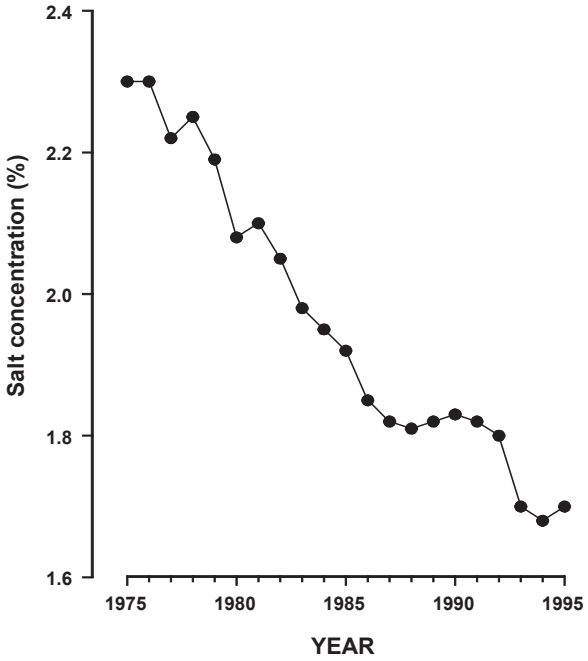


Figure 3 : Salt level in Finnish sausages

Simultaneously with the decrease in the intake of salt by the population of Finland the death-rates from stroke and heart attacks among the middle-aged population have decreased as much as 60-70% (see 1; Statistics of the National Public Health Institute of Finland). Age-adjusted gastric cancer and heart failure have also decreased remarkably. The life expectancy in Finland both among men and women has increased by several years since the late 1970s (Statistics of the National Public Health Institute of Finland).

Role of different factors in the salt changes

Role of publicity

It is obvious that Helsingin Sanomat, which is the biggest newspaper in Nordic countries and by far the most influential newspaper in Finland, has played a decisive role in the success of salt intervention. The first big article emphasising salt as a harmful dietary factor, was published on January 11, 1978. During the past 24 years this leading newspaper has published a big number of articles and editorials on this subject.

Moreover, thanks to the extensive reports on the inventions of sodium-reduced, potassium- and magnesium-enriched healthier salt alternatives, called “mineral salt” or “Pansalt”, Helsingin Sanomat has increased the interest of the population in salt.

With very few exceptions, smaller newspapers as well as TV and radio channels have more or less taken the same position as Helsingin Sanomat in the salt issues. Since January 1978 there have been hundreds of reports on both the harmful effects of salt and on the availability of healthier, good-tasting alternatives.

Role of official salt recommendations

Experience from our neighbouring country, Sweden, clearly shows that official dietary and medical salt recommendations, which are not connected with other activities, have relatively little effect on the average level of salt use (Figure 1). However, in Finland the official recommendations to decrease the intake of salt to one half of the prevailing levels,

have encouraged media to take a more clear anti-salt position than might have been the case in the absence of such recommendations.

Industrially manufactured foods are the principal salt sources

Since the early 1970s industrially manufactured food items, meals, and canteen foods have played an increasing, and recently a major, role in the total intake of salt in Finland (Figure 4).

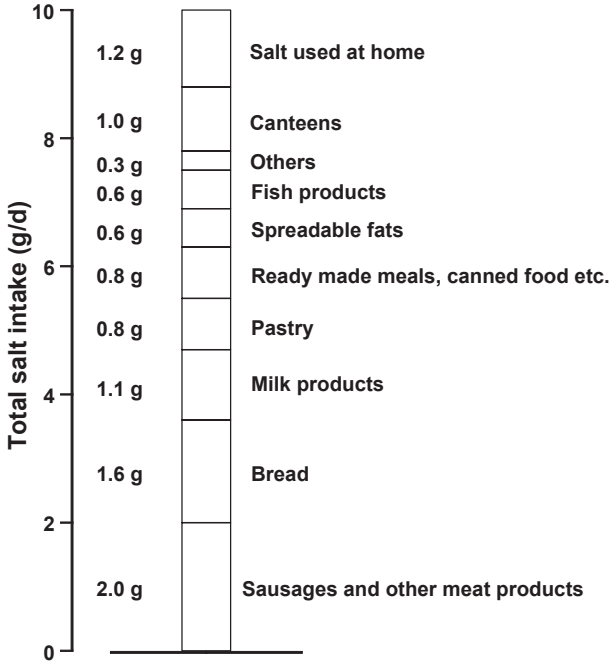


Figure 4 : Main salt sources in Finland

Salt labelling legislation

To reduce the intake of salt from industrial food items in Finland, the Ministry of Trade and Industry, in cooperation with the Ministry of Social Affairs and Health, prepared new salt labelling regulations in early 1990s. The legislation is applied to all the food item categories, which contribute markedly to the intake of salt in the average Finnish diets. This legislation has been fully implemented since June 1, 1993. The most effective part of the legislation, leading to markedly reduced average salt contents in the most important food categories, has proved to be the “high salt content” warning. The “high salt content” must be labelled, if the NaCl content is more than 1.3% in bread, 1.8% in sausages, 1.4% in cheese, 2.0% in butter, and 1.7% in breakfast cereals or crisp bread.

The launch of this legislation reduced the average salt content in breads by approximately 20% from about 1.5% to about 1.2%. In sausages the average decrease in salt content due to this legislation was approximately 10% (Figure 3).

To make healthier choices possible for consumers, the content of NaCl in % has to be labelled in breads, sausages and other meat products, fish products, butter, soups and sauces, ready-made dishes and salt-containing spice mixtures.

Moreover, it is allowed to emphasise a lower than conventional level of salt (low-salt label), if the NaCl concentration does not exceed 0.7% in breads, 1.2% in sausages, 0.7%

in cheese, 1.0% in fish products, breakfast cereals or butter, 0.5% in soups, sauces and ready-made dishes, and 1.2% in crisp bread.

Unfortunately, this approach has not gained popularity so far. One of the main reasons appears to be the fact that a vast majority of the population, due to the experiences in the 1980s, still seem to think that that “low-salt” also means lack of taste. The poor sales of the “low-salt” labelled products have not encouraged companies to use the label even on food items, which fulfil the criteria for this label.

Consensus agreement with food industry and canteens

To promote the reduction of salt use in food industry and canteens, the Ministry of Social Affairs and Health and the Finnish Heart Association arranged in November 1997 a consensus meeting for “the promotion of heart health”. Sixty different groups representing the most important food companies and a big number of different organizations, started the preparation of the consensus statement in February 1997. The statement very much emphasises the need for a 50% further decrease in the level of sodium in all food items and ready-made meals, which contain added salt. A number of measures, which are needed and believed to be useful for reaching the goal of reducing the intake of salt in the whole population to half of the 1997 level, i.e. to below 5 g/d per person, are pointed out in the statement (2).

