Potassium and Calcium Intake in Stroke Prevention: A Role for the Food Industry in the Prevention of Cerebrovascular and Cardiovascular Diseases

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The single most important risk factor for stroke is hypertension (1). Therefore, nutritional factors that reduce hypertension are also beneficial in stroke prevention. This chapter reviews the evidence from epidemiological and intervention studies for a role of dietary potassium and calcium in stroke prevention as well as in blood pressure control. The important role of nutrition in hypertension prevention has already found its way into the recommendations of hypertension societies (2) as well as medical texts and textbooks (3).

The relationship between nutrition and stroke can be evaluated in epidemiological studies in man. It is not feasible to investigate the effects of dietary modifications on stroke incidence in man, but modifications which lower blood pressure will certainly reduce stroke incidence and mortality and can be studied in experimental animals bred for their susceptibility to stroke. Therefore, I will also refer to animal studies investigating potassium and calcium effects on stroke and blood pressure control.

The hypertension rates in the Lausanne area are comparable to those in most Western societies (4) (Fig. 1). In a population of 50 years and older, 1 out of 2 or 3 persons is hypertensive. Not surprisingly, mortality due to cardiovascular and cerebrovascular diseases is the most important cause of death in the population over age 65 in the Lausanne area. Almost 50% of the men and 55% of the women in this age group die of a cardiovascular or cerebrovascular disease (4).

**DIETARY POTASSIUM AND PREVENTION OF STROKE AND HYPERTENSION**

**Dietary Potassium Sources**

Fruits, vegetables, soya flour, coffee\(^1\), chocolate, almonds, and nuts are rich in potassium (5,6). Daily potassium intake correlates well with the frequency of intake

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\(^1\) One cup of soluble coffee contains about 80–100 mg of potassium.
of fruits and vegetables. Compliance to the current recommendation to increase fruit and vegetable intake would therefore also result in increased potassium intake.

**Animal Studies**

Tobian reviewed a series of animal studies performed in his own laboratory which investigated the effects of potassium in two animal models of hypertension and stroke. He fed a high salt diet to aggravate the genetic predisposition to hypertension and stroke occurrence to *spontaneously hypertensive stroke prone rats* (SHRSP) and to Dahl salt-sensitive rats (Dahl S; 7). Dietary potassium supplements (a) attenuated hypertension-induced degenerations (renal damage with preservation of renal function and thickening of the renal artery wall in Dahl S rats), and (b) attenuated stroke mortality by over 90% (in SHRSP and in Dahl S rats). The protection from stroke mortality was also observed in animals matched for their blood pressures (7).

The effects of dietary potassium are not restricted to the reduction of degenerations and stroke mortality caused by hypertension, but also it effectively reduces development of hypertension in animals fed a high salt diet. Dahl S rats fed a diet with varying sodium/potassium ratios developed severe hypertension with Na/K ratios of 10:1, but not with a sodium potassium ratio of 1:1 (on molar basis) (8).

Dietary potassium supplements also reduce hypertension in animals fed a normal low salt diet. They reduced hypertension induced by renal artery clipping (reviewed...
in 8), by injection of pressor agents directly into the brain (reviewed in 8), and development of hypertension in SHR (reviewed in 8).

An interesting way to supplement potassium and to improve the potassium/sodium ratio is the replacement of a part of the sodium chloride in salt by other mineral salts containing potassium. In animal studies, such replacement has been shown to reduce blood pressure and to enhance the action of antihypertensive medication (9–11).

Dietary potassium supplements (a) protect susceptible rat strains from the renal and cerebral artery damages induced by ingestion of a high salt diet and this protection occurs independently of a reduction in blood pressure; (b) attenuate development of hypertension in rats on a high salt diet; and (c) also reverse hypertension and blood pressure increases in animals fed normal low salt diets.

Mechanism

Potassium exerts its powerful protective effects by inhibiting free radical formation from vascular and endothelial cells and macrophages, inhibiting proliferation of vascular smooth muscle cells, inhibiting platelet aggregation and thrombosis, and reducing renal vascular resistance and increasing glomerular filtration rates (12–14).

