Salt: blood pressure, the kidney, and other harmful effects

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undergoing renal transplantation, support the possibility that an abnormality of some aspects of renal function may both initiate and maintain hypertension (essential). The nature of this abnormality remains unknown, as does its genetic basis’. [1]

However, outside the nephrological world, there is considerable scepticism. Blood pressure is regulated by a myriad of mechanisms. Can only one organ be the cause of the rise in blood pressure, and thereby the major risk factor for stroke, coronary heart disease, and premature vascular disease? Nevertheless, the accumulating evidence is compelling, and suggests that salt intake, and the handling of salt by the kidney are critical factors. An increase in blood pressure is not the only harmful thing that follows from this chain of events, and recent attention has focused on other harmful effects of our current high salt intake, such as left ventricular hypertrophy, stroke, worsening of renal disease, asthma, cancer of the stomach, and bone demineralization (osteoporosis) [2].

The kidney. The cause of essential hypertension

Traube was the first to delineate this concept in 1871, and attributed the rise in pressure that occurs in Bright’s disease to a reduction in kidney function:

‘The shrinking of the kidney will act by decreasing the amount of liquid which is removed by urinary excretion. As a result, the mean pressure of the arterial system must increase.’ [3]

Not until 90 years later did Borst and Borst de Gues develop the concept that the kidney, in essential hypertension, had an underlying unwillingness to excrete salt [4]. And therefore, what seems a normal salt output is maintained at the expense of high blood pressure. Evidence for this concept is clear when there is underlying renal disease, but what is the evidence in essential hypertension? By far the most persuasive evidence comes from kidney crosstransplantation experiments in inherited hypertension in rats.

Introduction

A primary abnormality in the kidney can underlie some systemic disorders, and few nephrologists would deny that the kidney is the final arbiter of nearly all forms of secondary hypertension. However, essential hypertension is a greater diagnostic puzzle. Much evidence now suggests that an underlying abnormality in the kidney in essential hypertension may also cause the rise in arterial pressure. To quote Tony Raine,

‘These observations (cross-transplantation) in animal models of hypertension, and in patients

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These cross-transplant experiments have now been performed in Dahl, Milan and spontaneously hypertensive rats. In these different forms of inherited hypertension in rats, it is clear from the experiments that the kidney carries the underlying genetic message for the development of high blood pressure [5]. Clearly, evidence in inherited hypertension in man (essential hypertension) is more circumstantial. In six patients who had prolonged essential hypertension, which had caused renal failure, kidney transplantation resulted in cure of their high blood pressure [6]. Furthermore, in a separate study, the prevalence of hypertension in transplanted patients, when corrected for other factors, was found to relate to the family history of the donor family. In other words, if the donor kidney came from a family with a history of high blood pressure, the transplanted patients were more likely to have high blood pressure [7].

Further supportive evidence comes from secondary hypertension in man, where all forms of increased blood pressure, apart from phaeochromocytoma, are due either to an intrinsic abnormality in the kidney, particularly in its ability to excrete sodium, e.g. Liddle’s syndrome, or an imposed restraint on the kidney’s ability to excrete sodium, e.g. primary aldosteronism, or a variety of rare genetic disorders resulting in excess mineralocorticoid activity, e.g. glucocorticoid remedial aldosteronism [8].

**Impaired ability to excrete sodium**

In inherited hypertension in rats, if the kidneys are removed before the rat has developed high blood pressure, these kidneys have a reduced ability to excrete sodium for a given perfusion pressure, compared to normotensive rats. At the same time, it has been shown in several of these strains of rats that, at the time the blood pressure increases, there is retention of sodium [9]. Some studies in relatives of patients with essential hypertension have also suggested there may be an underlying impairment of the kidneys’ ability to excrete sodium [9].