Use of tempting health-related labels

Since the 1980s an increasing number of companies, have reduced the sodium content and increased the potassium and magnesium content of their food items by replacing the use of common salt by sodium-reduced mineral salt. Such products, including recently even Unilever margarines and McDonald’s hamburgers, usually have a visible “Pansalt” logo, which has proved to be a good marketing argument. The customers have learned that the products with this logo offer a healthier choice without compromising the taste.

A very recent approach is the “Better Choice” label, launched by Finland’s Heart Association in January 2000. Companies may buy the right to use the label on food items, which have a lower sodium content and an improved fat composition compared with the average products on the market. The exact criteria have been set for each food type. Many of the healthier food alternatives currently have both the “Pansalt” and the “Better Choice” labels.

Promotion of healthier choices by publicising salt contents

Studies comparing the sodium content between different brands of heavily consumed meat products, breads, ketchups etc. have been published in newspapers, on TV and radio in Finland. Such comparisons have demonstrated to the population that equally good-tasting products may have several-fold differences in their sodium and potassium contents. Such comparisons have produced marked changes in the sales of different products. This, in turn, has promoted product planning, which has resulted in products with lowered sodium contents.

Salt reduction has negative influences in beverage and food industry

Legislation-based, population-wide restrictions on the use of salt could cause huge economical losses to many food companies as well as to the gigantic beverage and beer corporations. A marked reduction in the salt level has a negative effect on taste and, hence, the sales of potato chips and many other foods. The decrease of water-binding, due to a reduced content of salt, is another concern for meat processors and many other companies. In Finland many companies have been able to avoid these problems by replacing a part of the added sodium chloride in their products by potassium and magnesium salts. Most commonly the use of the alternative (Pansalt) instead of common salt has been the chosen policy.

The amount of fluid intake is strongly dependent on the level of salt intake (3). The beverage and beer industries have revenue, which exceeds the revenue of the Republic of France. If the average salt intake decreased by 30 to 50 % as recommended, the sales of beer and beverages are likely to decrease remarkably.

Because of the economic importance of the maintenance of the current high levels of salt intake, the food and beverage industries have activities, which are in many respects similar to those of the tobacco industries.

In Finland we have informed the authorities and press of the fact that, in the use of salt, the public health needs and the economical needs of many companies are in a striking discrepancy.

During the salt intervention in Finland, a number of misleading conclusions from scientific reports have been launched as press releases. Such press releases have repeatedly claimed that the studies have demonstrated that the current levels of salt use produce no harmful effects. One of the most recent ones dealt with a report by Dr. Alderman and co-workers (4). In this case, like in all other similar cases, we have shown the weaknesses of the conclusions or the studies themselves to the press and public. This has increased the interest of the press and public in salt. In this way the salt lobbying, aiming at blocking of the salt legislation activities, has even promoted the salt restriction in Finland.

References

1. Karppanen H, Mervaala E: Adherence to and population impact of non-pharmacological and pharmacological antihypertensive therapy. Journal of Human Hypertension 1996; 10, Suppl. 1, S57-S61.

2. Ministry of Social Affairs and Health: Consensus statement. Action Plan for Promoting Finnish Heart Health, Publications 1998; 12.

3. He FJ, Markandu ND, Sagnella GA, MacGregor GA: Effect of salt intake on renal excretion of water in humans. Hypertension 2001; 38: 317-320.

4. Alderman MH, Cohen H, Madhavan S: Dietary sodium intake and mortality: the National Health and Nutrition Examination Survey (NHANES I). Lancet 1998; 351: 781-785.

The Experience of the UK in salt reduction

Lisa JACKSON
Food Standards Agency, London, United Kingdom

Good afternoon ladies and gentlemen. Thank you very much to the organisers for inviting me to take part in this conference. I come from the United Kingdom Food Standards Agency, and work in the Nutrition Division. The Agency was created in the wake of a number of serious food scares in order to protect the interests of consumers by following three core values. It will:

- put the consumer first
- be open and accessible and
- be an independent voice.

It might be appropriate to begin by describing our strategic objectives in nutrition which are firstly, to secure a sound evidence base for action, secondly, to develop appropriate means of informing the general population, thirdly, to identify and address barriers to changing dietary behaviour and most importantly perhaps finally, to evaluate and monitor effectiveness of our actions.

According to the latest Health Survey for England (Erens & Primatesta 1998), the prevalence of high blood pressure was 40.8% for men and 32.9% for women. The prevalence increased with age from 16.0% in men aged 16-24 to 72.8% in those aged 75 and over. In women the corresponding rise was from 4% up to 77.6%. The same age related pattern is seen in the Scottish Health Survey 1998 (Scottish Executive Health Department 2000) where the prevalence in men aged 16-24 was 9.8% to 73.5% in those aged 65-74 years. In the same age groups for women the prevalence increased from 0.5% to 29.8%. In Scotland the overall prevalence for men was 33.1 and 28.4 for women. The Welsh Health Survey (The National Assembly for Wales 1998) has shown a small rise in the proportion of people reporting raised blood pressure from 13.6% in 1995 to 15.2% in 1998. In Northern Ireland, the NI Health and Social Wellbeing Survey 2001 found that 19% of men and 27% of women reported having been informed by a health professional that they had high blood pressure.

*"*Observational studies indicate that both systolic and diastolic blood pressure are positively related to the risk of stroke and coronary heart disease not only among individuals who might be considered 'hypertensive' but also among those who would usually be considered 'normotensive'. In fact, within the wide ranges of blood pressure (BP) studied, there was no evidence of any 'threshold' below which lower levels of BP were not associated with lower risks of stroke and of coronary heart disease" (Erens and Primatesta 1998).

Hypertension as a risk factor for heart disease

Hypertension is a reversible risk factor for congestive heart failure, renal failure and peripheral vascular disease. There is agreement that cardiovascular disease can be prevented by altering diet and lifestyle and thus reducing risk factors such as high blood pressure.

Even small reductions in blood pressure may be beneficial. One estimate suggests that lowering the median blood pressure of the population by 2 mm Hg could be more effective

in reducing the rate of cardiovascular disease than medically treating individual patients who have diastolic pressures greater than 95 mm Hg (Cook et al 1995). At age 55 the blood pressure difference for a 100 mmol/24h sodium difference is about 10 mm Hg systolic (or 5 mm Hg diastolic): this is associated with a 34% difference in mortality from stroke and a 21% difference in mortality from ischaemic heart disease (Law 1996).