Epidemiological Studies

Today, several isolated communities continue to live as hunters and gatherers under conditions comparable to those encountered by our prehistoric ancestors. They consume food that is different from our Western industrialized diet. In spite of their increased energy expenditure, their diet is lower in fat, alcohol, salt, and total energy, but it contains more fiber and potassium. The daily excretion of sodium and the urinary potassium/sodium ratio reflecting dietary sodium intake and the dietary potassium/sodium ratio, is strikingly different between the so-called nonacculturated societies and our modern Western society (15,16) (Table 1).

Hypertension, coronary heart diseases, and strokes are very rare in aged members of nonindustrialized societies (16). It is evident that factors other than the dietary sodium, potassium, and the potassium/sodium ratio contribute to the lower rates

<table>
<thead>
<tr>
<th>Society</th>
<th>Na⁺ Excretion</th>
<th>K⁺ Excretion</th>
<th>Potassium/Sodium Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonindustrialized</td>
<td>0.9 mmol/day</td>
<td>63.3 mmol/day</td>
<td>70.333</td>
</tr>
<tr>
<td>Western</td>
<td>141.2 mmol/day</td>
<td>63.4 mmol/day</td>
<td>0.449</td>
</tr>
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</table>
of cardiovascular and cerebrovascular diseases, hypertension, and stroke in those societies. Likely contributing factors are the decreased intake of fat, energy, and alcohol, as well as increased energy expenditure (physical work; no electrical appliances and cars available), and the absence of age-associated weight gains and smoking.

Additional evidence for hypertension/stroke protection by dietary potassium is provided by large epidemiological studies (NHANES I and Intersalt, analyzing data from over 10,000 randomly selected adults, reviewed in 17) which show an inverse relationship between dietary potassium intake and stroke incidence. Intake of fruits and vegetables—both rich in potassium—protects against stroke in men (18,19). Lower stroke rates and blood pressure were reported in an apple farming area of Japan (Aomori) (16). This effect was attributed to the potassium content of the apples. In line with these findings, the blood pressure lowering effect of vegetarian diets have also been attributed in part to the increased potassium intake (20).

**Intervention Studies**

A meta-analysis of 19 potassium intervention studies in man revealed significant blood pressure reduction (21). Supine blood pressure was reduced by 5.9/3.4 mm Hg (systolic/diastolic); standing blood pressure in hypertensive patients was reduced by as much as 10.1/5.4 mm Hg. Substitution of table salt by other potassium-rich mineral salts in almost 60% of the diet resulted in significant blood pressure reduction in an elderly Dutch population (22); Grobbee, this volume).

**Conclusions**

Potassium protects against stroke, and independently of its beneficial effects on stroke occurrence, also against hypertension. The latter effect could further potentiate stroke protection. The current nutritional recommendations to increase fruit and vegetable intake ("Mediterranean diet") integrate knowledge of the beneficial effects of potassium on cerebrovascular and cardiovascular disease. At present, potassium supplements are already prescribed (23–25). Saunders suggests modifications of the current recommendations to African Americans to include potassium supplementation (23).

**DIETARY CALCIUM IN PREVENTION OF STROKE AND HYPERTENSION**

**Dietary Calcium Sources**

Dairy products, cheeses, some green vegetables such as broccoli and chervil, fish with soft bones, calcium-precipitated tofu, corn tortilla processed with lime, almonds,
and calcium-containing mineral waters are the main dietary sources of calcium (5,6). Calcium intake can be estimated by the frequency of milk and cheese intake.

Animal Studies

Hatton and McCarron (26) reviewed over 80 animal studies on the effect of dietary calcium manipulations on blood pressure. A total of 67 studies reported an inverse relationship between dietary calcium intake and blood pressure, 8 studies observed no effects, 3 found blood pressure increases, and 3 found divergent blood pressure increases or decreases depending on the model of hypertension screened. Most studies were carried out in rats, using a large variety of rat strains, for example, Zucker rats, spontaneously hypertensive rats, stroke-prone spontaneously hypertensive rats, Wistar-Kyoto rats, Sprague-Dawley rats, Wistar rats, Dahl rats, and parathyroidectomized rats (26).