By far the best illustration of hypertension in humans caused by an impaired ability to excrete sodium is Liddle’s syndrome. In this syndrome, mutations occur in the subunits of the epithelial sodium channel. These result in increased sodium channel activity in the distal tubule and collecting duct. The excess sodium re-absorption causes an increase in blood pressure. This can be corrected by the administration of amiloride, which specifically acts to reduce the overactive sodium channels [10]. It is possible, particularly in patients of African origin, that less overt mutations of the sodium channel may possibly underlie the cause of some patients’ essential hypertension. Work from Bianchi’s group suggests that a modification of a cytoskeletal protein, adducin, may play a role in essential hypertension, through impairing the kidneys’ ability to excrete sodium.

The inheritance of kidneys that are less able to excrete sodium is likely to have bestowed a considerable biological advantage during evolution when man had no access to salt, and this would have been particularly evident in hot climates. Over the last 5000 years, our diet has changed radically, so that it is now very high in sodium, and this difficulty in excreting sodium can now be seen as a distinct genetic disadvantage.

**Control of sodium balance**

The interplay between salt intake and salt excretion plays a critical role in determining extracellular volume. This is clearly evident in humans when a salt intake of 10–20 mmol/day (the same intake as during evolution) is increased to our current salt intake of 150–200 mmol/day, causing an approximate 1–2 increase in extracellular volume. This increase in extracellular volume is essential in order to stimulate a variety of mechanisms that increase sodium excretion, so that salt balance is now maintained, but at the expense of this sodium retention and a continued sustained increase in the compensatory mechanisms necessary to excrete the increased salt intake.

As Borst and Borst de Gues, and Guyton subsequently, pointed out, one mechanism for the increase in sodium excretion, with an increase in salt intake, is an increase in blood pressure. At the same time, several hormonal mechanisms, suppression of the renin–angiotensin–aldosterone system and stimulation of the atrial natriuretic peptide system, directly increase sodium excretion and also buffer the increase in blood pressure that would otherwise occur. The role of other hormonal mechanisms controlling sodium excretion is more controversial, e.g. sodium transport inhibitors and the sympathetic nervous system.

Therefore, in those that inherit a kidney that is less able to excrete salt, there will be a much greater need for these compensatory mechanisms in order to increase salt excretion to maintain sodium balance. It is perhaps not surprising that over many years of a high salt intake there is then a gradual elevation in blood pressure.

**Salt intake and blood pressure**

Evidence that our current high intake of salt relates to population blood pressure and development of high blood pressure comes from many sources. Epidemiological studies demonstrate that the amount of salt consumed in different communities is a major factor in determining blood pressure differences between these communities [11]. However, these individual studies were criticised on many methodological grounds, and it was with this in mind that a large international ‘Inter-Salt study’ was set up. This study clearly confirmed that the amount of salt consumed, as judged by urinary sodium excretion, related to blood pressure levels, both within populations and between
populations, and was responsible for much of the increase in blood pressure that occurs with increasing age in Western populations [12]. Other factors, which were also found to be important, were potassium intake, weight, and alcohol intake, although the latter only has a transient effect on blood pressure.

Two recent intervention studies, one in newborn babies and one in adults in Portugal, clearly demonstrated the importance of salt intake in regulating blood pressure. Just under 500 newborn Dutch babies were randomized to either receive a modestly reduced salt intake (~30% reduction) for the first 6 months of life. In the group that had the lower salt intake, there was a significant reduction in systolic blood pressure at 6 months. At this time, the study was discontinued, but a follow-up of a subgroup of these individuals showed that, when they were 15 years of age, the corrected difference in systolic blood pressure remained, in spite of the fact that the babies who had had the low salt intake for the first 6 months of life had reverted to a normal salt intake subsequently (Figure 1) [13]. A study in two villages in Portugal, where salt intake was reduced in one by advising how to reduce salt in the cooking and the provision of processed food, such as bread with less salt, showed that, at the end of the intervention period of 2 years, blood pressure was significantly lower in the village given such advice, compared to a village where no such advice had been given (Figure 2) [14].

Migration studies have shown that subsistence farmers in rural Kenya, who consume a low sodium/high potassium diet, on migration to an urban community have a marked increase in blood pressure. This was associated with an increase in salt intake and a decline in potassium intake [15].