Sodium and hypertension

The view that there is a relationship between salt intake and hypertension is not new. Suggestions of a relationship go back further than 50 years. A critical review from 1973 of published studies (Gleiberman, 1973) concluded that there was a relation between salt intake and blood pressure but it could not conclude whether salt or other cultural changes or both were responsible for the increase in blood pressure. However, criticism of most of the studies included in the review is that the methodology used to assess dietary sodium and blood pressure were inadequate (Garrow et al 2000).

Other EU countries also recognise a possible relationship between salt intakes and the incidence of certain diseases and so have taken steps to reduce salt intakes within their respective countries. Recommendations for salt intakes are between 5 g/day to 8 g/day.

Basis of current UK recommendations on sodium/salt intake

Table salt is sodium chloride. 6 g salt contains about 2.4 g sodium.

Urinary sodium excretion is the best measure of intake. The Dietary and Nutrition Survey of British Adults (Gregory et al 1990) estimated average sodium excretion in 1986/87 to be equivalent to about 9 g/day of salt. Sodium intakes can also be assessed in the annual National Food Survey (NFS) which has looked at household food purchasing patterns since the 1950s.

Data from the National Diet and Nutrition Survey of Young People age 4-18 years carried out in 1997 showed that 1% of boys in the 11-14 age group and 8% of 15-18 year old boys had intakes at 11.4 g of salt per day or more. There were a few older boys in the survey with salt intakes at around 12 g per day, and this was excluding salt added in cooking or at the table. The average for the whole group was 6.7 g salt per day for boys and 5.5 g per day for girls.

COMA (Committee on Medical Aspects of Food and Nutrition Policy) considered sodium in its report on Dietary Reference Values, published in 1991 (DH 1991). It set a RNI of 1.6 g sodium (equivalent to 4 g salt) as the level that is likely to meet the needs of 97% of the population. Its considerations at the time focused on the requirements for sodium as an essential nutrient and did not directly address "optimum" intakes in respect of the link between dietary sodium and blood pressure.

The relationship between salt and blood pressure was considered in COMA's subsequent report on the "Nutritional Aspects of Cardiovascular Disease" (DH 1994) which made dietary recommendations to reduce cardiovascular disease, including coronary heart disease and stroke, in the population. COMA concluded that sodium intake appears to be an important determinant of blood pressure in the population as a whole at least partly by influencing the rise of blood pressure with age. A diet lower in common salt, which is a major source of sodium, and higher in potassium would be expected to result in lower blood pressure and a smaller rise in blood pressure with age.

COMA recommended a reduction in the average intake of common salt (sodium chloride) by the adult population from the current level at the time of 9 g/day to about 6 g/day. As men eat more food than women this equates to 5 g/day in women and about 7 g/day in men. A similar proportionate reduction in the sodium content of children's diets was also recommended, although it was acknowledged that because of insufficient data it was not possible to quantify this.

The main sources of sodium intake (excluding table salt) in the British diet are cereals and cereal products (including bread, breakfast cereals, biscuits, cakes and pastries), which provide nearly 40% of averageintake, and meat and meat products which provide over 20% of average intake. More recent figures from 2000 confirm these percentages and show that bread as a total constitutes about 22% of sodium intake.

Contribution made by selected foods to average salt intake

Food	% contribution to sodium intake		
	Population M[1]	Young people ag[2] 15-18 years	People aged 65 ye[3] and over
Bread	24	19	22
Breakfast cereals	5	7	9
Biscuits, buns, cakes & pastries	5	4	7
Meat & meat products	21	25	21
Vegetables & potatoes	10	9	6*
Crisps & savoury snack	3	5	
TOTAL INTAKE (g/d)	6.3	6.8	5.8

1 MAFF National Food Survey 1999;excluding sodium from table salt

2 National Diet and Nutrition Survey: young people aged 4-18 years; Excludin sodium from salt added at the table or in cooking

3 National Diet and Nutrition Survey: people aged 65 years and over;free-livin group. Excluding sodium from salt added at the table or in cooking

* includes contribution from crisps and savoury snacks (<1%).

Recent initiatives

In December 1997 a workshop was organised at the English Department of Health's request by the Faculty of Public Health Medicine (FPHM) in collaboration with the British Heart Foundation (BHF) to explore the basis of the disagreements surrounding salt consumption and its effect on blood pressure and subsequent cardiovascular disease. It endorsed COMA's advice. It concluded that salt intake was one of a number of dietary and other lifestyle factors influencing blood pressure and that reducing salt intake would be an appropriate public health measure.

In the 1998 report from the then Chief Medical Officer, Sir Donald Acheson, it was recognised that at any level of blood pressure, people from lower socioeconomic groups were more vulnerable to associated diseases such as cardiovascular diseases and stroke. Recommendations to reduce the salt content of manufactured foods were made based on the concept that there should be no additional cost to the consumer.

In January 1999, in recognition of the fact that an estimated 75% of salt consumed comes from processed foods, the government announced that it would discuss with the food industry the scope for broadening public choice in, and reducing the salt content of, manufactured foods.

The UK Government has always recognised that there are differences of opinion in this area. However the Government's policy remains to seek a reduction in the salt content of processed food where it is present beyond technical, safety and palatability needs.

It has always considered its policy to be proportionate to the evidence and that there are public health gains to be derived from this policy compared with one of inaction.

Salt is one of a number of dietary and other lifestyle factors influencing blood pressure. Recognising this the Food Standards Agency/Department of Health initiatives include:

- To promote healthy eating, in particular increased fruit and vegetable consumption through the healthy schools programme and promotion of the "5 a day" message on fruit and vegetable consumption in pilot sites around the country

- Development of sensible drinking messages through an alcohol health education campaign

- To promote increased levels of physical activity (via GP referral schemes, healthy transport modes, and the National Healthy Schools programme).

The Department of Health National Health Service (NHS) Plan published in July 2000 stated: "The role of Government is to ensure people have information and proper access to healthy food wherever they live so by 2004 action will include: initiatives with the food industry - including manufacturers and caterers - to improve the overall balance of the diet including salt, fat and sugar in food, working with the Food Standards Agency".

COMA recommended that food manufacturers, caterers and individuals explore and grasp the opportunities for reducing the sodium content of foods and meals. In his annual report in 2001 the Chief Medical Officer for England has reiterated the position that lifestyle changes, and particularly improved nutrition through reductions in salt consumption and increasing fruit and vegetable consumption can help prevent high blood pressure.

Initiatives with Industry

It is estimated that three-quarters of the salt consumed comes from processed foods, whilst the remaining quarter comes from additions in cooking or at the table (Gregory et al 1990; Sanchez-Castillo 1987). Reductions in the levels of salt in processed foods would therefore have a significant impact on the average consumption of salt in the population.