Mechanism

Several mechanisms by which dietary calcium could exert its blood pressure lowering effect have been proposed (26). These include (a) reduction of membrane permeability and increases of Na,K-ATPase and Ca$^{2+}$-ATPase, which reduce intracellular free calcium. Thus, calcium influx into vascular smooth muscle cells is reduced and its consequent improved ability to extrude calcium reduces vasoconstriction; (b) changes in calcium-regulating hormones—decreases in parathyroid hormone and 1,25 dihydroxyvitamin D$_3$, and increases in calcitonin—these vasoactive calcium regulating hormones influence blood pressure; (c) changes in calcium-sensitive hormones—decreases in parathyroid hypertensive factor and the renin angiotensin system, and increases in atrial natriuretic factor and in calcitonin gene-related peptide, all of which exert powerful effects on blood pressure; (d) inhibition of the sympathetic nervous system and central nervous system outflow; (e) alteration of the electrolyte metabolism—reduction of salt-induced hypertension by natriuresis and by preventing sodium chloride-induced calcium wasting that would result in increases in calcium-regulating hormones.

Epidemiological Studies

Higher levels of dietary calcium were associated with lower levels of blood pressure in the NHANES I and in the U.S. nurses survey using very large populations, that is, over 10,000 and 58,000 people respectively (27–29). Another line of evidence for the involvement of calcium in hypertension derives from the changes in calcium metabolism occurring in hypertension. Hypertensive subjects have higher intracellular free calcium, lower serum ionised calcium, higher urinary calcium excretion, and higher blood parathyroid hormone concentrations (30–33).
Intervention Studies

While a sound, inverse relationship between dietary calcium intake and blood pressure was established in large scale epidemiological surveys, the outcome of calcium intervention studies is not unequivocal (27–29,31,34). One review of 20 calcium intervention studies reported that 15 studies found blood pressure reductions with calcium supplements, whereas 5 did not (29). Seven out of eight calcium studies cited by a second, more optimistic, review obtained significant blood pressure reductions with calcium (27). A third very recent review of 30 calcium studies concludes that about two-thirds of the studies obtained blood pressure reductions with calcium (28). A meta-analysis of 15 calcium studies concluded that the overall effect of calcium on blood pressure, if any, is very small but an effect on a subset of subject cannot be excluded (34). Evidently, the efficacy of calcium supplements is not universal but is limited to specific groups of hypertensives, for example, salt-sensitive groups of hypertensives (the aging population and African Americans) and to pregnancy-induced hypertension (31–33).

Conclusions

Calcium supplements (also in the form of calcium-fortified or calcium-rich food items) are probably efficient in the treatment of part of the hypertensive population. People consuming a diet insufficient in calcium, salt-sensitive subjects on a high salt diet, aged hypertensives, and African Americans are the target populations that would benefit from such interventions. Saunders included calcium supplements in his modification of dietary advice to African American hypertensives, a group with particularly low calcium intake (23).

A ROLE FOR THE FOOD INDUSTRY IN THE PREVENTION OF CEREBROVASCULAR AND CARDIOVASCULAR DISEASES

Good nutrition cannot guarantee health; nor can it easily reverse the adverse health effects of obesity, hypertension, and diabetes, which develop over decades. Discovery of a magic remedy cannot be a realistic goal of nutritional sciences. However, research efforts must be made to obtain precise knowledge of all nutritionally-related health aspects. The application of nutritional knowledge and the possibility of intervention are discussed next using salt content in processed food as an example.

A general consensus about dietary/lifestyle modification in health maintenance and attenuation of nutritional related diseases has been achieved. The most important dietary/lifestyle modifications for the prevention of cardiovascular and cerebrovascular diseases, hypertension and diabetes are (a) weight reduction and maintenance, in the case of excessive weight; (b) smoking abstinence; (c) moderation of alcohol consumption; (d) increase in physical activity in the case of sedentary lifestyle; and
finally (e) moderation of salt consumption. Daily sodium intake should not exceed 88 mmol/day\(^2\) [(i.e., 2 g of sodium or 5 g of salt per day (3,35)].