Short-term studies of salt restriction have shown that a reduction of our current salt intake by approximately half, i.e. from 10 to 5 g per day, causes a decrease in pressure in patients with high blood pressure and a smaller, but still highly significant, decrease in normotensive subjects [16]. A recent, carefully controlled study in older subjects has now shown that the decrease in blood pressure in the normotensive subjects with modest salt restriction is the same as in hypertensive subjects, and is very similar to that seen with a thiazide diuretic [17].

Studies in other mammals provide a wealth of evidence for the importance of salt intake in nearly all forms of elevated blood pressure [9]. A recent, elegant experiment in chimpanzees, a group of which were fed their natural diet, i.e. similar to that which humans and chimpanzees ate during evolution (10 mmol sodium per day), was compared to a group where salt intake was increased to the same amount that we now consume, 150–200 mmol per day. Over the 2 years of the study, there was a progressive increase in blood pressure (systolic blood pressure increasing by >30 mmHg) in those chimpanzees on the higher salt intake diet (Figure 3) [18]. Following this study, chim-

![Salt Restriction for Six Months in Newborn Babies](https://academic.oup.com/ndt/article-abstract/13/10/2471/1838692/fig1)

**Fig. 1.** Difference in blood pressure in newborn babies, randomized to either a normal salt intake or a moderate reduction in salt intake over the first 6 months of life. At 6 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.
Fig. 2. 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 for blood pressure, but no advice on diet. Note the significant differences in blood pressure at 1 year, and continuing differences at 2 years.

Fig. 3. 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.
panzees living in captivity have now had their salt intake reduced (D. Denton, personal communication).

Several rare genetic mutations have now been shown to cause high blood pressure in man. All of these either affect, directly or indirectly, the kidneys’ ability to excrete sodium and are aggravated by a high salt intake [8]. Interestingly, patients with low blood pressure have the opposite, i.e. the kidney can no longer hold on to sodium, e.g. pseudo-hypoaldosteronism, Addison’s disease, phenacetin nephropathy. In this situation, where the kidney cannot hold on to sodium, there is low blood pressure which is ameliorated by a high salt intake.

Salt intake and the food industry

Given all the evidence that relates salt intake to blood pressure, most medical advisory committees, and indeed most governments in the Western world, have recommended a reduction in population salt intake. For instance, the 1994 report in the United Kingdom, *Nutritional Aspects of Cardiovascular Disease*, recommended a reduction from an average of 9 to 6 g salt per day (30% reduction). None of these worldwide recommendations have been implemented. This is the direct result of an entirely artificial debate created by the salt industry and some processed food manufacturers to suggest that the evidence that our current high salt intake relates to blood pressure is not substantial, or that the evidence is not sufficient to act on, or that reducing salt intake might be dangerous.

The reasons for this are not difficult to find (Figure 5). Seventy to 80% of our salt intake now comes from salt added to processed food by the food industry. Maintaining a very high salt concentration in processed foods is important, firstly because most of these foods would be inedible and salt is by far the cheapest flavour enhancer. At the same time, if high salt foods are consumed, the salt taste receptors are suppressed. There is then a marked preference for high salt foods and habituation to high salt processed foods. Furthermore, a high salt concentration in processed food, particularly meat products, allows more water to be added at no extra cost. Some meat products can have their weight increased by 20–30%. Salt intake in temperate climates is the most important determinant of fluid intake. This is seen when going from a low to a high salt intake, when there is just under a 1-l increase in urinary volume (Figure 4). Similar results have been shown in the Inter-Salt study, both within and between populations. Soft drink manufacturers, therefore, have a tremendous commercial interest in keeping our salt intake high. Indeed, a 30% reduction in salt intake would result in a decline in soft drink sales.

The food industry in the Western world is the biggest single industry and can exert immense political influence [19]. At the same time, the salt manufacturers and their trade organizations, particularly the Salt Institute, have run an expensive and largely surreptitious public relations campaign to try to suggest to politicians, other members of the food industry, nutritionists, and other health care professionals that the evidence for salt is not substantial. As occurred with the tobacco industry, there is now only a small number of doctors and scientists who are prepared to lend their support to such activities. Nevertheless, in view of the huge commercial interest of maintaining the current concentrations of salt in processed food, it is unlikely that the food industry is going to give way, particularly as the public are unaware of the huge amounts of salt that are now contained in processed food.