Some retailers have started to reduce salt in their own brand products. Kelloggs announced their decision in February 2000 to reduce the salt content of selected products by 30-40%. The Bread industry has claimed a 10% reduction of sodium in bread in 1988 and a further 2.5% in 1989. This followed agreement by the Federation of Bakers and the Health Education Authority. However, analysis of composite samples of bread in the early 1980s (Wenlock et al 1983) compared to samples analysed in 1998 (MAFF 2000) show that there was very little change. Information provided by retailers show that since then significant reductions have taken place, and a recent survey of sodium levels in bread has shown reductions in five most commonly consumed breads of up to 21%.

A new adult dietary survey has recently been completed in which sodium intakes will be estimated from sodium excretion. These new data will be able to give some indication of the pattern of intakes since the last survey was carried out (Gregory et al 1990). However, these data will not be available until early 2003.

Simplified labelling - EU Developments

In 1994 the European Commission issued its Green Paper on Food Law. As part of the UK's response MAFF proposed a number of recommendations for the improvement of nutrition labelling rules. These included a recommendation for the use of salt rather than sodium in the nutrition panel. The response highlighted that many consumers do not understand what sodium is, but are aware of dietary advice about the need to cut down on salt consumption.

The European Commission, in its White Paper on Food Safety, made a commitment to adopt, by July 2001, draft legislative proposal to bring the nutrition labelling directive in line with consumer expectations. Publication of the proposal has been delayed. The Commission is expected in the first instance to issue a discussion document inviting Member States views.

FSA food labelling section recently met with health professionals, consumer groups and industry groups to explore their views about consumer's nutrition information requirements, with a view to identifying nutrition labelling formats for consumer testing. These discussions considered a wide range of issues including salt/sodium labelling. Initial qualitative research on proposed formats has now been completed, and quantitative research will then be commissioned.

Current Agency advice on the use of nutrition claims in food labelling and advertising is that information in the nutrition panel on sodium levels should be accompanied by an equivalent figure for salt. The Agency has recently funded qualitative research on nutritional labelling. This research has not yet been published, but I can tell you that it confirms an impression that consumers tend to find the concept of sodium as opposed to salt on the label difficult to understand and consequently of low priority. The research has looked at consumer views on a variety of formats, including formats which include guideline daily amounts, boxing and emboldening to highlight certain nutrients. Further quantitative research is due on a selection of formats which were most clearly understood in the qualititative phase.

The concept of mini-surveys of the actual nutrient content of foods by chemical analysis will enable the Agency to give consumers further information in order to aid choice. The Agency will choose relevant categories of foods, for example because they are frequently consumed, because they are high in a particular nutrient of interest or because particular categories of the population might be more at risk (for example children).

Present position

In January 1999, the Government announced that it would discuss with the food industry the scope for broadening public choice in, and reducing the salt content of manufactured foods. This commitment was reaffirmed in the Government's White Paper *Saving Lives: Our Healthier Nation.* The Government's response to the Acheson report entitled *Reducing Health Inequalities: An Action Report* published in June 1999 also mentioned the Government's discussions with the food industry and made the commitment to 'provide clear information on the risks of high salt intake'. A number of the Government's publications promoting healthy eating advise salt reduction, and the NHS Plan reiterates the position.

At the request of Ministers, the government's officials held initial discussions with the Food and Drink Federation (FDF) which represent major food manufacturers. Following these

discussions, the FDF announced in June 1999 that it was going to conduct a systematic review of the purpose and usage of sodium in manufactured foods. The review was submitted to the FSA and DH in May 2000 but has not been made publicly available. The two departments have since started ongoing discussions to look at what further steps can be taken in salt reduction. The next steps will include discussions with individual sectors but involvement of the retail sector is also important. The FSA for its part intends to raise awareness of the issue of salt and health amongst consumers, initially via the newly developed FSA website.

Both the Agency and Health Departments continue to receive representations about the extent to which evidence in this area has been fully considered. In September 2001, the Food Standards Agency asked the Scientific Advisory Committee on Nutrition (SACN) to consider reviewing any new evidence since the 1994 COMA report. Interested parties, including industry, academics and clinicians, have submitted evidence which will be considered by a sub-group of SACN in January 2002. In the meantime, the FSA/DH continue to pursue their previously stated position.

It is important to recognise that no one nutrient or food is the key to improving health. Conveying how to achieve a healthy balance to people in wide variety of circumstances is not an easy task. I have already alluded to the concept of health inequalities, and the Agency is particularly concerned to consider the needs of those on lower incomes or in other circumstances which militate against making healthier lifestyle choices.

Salt and Public health policies : regulations and policies on salt in the US

Martha HILL, PhD
John Hopkins University School of Nursing, Baltimore, USA

Situation

Americans, on average, eat 4-6 grams of salt (4,000 to 6,000 mg) daily. Therapeutic restricted diets range from less than 1,000 to 3,000 mg per day. The challenge for policy makers is to educate the consumer to understand the role of sodium, sodium chloride and all other products containing sodium and how to reduce their intake, especially if indicated.

Objectives

To establish consensus on the scientific basis for and methods of consumer education.

Methods

Federal Programs

Federal Regulations: The Code of Federal Regulations, Title 21, -- Food and Drugs -– Chapter 1, Section 101.74 Health claims on sodium and hypertension were published in 1993 and revised in April 2001. They provide statements such as “Diets low in sodium may reduce the risk of high blood pressure, a disease associated with many factors.” The Nutrition Labeling and Education Act of 1990 and regulations from the US Food and Drug Administration and the US Department of Agriculture (USDA) have produced regulations. Since 1994, manufacturers have been required to place a standard label on the package to help consumers know how much of a nutrient is contained per serving.

Federal Education Programs: At NIH, the NHLBI National High Blood Pressure Education Program (NHBPEP) advocates a universal policy of sodium restriction. The rationale is that general consistent messages that apply to the whole population and are consistent with universal nutritional messages are more appropriate for a national campaign. Common messages include “Cut back on salt” and “Limit salt intake.” Since the publication of the DASH Diet results, the message says, “Eat more fruits, vegetables, and low-fat dairy products.” These messages do not focus on salt sensitivity. Despite the nearly 30 yearlong NHLBI – NHBPEP national campaign the public does not follow these recommendations closely.

Non-Federal Programs

The American Heart Association: The AHA diet statement recommends a population based approach to salt restriction, i.e., no more than 2,300 mg of sodium or 6 g of salt per day.

The Salt Institute: The Institute advocates a public health policy to identify and treat the salt-sensitive subset of the population to lower their risk of cardiovascular disease. As a public health policy, the Institute has recommended a campaign to promote the DASH diet.

Results

Many consumers know that salt is associated with the risk of developing hypertension. They are unaware that most of the salt and sodium they consume comes from processed food and food preparation and that in restaurants there is limited availability of low salt foods. Food manufacturers are reluctant to reduce sodium in their products since the public perceives low salt products as untasty and sales do not benefit. Public awareness of the relevance of salt sensitivity and associated health benefits from salt restriction is not known.