Moderation of salt consumption is not the top priority topic in dietary/lifestyle modifications for reduction of stroke and hypertension risk. The question remains whether to reduce salt or to achieve a more equilibrated dietary potassium/sodium ratio. While moderation of salt consumption is unanimously advised by medical authorities (2,3,35), supplements of potassium and/or calcium are already given (23–25), although still under discussion. Salt reductions concomitant with increases in the potassium/sodium ratio can be obtained by replacing part of the salt by other mineral salts (22; Grobbee, this volume; see later).

Salt Reduction—Past, Present, and Future

Past

Introduction of refrigeration/freezing of staple foods in Europe after World War II permitted important reductions of the use of salt. Estimations of daily salt consumption from the sales of food grade salt in Switzerland revealed a 40% reduction from 18 to 11 g/day in Switzerland between 1951 and 1976. Concomitant to these reductions in salt intake, stroke (and stomach cancer) rates dropped very significantly (36). Comparable observations were made in Belgium and in Japan (36,37). Daily salt intake in Belgium fell from 15 to 9 g between 1968 and 1981, and in Japan, from 14.5 to 11.7 g between 1972 and 1987. The trend in salt reduction continues and is still evident today. Stouffer's Lean Cuisine\(^{\text{®}}\), a brand of the Nestlé Frozen Food Company, has reduced the salt content in its product by 37% between 1988 and 1995. The salt content of the five most salty products of the Lean Cuisine line, containing more than 1000 mg sodium per serving, was reduced by over 48% in the same time period (Fig. 2). These important reductions in salt were achieved without any loss in palatability of the food: part of the reduction was compensated for by other spices or by the better distribution of salt in the food. A similar decrease in salt content was observed in bread in Belgium and in Spain (38).

Present

A daily salt intake of up to 88 mmol (5 g of salt) is recommended for reduction of hypertension and stroke/infarct risk, but the actual intake in industrialized societies is more than double this amount, that is, around 12–15 g per day. Three quarters of the daily salt intake is provided by home or industrially processed food (Fig. 3) (2,39). Processing of food increases sodium content and profoundly alters potassium/sodium ratios (Fig. 4 and Fig. 5) (5,6). This change in the dietary potassium/sodium ratio is possibly as important as the absolute levels of salt. A reasonable salt reduction or improvement of the potassium/sodium ratio is only achievable by reducing the

\(^2\) The German Hypertension Society advises to limit salt intake to 5–6 g per day (2).
Future

In spite of the discrepancy between recommended and actual intake, a revision of the current recommendations is unlikely. Even though only the salt-sensitive individuals\(^3\) profit from reductions in salt intake, a gradual decrease of intake toward the recommended levels is likely to occur in the future. This could be achieved by further substitution of salt by spices or by replacement of some salt by other mineral salts (22; Grobbee, this volume, and see later). Additional improvement of the potassium/sodium ratio could be achieved by potassium supplements, or by dietary modifications favoring potassium-rich food items, for example, fruits and vegetables ("Mediterranean diet").

\(^3\) The prevalence of salt-sensitivity appears to be greater in blacks, older, obese, and obese/diabetic patients as compared to whites, younger hypertensives, and normal weight hypertensives (40).
FIG. 3. Dietary sodium sources.
FIG. 4. Reduction of potassium/sodium ratios by food processing in tomatoes and corn.

FIG. 5. Reduction of potassium/sodium ratios by food processing in potatoes and herring.
TABLE 2. Sodium, potassium, calcium content (mg/100 g) and the sodium/potassium ratio (on molar basis) of selected commercialized food items from Switzerland as determined in our own laboratories