One simple way of realizing this is to compare the concentration of sodium in food to that contained in Atlantic seawater. Atlantic seawater contains 1.0 g sodium per 100 g water. Cornflakes contain 1.1 g of sodium per 100 g, and are therefore 10% more concentrated than seawater. Bread varies from 0.5 to 1.2 g sodium per 100 g and is therefore 50–120% the concentration of seawater. This simple method allows those who wish to restrict their salt intake to relate the salt concentration of food, and to decide whether they wish to eat the equivalent of seawater or not.

This contrived ‘debate’ on salt has focused attention on the relationship between salt and blood pressure and other major adverse problems that our current high salt intake causes have been quietly and conveniently ignored.
Other harmful effects of a high salt intake

Exacerbation of conditions where there is sodium water retention

As our current high salt intake already causes an increase in extracellular volume of 1–2 l, any condition where there is already sodium and water retention will be considerably exacerbated by a high salt intake, and is ameliorated by a reduction in salt intake. This is particularly true of patients with heart failure, nephrotic syndrome, and cirrhosis with sodium retention. Many women with idiopathic and cyclical oedema also find, by reducing their salt intake, considerable improvement in their symptoms.

Left ventricular hypertrophy

Left ventricular hypertrophy is a major independent risk factor for sudden death and vascular disease. Whilst previously it was always felt that the most important factor determining the degree of enlargement of the left ventricle was the level of blood pressure, it has now been shown that salt intake, independent and additive to that of blood pressure, plays a critical role. Indeed, some studies have shown that salt intake is a more important determinant of the degree of hypertrophy than the blood pressure itself [20].

Stroke

Evidence in rat models of hypertension and stroke suggest that, for a given level of blood pressure, an increase in salt intake causes a dramatic increase in the number of strokes. Circumstantial evidence in man suggests that the same may be true, in that when different populations are compared, there is a very close correlation between the prevalence of strokes, or stroke mortality, and salt intake which is much closer than that for blood pressure, suggesting that salt may have an additive effect on strokes independent of its effect on blood pressure [21,22] (Figure 6).

Progression of renal disease

In animal models, an increase in salt intake increases renal blood flow with an increase in glomerular pressure. Several forms of experimental renal disease are considerably exacerbated by an increase in salt intake. Studies have shown that a reduction in salt intake slows down the rate of deterioration of renal function.
in these animals more than when a thiazide diuretic is administered, and to the same extent as when ACE inhibitors or calcium antagonists are administered [23]. Much circumstantial evidence suggests that the same may apply in man. Similar changes are known to occur in renal blood flow and studies have shown that increasing salt intake increases proteinuria and contrariwise a decrease in salt intake reduces proteinuria. This is particularly seen when the effects are compared to an ACE inhibitor where most of the antiproteinuric effects of the ACE inhibitor are abolished by an increase in salt intake [24]. These effects on proteinuria are independent of those on blood pressure and clearly the increase in blood pressure that occurs with the increase in salt intake would have a further damaging effect.

**Asthma**

Bronchial reactivity is related to sodium balance, and an increase in salt intake increases bronchial arteriolar smooth muscle reactivity. A carefully controlled, double blind study of salt restriction showed that a reduction in salt intake was associated with a reduction in the consumption of bronchodilators, improved symptom scores and objective measurements of higher peak flow and forced expiratory volume [25]. It would seem, therefore, from these studies that, whilst salt is clearly not a direct cause of asthma, a high salt intake can act as a major aggravating factor.

**Stomach cancer**

Joosens, many years ago, pointed out the close relationship between the prevalence of stroke and cancer of the stomach in different communities. More recently, studies in Japan, where cancer of the stomach is common, have shown a close relationship between stomach cancer and the amount of salt consumed in the diet. A recent meta-analysis of all of the epidemiological studies has demonstrated a close relationship between salt consumption in different countries and stomach cancer [26] (Figure 7). The conclusion of this analysis was that salt intake was the rate-limiting factor for the development of cancer of the stomach. It is possible that the effect of salt on the stomach, in that a high salt meal strips the lining of the stomach, makes infection with *Helicobacter pylori* more likely or may exacerbate infection [26].