Une politique de santé publique pour réduire les apports de sel en France

Dr. Serge HERCBERG
Président du Groupe de travail « sel » de l'Afssa
USEN, INSERM/CNAM, Paris, France

En mars 2001, à la demande de l'Afssa, un Groupe de travail associant scientifiques, administrations, agences, acteurs économiques et associations de consommateurs a été mis en place. Ses objectifs : proposer des mesures à mettre en œuvre pour respecter une distribution statistique de consommation de sodium de 5 à 12 g/j ; identifier les aliments vecteurs de l'essentiel de l'apport sodé alimentaire ; proposer des recommandations effectives d'abaissement de la teneur en sodium de certains aliments vecteurs ; effectuer des études de simulation de l'apport sodé de la population française ; réfléchir sur les moyens de communication à adopter pour accompagner les mesures d'abaissement de la consommation de sodium. Après une analyse de la situation française, le Groupe de Travail a proposé un ensemble de recommandations.

La stratégie retenue est de diminuer la consommation moyenne de sel au niveau de la population, les mesures proposées devant avoir un impact particulièrement net sur les grands consommateurs (> 12 g/j), ce qui paraît assuré par le fait que les principaux aliments vecteurs de sel chez les forts consommateur sont les mêmes que ceux de l'ensemble de la population, consommés en plus grandes quantités (pain/produits de boulangerie, charcuteries, soupes, plats composés, fromages et snacks).

L'objectif fixé à 5 ans est une réduction de 20 % de l'apport moyen de sel, soit une réduction de 4 % des apports sodés moyens par an. Les recommandations proposées au niveau de la réduction de la teneur en sel des aliments et de la communication visent à avoir un impact proportionnellement plus fort chez les grands consommateurs de sel.

Les recommandations envisagent 1) l'optimisation de la teneur en sel des produits, c'est-à-dire la réduction de la teneur en sodium des aliments principaux vecteurs de sodium (et notamment ceux favorisant le risque d'excès) qui soit acceptable sur les plans gustatif, technologique et sécuritaire, et 2) l'éducation et l'information du consommateur pour le responsabiliser dans le contrôle et la gestion de ses apports sodés.

Recommandations sur les produits alimentaires

Les recommandations proposées visent les principaux aliments vecteurs de sodium pour l'ensemble de la population et notamment ceux qui sont des contributeurs majeurs chez les grands consommateurs de sel.

Recommandations vis-à-vis des produits de boulangerie

Sur la base actuelle des produits de boulangerie, il est proposé de réduire la quantité de sel ajoutée par le professionnel d'environ 5 % par an pendant 5 ans. Le principe de réduction progressive de la teneur sodée (non perceptible par le consommateur) devra être adapté à l'ensemble des produits de panification de la boulangerie courante et fine, mais il conviendra de prévoir pour ces produits, compte tenu de leurs spécificités, une teneur de départ avant la mise en place de cette réduction.

Diverses mesures d'accompagnement sont prévues :

- *pour les consommateurs*, des campagnes institutionnelles de sensibilisation valorisant l'intérêt santé d'éviter de manger des produits trop salés et des mesures visant à réduire les teneurs sodées des produits alimentaires et à valoriser l'image du pain, source de glucides complexes et de différents micronutriments.

- *pour la boulangerie*, des actions pédagogiques montrant l'importance du pain dans l'apport sodé et la façon dont la boulangerie peut contribuer à la diminuer en tenant compte des différents types de pain ; une formation auprès des boulangers afin de faire comprendre la mesure ; des moyens de communication pour expliquer à la clientèle les raisons et l'intérêt de la diminution de la teneur en sel du pain et son absence de conséquences sur le plan gustatif, …

Compte tenu du fait que dans le cadre du PNNS (Programme National Nutrition Santé), il est prévu d'encourager la consommation de pain (et des autres produits céréaliers sources de glucides complexes) et que le pain est actuellement un des principaux vecteurs alimentaires du sel, on ne peut accepter le risque que cette mesure de réduction sodée ne soit que partiellement mise en pratique (sous peine de voir augmenter les apports sodés au travers de l'encouragement des consommateurs à augmenter leur consommation de pain). Pour ces raisons, la voie réglementaire est souhaitable.

Recommandations vis-à-vis des produits de charcuterie

- incitation des professionnels à poursuivre leurs efforts pour réduire la teneur en sel, pour les produits qui le tolèrent,

- mise à disposition des consommateurs, quand cela est possible, de produits de charcuterie fabriqués avec des sels de substitution réduisant d'environ 50 % les apports de sodium,

- communication d'informations sur les teneurs en sel et/ou sodium des différentes charcuteries (diffusion de tables de valeurs nutritionnelles moyennes de référence, étiquetage sur les produits ou mise à disposition de cette information sur les points de vente,…),

- communication auprès des consommateurs de l'intérêt d'une consommation raisonnable de charcuteries, dans le contexte d'une consommation alimentaire diversifiée et équilibrée (et en prenant en considération la teneur en sel des différentes charcuteries et la taille des portions consommées).

Recommandations vis-à-vis des fromages

- sensibilisation et incitation des professionnels à poursuivre leurs efforts pour réduire la teneur en sel dans les fromages pour lesquels cela est possible sur les plans technologique et hygiénique, et diminuer la variabilité des teneurs en sel pour un fromage donné.

- communication d'informations sur les teneurs en sel des différents fromages (diffusion de tables de valeurs nutritionnelles moyennes de référence),

- communication auprès des consommateurs sur l'intérêt d'une consommation raisonnable de fromage dans le cadre d'une alimentation diversifiée et équilibrée (et en prenant en considération la teneur en sel des différents fromages et la taille des portions consommées).

- étiquetage de la teneur en sodium ou en sel des produits pré-emballés et mise à disposition de cette information sur les points de vente des fromages à la coupe.

Recommandations vis-à-vis des produits des autres secteurs

- sensibilisation et motivation des industriels à poursuivre leurs efforts pour réduire, pour les produits qui le tolèrent, la teneur en sel et pour diminuer la variabilité des teneurs en sodium pour une même catégorie de produit, notamment en diminuant les teneurs vers les niveaux les plus bas (analyse au cas par cas lors du développement ou de la révision des recettes),

- incitation à l'utilisation de produits de substitution réduisant les apports de sodium,

- incitation à l'utilisation d'épices et autres exhausteurs de goût en remplacement du sel,

- communication auprès des consommateurs de l'intérêt d'une consommation raisonnable de produits industriels salés (snacks, produits apéritifs, …), dans le contexte de l'équilibre nutritionnel, en évitant les excès,

- étiquetage, sur l'emballage, de la teneur en sodium des produits industriels.