<table>
<thead>
<tr>
<th></th>
<th>Na⁺</th>
<th>K⁺</th>
<th>K⁺/Na⁺</th>
<th>Ca²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofu (14371)</td>
<td>676</td>
<td>348</td>
<td>0.303</td>
<td>150</td>
</tr>
<tr>
<td>Tofu (14372)</td>
<td>504</td>
<td>169</td>
<td>0.179</td>
<td>89</td>
</tr>
<tr>
<td>Crisps (14373)</td>
<td>136</td>
<td>1191</td>
<td>5.149</td>
<td>29</td>
</tr>
<tr>
<td>Crisps (14374)</td>
<td>622</td>
<td>1191</td>
<td>1.126</td>
<td>27</td>
</tr>
<tr>
<td>Bread</td>
<td>883</td>
<td>176</td>
<td>0.117</td>
<td>299</td>
</tr>
<tr>
<td>Camembert</td>
<td>602</td>
<td>140</td>
<td>0.137</td>
<td>481</td>
</tr>
<tr>
<td>Gruyère</td>
<td>495</td>
<td>73</td>
<td>0.087</td>
<td>1224</td>
</tr>
</tbody>
</table>

Partial Salt Substitution by Other Mineral Salts

Substitution of salt by other mineral salts was successfully applied in a Dutch study (22; Grobbee, this volume) and the same approach has been applied to a commercially available tofu product (Tofu-14371) in Switzerland. Whereas the overall salt content and saltiness is enhanced when compared with another commercial product on the Swiss market, the potassium/sodium ratio is slightly improved (Tofu-14372; Table 2).

Application of salt substitution by other mineral salts performed in the same way as the Dutch study (22) would improve the potassium/sodium ratio and reduce overall salt content of standard cornflakes as summarized in Fig. 6.

![Cornflakes](image)

**FIG. 6.** Reduction of sodium content and improvement of the potassium/sodium ratio in cornflakes by partial substitution of sodium chloride by mineral salts.
Low Salt Products

The sodium content of food cannot always be appropriately estimated. We found two types of commercially available crisps in Switzerland (Crisps 14373 and Crisps 14374; Table 2). One product (14373) contains low amounts of added salt, the other (14374) with usual amounts of salt added, contains 4.6 times more sodium. The latter’s potassium/sodium ratio is also 4.6 times lower (Table 2). Not surprisingly, crisps 14373 obtained higher ratings from a Swiss consumers’ organization than the standard product 14374 (41). The low salt content of crisps 14373 is not highlighted or used for advertising purposes and only becomes evident on careful reading of the product composition. Both types of crisps coexist and are evidently well sold. Bread is another example of the difficulty to correctly perceive dietary salt content. It contains more salt than crisps, soft (Camembert), or hard cheese (Gruyère; Table 2) which again confirms the difficulty to correctly estimate salt content of food items. The potentiated saltiness of crisps is due to the presence of the salt on the surface. This effect was used to reduce the salt content in commercially available Lean Cuisine products. The increased salt perception of cheese as compared to bread is likely to depend on the interaction with other constituents of cheese (e.g., calcium salts, or other constituents). The latter salt taste enhancement could probably be exploited for further salt reductions in a variety of products.

CONCLUSION

Salt content and potassium/salt ratio in standard food products could be decreased or improved respectively by partial salt substitution by other mineral salts (see Table 2; Fig. 6). The calcium issue needs further evaluation. It is of prime interest for the food industry to evaluate whether calcium effects on blood pressure are more consistent when limited to calcium-sensitive individuals. Abundant preliminary evidence for such a calcium sensitivity exists, and application of calcium-rich milk products and mineral waters in these individuals would be of great interest. The food industry could continue to play a major role in reduction of cardiovascular and cerebrovascular diseases by providing designed food that is nutritionally balanced.

ACKNOWLEDGMENT

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REFERENCES

DISCUSSION

Dr. Guesry: Of course, like you I love the simplistic approach, like 10 apples a day to keep the stroke away—it is certainly very good for the lay public. However, for science, it is not very helpful because people eating 10 apples a day probably have a very low energy intake, a very low fat intake, a very low sodium intake, and a high fiber intake, all of which influence cholesterol. You may obtain beautiful correlations with almost anything if you disregard all the other factors which are also present in the diet!

Dr. Ornstein: I agree, but if you take the case of potassium supplements, they not only have an effect in animals, but also reduce blood pressure in humans, so we are safe to assume that they are active in this regard. But if other components in apple enhance the effect, it is even better.