Recommandations pour des actions au niveau des consommateurs

Des campagnes et actions d'information sur le sel doivent être mises en place dans le cadre d'une approche nutritionnelle globale, et notamment, en cohérence avec le PNNS. L'information des consommateurs doit permettre d'orienter les choix du consommateur :

- dans ses choix alimentaires pour limiter la consommation des aliments riches en sodium, et réguler ses choix en fonction de son équilibre nutritionnel global,

- dans ses pratiques culinaires pour limiter l'utilisation du sel dans les méthodes de cuisson et de cuisine,

- dans ses pratiques comportementales pour ne pas saler ou resaler les aliments,

En outre, une communication spécifique à destination des mères de jeunes enfants devrait être mise en place, afin qu'elles habituent leurs enfants à manger peu salé.

Actions au niveau de la restauration collective

Au niveau de la restauration scolaire

- application de la circulaire du 25 juin 2001, sur la composition des repas servis en restauration scolaire, qui se propose « d'habituer les enfants à manger peu salé ».

- ne pas mettre à disposition des enfants des sachets - dosettes de sel et éviter ou limiter la présence de salières sur les tables.

Action au niveau de la restauration hors foyer

Encourager les actions mises en place afin d'influencer favorablement les comportements alimentaires des convives ; inciter les structures et sociétés de restauration collective à :

- promouvoir des actions de formation des équipes de restauration sur l'utilisation du sel de cuisine,

- informer les convives sur la problématique du sel et du sodium,

- limiter la mise à disposition de sachets - dosettes ou réduire (dans un premier temps) leur volume (passage de 1 g à 0,5 g par sachet),

- limiter la mise à disposition de salière sur la table, mais éventuellement une salière au niveau des sauces et condiments.

Action au niveau du système de soins

Mise en place d'actions permettant la formation, l'information et la sensibilisation des professionnels de santé sur la problématique du sel.

Etiquetage

- étiquetage systématique de la teneur en sodium, en g/100 g ou /100 ml, et éventuellement par portion,

- indication systématique de l'équivalence approximative en sel (NaCl) de la teneur en sodium, sous la forme « équivalent à environ » ou « correspond à environ » et exprimée en g/100 g ou /100 ml et éventuellement par portion. En première approche, l'équivalence approximative en sel (NaCl) de la teneur en sodium serait obtenue en multipliant par 2,54 la teneur en sodium du produit. Pour les produits dans lesquels sont incorporés des additifs technologiques ou des substances à but nutritionnel ou physiologique contenant du sodium, la détermination du coefficient de conversion devrait faire l'objet d'une évaluation spécifique.

- la détermination par une instance scientifique ad hoc d'une valeur « repère » (et non une valeur « de référence », cette valeur n'étant ni un ANC, ni un AJR), et la mention sur l'étiquetage de cette valeur sous la forme d'un chiffre ou d'une fourchette, dans une phrase du type « il est recommandé de ne pas dépasser X g de sodium par jour, soit Y g de sel par jour ».

- l'affichage dans les points de vente de la teneur en sel des produits non emballés, tout au moins pour les produits fabriqués en quantité industrielle, et, dans la mesure du possible, pour les produits élaborés par des artisans et sur les lieux de vente.

- l'incitation à utiliser des allégations nutritionnelles absolues concernant le sodium (faible / pauvre, très faible / très pauvre et exempt), au détriment des allégations comparatives.

- l'incitation à utiliser une formule telle que « la teneur en sel de ce produit a été précisément étudiée, il est inutile de resaler».

Des outils de surveillance et d'évaluation, notamment par l'Afssa et l'Invs (mesure des apports sodés réels dans le cadre de l'étude nutritionnelle Inca2/ENNS programmée tous les 5 ans) devrait permettre de mesurer l'impact des mesures mises en place.

Les recommandations proposées devront être adaptées dans le futur en fonction des bilans de surveillance et de l'évaluation des mesures proposées, mais également en fonction des résultats des travaux de recherche et des progrès des connaissances dans le domaine de la problématique du sel.

La consommation de sel, ses déterminants et ses possibles évolutions en France

Jean-Luc VOLATIER
Observatoire des consommations alimentaires (OCA), Afssa, Maisons-Alfort, France

Comment mesurer la consommation de sel

La mesure de l'excrétion urinaire de sodium ou natriurèse des 24 heures, répétée plusieurs fois, constitue la méthode de mesure la plus précise. Elle est toutefois difficile à mettre en place sur des échantillons représentatifs de la population générale.

L'estimation indirecte réalisée à partir des enquêtes alimentaires et des tables de composition des aliments (gérées en France par l'Afssa-Ciqual) constitue la seconde méthode de mesure de la consommation de sel. Elle permet de relier les apports en sel aux groupes d'aliments consommés. Elle ne tient cependant pas compte du sel ajouté à table ou en cuisson.

Les études françaises

Quatre enquêtes sont actuellement menées en France afin d'estimer la consommation de sel. Deux enquêtes concernent la natriurèse de 24 heures, la première étant répétée deux fois alors que la seconde n'est répétée qu'une seule fois. Ces deux enquêtes sont menées en Languedoc-Roussillon et en Région Parisienne. Elles établissent des niveaux de consommation moyenne de sel de 10 g/j pour les hommes et de 7 g/j pour les femmes. 20 % des consommateurs dépassent néanmoins 12 g/j de sel, hommes et femmes confondus.

Deux autres études doivent être mentionnées. Elles recensent les données de consommation alimentaires issues des enquêtes de consommation individuelle. Leurs résultats sont relativement cohérents. L'enquête SU.VI.MAX. concerne des volontaires. Elle n'est donc pas représentative au niveau national. Elle avance les chiffres suivants :

- 8 g/j (hors sel ajouté) pour les hommes ;
- 5,5 g/j (hors sel ajouté) pour les femmes.

L'enquête INCA 1999, qui est une enquête représentative, avance les chiffres suivants, pour une population de 1 474 individus de plus de 15 ans :

- 9 g/j (hors sel ajouté) pour les hommes ;
- 6,9 g/j (hors sel ajouté) pour les femmes.

Il faut noter que 8 % des consommateurs dépassent 12 g/j (hors sel ajouté), hommes et femmes confondus.

Distributions statistiques des consommations de sel

Ces distributions, qu'elles soient mesurées par la natriurèse de 24 heures ou par la consommation alimentaire, sont nettement asymétriques, d'allure lognormale et demeurent cohérentes. Le pic de consommation est situé entre 6 et 9 g/j de sel. Il faut toutefois noter que la distribution de la natriurèse de 24 heures ne corrige pas la variance intra-individuelle de la consommation et que la dispersion de cette mesure est forte.