Dr. Grobbee: I agree with most, but not all, of what you said. For example, in relation to the stroke rate trends: I very much doubt whether the 35% of reduction in stroke rates in Switzerland has any relation to the change in sodium intake over the same period; if we go further back in history, we can see that there was also a 35% reduction in stroke rate between the beginning of the century and 1968 without a concomitant change in salt intake. One other thing in the calcium story is that it is very difficult to connect the cellular findings to the intake findings. It does make sense that whatever form of hypertension you have, eventually in order for the peripheral resistance to increase, you do need increases in intracellular calcium. Thus, this is a completely nonspecific phenomenon and in my view, it does not require any general change in calcium metabolism, even though calcium appears to be important and does have effects on blood pressure in certain sensitive individuals. However, the eventual common pathway for whatever form of hypertension should be increased intracellular calcium.
Dr. Elmadfa: Stroke and cardiovascular disease are multifactorial and we should not look at only one factor, say potassium, or calcium, or sodium. My question is, how much of the nutrients that you discussed do we need for stroke prevention? Are the current dietary recommendations sufficient for prevention, or are you implying the need for supplements?

Dr. Ornstein: Green showed that in the so-called stroke belt in the southeastern United States, there was a reduced potassium excretion 20 years ago (1). There is presently an indication that many elderly people attending clinics are in a hypokalemic state. I think these phenomena are important. Normally, in young healthy people, I believe the intake should be sufficient for most, but if a person does not eat fruits and vegetables at all, then most probably there will be an inadequate potassium supply. The same is true for calcium: if a person does not take any mineral water or milk products, the chances are that the intake will be low in calcium.

Dr. Elmadfa: But is there a need to increase the recommendations for calcium intake to more than 1000 mg?

Dr. Ornstein: I don’t think there is a need to change the recommendations, but there is a need to stick to them. For the salt issue, the recommendations are clear, and we eat double what is recommended.

Dr. Hossmann: I have a question concerning these amazing findings of a substantial reduction in mortality of spontaneously hypertensive rats which you put on a potassium-rich diet. Do you get a change in the extracellular potassium activity as a consequence of the change in the diet? I thought it was regulated.

Dr. Ornstein: There are slight changes in the blood with the potassium-rich diet, yes. Variations in plasma potassium concentrations between 3.1 to 4.6 mmol/l have been produced by changes in dietary potassium intake (2).

Dr. Hossmann: Then, of course, if you change extracellular potassium activity in the brain, you would expect a slight increase in collateral flow, for instance, but I think this needs to be proved. I am skeptical.

Dr. Ornstein: It has been shown. Extracellular potassium induces vascular smooth muscle relaxation which could result in increased collateral flow. This has been reviewed by Young (1990, 1995, 1995). My statement was too strong. The evidence is indirect and I believe Dr. Hossmann’s point is worth being tested (2-4).

Dr. Hossmann: My other question concerns the cause of death of these animals. You said all the animals die as a result of stroke. A couple of years ago, we looked at the brains of Dr. Yamori’s stroke-prone SHRs when they were still alive, and we did physiological studies. Although they were all alive, they all had ischemic lesions, so apparently these animals get brain infarcts before they die. So maybe death is due to something else, like bleeding.

Dr. Ornstein: The reports on calcium supplementation show that with calcium supplements, you reduce the lesion size but you increase lesion numbers, so if you don’t take an end point like mortality, you don’t know what happens to stroke.

Dr. Hossmann: We had the impression from that series of brains that the most extensive lesions in the brain were not produced by the stroke but by the edema around the stroke. If there were lesions in the white matter, in particular, there was a tremendous amount of vasogenic edema which led to a mass lesion because the volume of the brain was substantially increased. I wonder if some of these dietary effects could be indirect effects on edema formation.

Dr. Ornstein: I don’t know, but Tobian’s work may clarify this. The question whether dietary potassium can indirectly reduce oedema formation is an important question. Tobian’s
work actually does not give any indication whether such an indirect potassium effect occurs (5).

Dr. Pertuiset: A comment regarding daily neurologic practice and stroke in general: I think I see more patients with a deficit in sodium and dehydration, especially older patients. I understand the possible importance of excess sodium, but we must not forget this aspect.

REFERENCES