Les groupes d'aliments vecteurs de sel

Une très grande cohérence est également observable dans ce domaine. Les catégories suivantes sont mises en avant par l'étude SU.VI.MAX. ainsi que par l'étude INCA :

- pain, biscottes ;
- charcuteries ;
- fromages ;
- soupes ;
- pizzas, sandwiches ;
- légumes ;
- plats cuisinés ;
- poissons et crustacés ;
- viandes et volailles.

Seul 10 % de la population déclare éviter le sel dans son alimentation. Ceci est la démonstration du réel besoin d'information du consommateur.

Effet de la baisse de 25 % de la teneur en sodium du pain

Cette réduction de 25 % de la teneur en sel du pain, proposée par le groupe de travail « sel » de l'Afssa, est techniquement possible. Elle est d'ailleurs envisagée par l'interprofession de la boulangerie. Une simulation de l'impact d'un abaissement de 25 % de la teneur en sel du pain et des produits de boulangerie a permis de constater la réduction de la variabilité de la consommation de la population, puisque les forts consommateurs de sodium voient leurs apports en sodium se réduire davantage que la moyenne de la population.

Conclusion

La qualité des données de consommation de sel est fondamentale pour la surveillance de la consommation, dans la mesure où les enquêtes actuelles de consommation alimentaire ne tiennent pas compte des ajouts de sel par le consommateur. Une étude est actuellement menée sur 160 sujets. Elle permet de corréler la natriurèse de 24 heures répétée 3 fois sur 7 jours, avec à la fois les données des carnets de consommation de 7 jours utilisés dans l'étude INCA et celles issues des questionnaires complémentaires portant sur les habitudes d'ajout de sel et sur la mesure de la consommation de sel à travers la pesée de la salière. Cela permettra de mieux apprécier la consommation de sel totale mesurée par la future enquête INCA2-ENNS, qui devrait être menée en 2003.

De la salle

Je pense que la principale fonction du sel de substitution finlandais est d'annuler les conséquences économiques de la réduction du contenu en sel des aliments préparés. Je me demande par ailleurs si l'existence d'un « Salt Institute » américain ne constitue pas un exemple qui devrait nous inspirer.

Heikki KARPPENEN

Il n'existe pas de « Salt Institute » en Finlande. Il demeure que la presse se fait souvent l'écho du fait que notre consommation de sel est trop élevée. Nous savons par ailleurs que la consommation de magnésium est très faible dans notre pays. Nous nous efforçons par conséquent de la développer. Notre expérience en matière de supplément iodé est satisfaisante. Nous pensons par conséquent qu'il est possible de remplacer une partie de la consommation de sodium par ces produits plus bénéfiques. Dans le même temps, le potassium et le magnésium ont le même effet gustatif, bien que leur saveur soit légèrement plus amère. Toutefois, en ajoutant de la lysine, il est tout à fait possible de simuler le goût du chlorure de sodium. Nous avons donc essayé de réconcilier les intérêts commerciaux avec les intérêts médicaux et nutritifs. Les commerces ne subissent actuellement aucune perte, même si les ventes de sel diminuent. Les sociétés ont remplacé le sel ordinaire par le sel de substitution. Il faut toutefois noter que le nouveau sel de substitution finlandais coûte deux ou trois fois plus cher que l'ancien, puisqu'il s'agit d'un produit haut de gamme.

Martha HILL

Suite à mon intervention, je souhaiterais préciser que le public peut être tout à fait résistant à nos messages. Par ailleurs, notre administration est très « pro-entreprise ». Nous voulons réduire le rôle de l'Etat dans la vie individuelle. Il faut néanmoins noter que les changements de mode de vie ne sont pas sans susciter quelques frustrations dans le corps médical. L'éducation de la population se limite à recommander la réduction de la consommation de sel, ce qui n'est pas sans inspirer un certain cynisme. Le public veut pouvoir choisir en toute connaissance de cause. Par conséquent, il est important de développer des actions de communication adaptées à ses exigences.

De la salle

Le chlorure n'a-t-il jamais été pris en considération dans les différentes études citées au cours de ce colloque ? Des expériences ont pourtant montré que les conséquences néfastes du chlorure sur la tension étaient peut-être plus importantes que celles du sodium.

Serge HERCBERG

Il est difficile de répondre à cette question, car elle implique de passer en revue la physiologie rénale, ce qui dépasserait le cadre de notre discussion. Le chlore a fait l'objet de discussions au sein de notre groupe de travail. L'énorme majorité du sel de notre

alimentation vient du chlorure de sodium. Telle est d'ailleurs la raison pour laquelle la traduction pour le grand public du mot sodium est le chlorure de sodium.

De la salle

Ne faudrait-il donc pas mieux ne parler que de sel et non pas de sodium sur l'étiquetage ?

Joël MENARD

Le chlore est parfaitement dosé dans certains procédés de fabrication, comme par exemple ceux utilisés pour certains fromages. La réalité scientifique du sodium et du sel est préservée dès lors que les deux vocables sont utilisés.

De la salle

J'aimerais connaître un peu mieux les produits de substitution au sel développés par les Finlandais. A plusieurs reprises dans ce colloque, des spécialistes de l'hypertension ont affirmé qu'il était très facile d'adopter un régime hyposodé. Je pense pour ma part que le passage à un régime hyposodé demande quelques efforts. Je pense en outre qu'un changement trop brutal induirait une réelle modification du régime alimentaire et des habitudes gustatives. La salière ne représente pourtant que 10 % de la consommation globale de sel. Il est donc tout à fait possible de la laisser à la disposition du consommateur.

Joël MENARD

A l'occasion des discussions menées dans le cadre de colloque comme celui-ci, il est important de tenir compte des questions que les uns et les autres peuvent se poser au moment précis des échanges entre les différents experts.

Entre 1970 et 1990, une discussion a été menée au sein du monde scientifique au sujet de la plombémie et du rôle du plomb dans le plasma. Le plomb a de nombreux inconvénients. Il a d'ailleurs été étudié dans le cadre de l'hypertension artérielle. Les taux moyens de plomb dans les différents pays étaient d'ailleurs connus grâce aux enquêtes épidémiologiques. Beaucoup pensaient cependant que le rôle du plomb n'avait pas été démontré.

Une première étude effectuée en 1973 aux Etats-Unis a pourtant montré que la distribution de la plombémie atteignait des valeurs importantes. Au début des années 80, les Etats-Unis et le Canada ont ainsi pris des mesures pour limiter la teneur en plomb de l'essence. Les enquêtes épidémiologiques montrent que la courbe logarithmo-gaussienne a alors diminué en l'espace d'une quinzaine d'année.

A la même époque, l'industrie automobile française défendait la présence de plomb dans l'essence. Les différentes études montrent pourtant, sans équivoque, que la diminution de la teneur en plomb au sein des populations d'Amérique du Nord est une conséquence directe de la politique suivie par les autorités américaines et canadiennes.

Le sodium urinaire, la pression artérielle ou le cholestérol sont des variables biologiques parmi d'autres. Elles peuvent néanmoins évoluer positivement, au plus grand bénéfice des populations, grâce à des actions de santé publique adaptées. J'ai cependant

remarqué que les questions qui m'ont été posées ne semblent pas avoir totalement intégré ce fait. Il faut néanmoins noter que ces variables sont évaluées grâce à des études au sein de la population, menées dans des intervalles de cinq à quinze ans. Ceci montre en outre l'importance de la politique de surveillance adoptée lors de la prise de mesures de santé publique.

Conclusion

Conclusion

Martin HIRSCH

Directeur général
Agence française de sécurité sanitaire des aliments (Afssa), Maisons-Alfort, France

---

Il me paraît essentiel de dire que nous n'avions pas prévu que la date de remise de nos recommandations et celle de la tenue de ce colloque seraient aussi proches l'une de l'autre. Ce rapprochement me paraît néanmoins très intéressant. En effet, si les membres du groupe de travail présidé par Serge Hercberg connaissaient l'ensemble des études qui vous ont été présentées, je pense en revanche que ceux qui recevront ces recommandations, qu'il s'agisse des pouvoirs publics, du public, des journalistes, etc…, ne connaissent pas ces différents travaux. Il me paraît extrêmement intéressant et relativement rare d'assister au processus d'élaboration de telles recommandations et de constater le tri qu'elles opèrent entre les acquis et les incertitudes.

Dans plusieurs des exposés présentés, il a été à la fois question d'alimentation et de médicament. Nous vivons dans un pays où il est souvent considéré que certains comportements sont une fatalité et que la prévention à leur égard relève d'une mission impossible, voire inutile, puisque les médicaments permettent de résoudre tous les problèmes, qu'ils soient naturels ou que nous en soyons à l'origine. J'ai donc trouvé très plaisant de constater, durant ce colloque, que les scientifiques considéraient qu'il était tout à fait possible d'agir de façon préventive afin de corriger ces comportements. Plusieurs présentations ont ainsi montré que cette action pouvait être soit alternative aux médicaments, soit complémentaire.

Je voudrais à présent remercier tous les intervenants pour la qualité de leur présentation. Je remercie également le Comité scientifique pour son excellent travail de sélection et d'organisation.

Les recommandations sont déjà sur le bureau des Ministres. Le Ministre de la Santé a d'ailleurs clairement exprimé devant nous son intention de les mettre en œuvre. Nous espérons par ailleurs travailler sur les différentes pistes définies par le groupe de travail de l'Afssa sur le sel, en particulier celles consistant à ne pas mettre en place une politique sans développer les outils permettant sa surveillance et l'évaluation de ses effets sur la santé et la consommation. Ces questions sont fondamentales, au niveau national aussi bien qu'au niveau européen. J'espère par conséquent qu'à court terme, il sera possible d'organiser une réunion des différents organismes sanitaires des quinze pays de l'Union, afin de développer des réflexions européennes et scientifiques, en appui à l'action mise en œuvre par les gouvernements. L'organisation de tels colloques peut très bien porter sur d'autres sujets. Après le sel, pourquoi pas le sucre ?

ACE : angiotensin converting enzyme
Afssa : Agence française de sécurité sanitaire des aliments
AHA : American Heart Association
ANC : apport nutritionnel conseillé
ANP : atrial natriuretic peptide
AJR : apport journalier recommandé
Afssa : Agence française de sécurité sanitaire des aliments
BHF : British Heart Foundation
BIRNH : Belgian interuniversity research on nutrition and health
BMD : bone mineral density
BMI : body mass index
BP : blood pressure
cAMP : cyclic adenosine monophosphate
CASH : Consensus action group on salt and health
CHD : coronary heart disease
CI : confidence interval
CIQUAL : Centre informatique sur la qualité des aliments (au sein de l'Afssa)
COMA : Committee on medical aspects of food and nutrition policy
COT : cotransport
CNAM : Conservatoire national des arts et métiers
CVD : cardiovascular disease
DASH : Dietary approaches to stop hypertension
DBP : diastolic blood pressure
DH : Department of Health
ENaC : epithelial sodium channel
ENNS : Etude national nutrition - santé
ERPF : effective renal plasma flow
FDA : Food and drug administration
FDF : Food and Drink Federation
FE : fractional excretion
FPHM : Faculty of Public Health Medicine
FSA : Food standards agency
GCGR : glucagon receptor
GFR : glomerular filtration rate
HCTZ : hydrochlorothiazide
INCA (enquête) : enquête individuelle et nationale sur les consommations alimentaires
INSERM : Institut national de la santé et de la recherche médicale
INTERMAP : international cooperative study of macronutrients and blood pressure
InVS : Institut national de veille sanitaire
LVH : left ventricular hypertrophy
MAFF : Ministry of Agriculture, Food and Fisheries
MAP : mean arterial pressure
MHS : Milan hypertensive strains
MNS : Milan normotensive strains
MONICA : monitoring trends and determinants in cardiovascular diseases
MRFIT : multiple risk factor intervention trial
NCHS : National Center for Health Statistics
NHANES : national health and nutrition examination survey
NHBEP : National High Blood Pressure Education Program
NHLBI : National heart, lung and blood institute

NHS : National Health Service
NIH : National Institutes of Health
NOS : nitric oxide synthase
OCA : Observatoire des consommations alimentaires (au sein de l'Afssa)
PCR : polymerase chain reaction
PKC : protein kinase C
PNNS : Programme National Nutrition - Santé
PRA : plasma renin activity
PRC : People Republic of China
PTH : parathyroid hormon
RNI : Reference nutrient intake
RR : relative risk
RT-PCR : reverse transcription - polymerase chain reaction
SACN : Scientific Advisory Committee on Nutrition
SBP : systolic blood pressure
SEM : standard error of measurement
STRIP : Special Turku coronary risk factor intervention project
SU.VI.MAX (étude) : Supplémentation en vitamines et minéraux antioxydants
TOMHS : Treatment of mild hypertension study
TONE : Trial of nonpharmacologic interventions in the elderly
TOHP : Trials of hypertension prevention
USDA : United States Department of Agriculture
USEN : Unité de surveillance et d'épidémiologie nutritionnelle
VSMC : vascular smooth muscle cell
WHO : World Health Organization

Impression d'après documents fournis
bialec, nancy
Dépôt légal n° 58112 - mars 2003

27-31, avenue
du Général Leclerc
BP 19, 94701
Maisons-Alfort cedex
www.afssa.fr

REPUBLIQUE
FRANÇAISE