**Renal stones and osteoporosis**

Salt intake is the main determinant of urinary calcium excretion [27]. However, it has always been assumed that this increase in calcium excretion, with an increase in salt intake, was exactly compensated by an identical increase in calcium absorption from the gastrointestinal tract with no mobilization of calcium from bone. However, several recent studies now suggest that this concept is incorrect. With an increase in salt intake, there is a marked increase in urinary calcium excretion, probably as a direct result of extracellular volume expansion. This increase in calcium excretion causes a tendency for a reduction in calcium concentration in the blood, which stimulates compensatory hormonal mechanisms to increase gastrointestinal absorption of calcium (Figure 8). However, at the same time, there is mobilization of calcium from bone. For instance, when salt intake was increased in a group of post-menopausal women, there was the expected increase in calcium excretion, but also an increase inpara-thyroid hormone and hydroxyproline excretion [28]. In a separate study, where salt intake was reduced, there was again the expected reduction in calcium excretion, but this was associated with a decrease in 1,25-dihydroxy vitamin D and serum osteocalcin, indicating a decrease in bone mobilization [29]. Based on these observations, a 2-year longitudinal study of bone density in 124 post-menopausal women has now shown that the most important determinant of the reduction in hip bone density was the urinary sodium excretion on entry to the study [30]. There was no bone loss at the hip over the 2 years of the study if sodium excretion was <90 mmol/day. From their results, it was calculated that a modest reduction in salt intake from 10 to 5 g would have the same effect on hip bone density as an increase in calcium excretion of ~1 g, a difficult amount to achieve in the diet without taking calcium supplements.

In patients with essential hypertension, it is already known that, for a given urinary sodium excretion, there is an increase in urinary calcium excretion, compared to normotensive subjects. Hypertensive patients also have a tendency for a lowered ionized calcium, a higher parathyroid concentration and higher 1,25-dihydroxy vitamin D. All of these findings indicate that the increase in urinary calcium excretion is not fully compensated for by an increase in calcium absorption from the gastrointestinal tract; there is the likelihood of long-term mobilization of calcium from bone [31]. Patients with essential hypertension would appear, therefore, to be
at greater risk of bone demineralization at a given sodium intake than normotensive subjects. It is of some interest that in inherited hypertension in rats, if they are allowed to survive for long enough, they develop severe bone demineralization. In essential hypertension, the position is complicated by the use of drugs to treat the elevated blood pressure, particularly the use of thiazide diuretics which are known to reduce calcium excretion, with a positive calcium balance. Studies have shown that with longterm use of thiazide diuretics there is an increase in bone density and a reduction in the rate of hip fractures. A modest reduction in salt intake is also known to reduce urinary calcium excretion and cause a positive calcium balance. It is therefore likely that a modest reduction in salt intake will likely have the same effect on bone density and fractures as a thiazide diuretic.

**Conclusion**

The discovery of the magical property of salt to preserve food played a vital role in the development of civilization. At the same time, salt was found to remove the bitter taste of tainted or bad food, and was therefore felt to be a purifying agent. With a high salt intake, there is suppression of the salt taste receptors, and food and higher salt concentrations are craved. However, our current addiction to salt is recent, as man only discovered the magical properties of salt for the last 5000 years. Salt allowed the development of settled communities and became of great economic importance, responsible for many wars and the main source of tax revenue. However, with the development of the deep freezer and refrigerator in the late 19th century, salt was no longer needed for the preservation of food. Salt consumption since then has started to fall. However, this reduction in salt intake is now being reversed by our increasing demand for ready-prepared instant and processed foods.

Salt is deeply imbued into our culture. It is difficult, given this background, for us to concede how dangerous this substance has now become. This, coupled with the intransigence of the food industry who for purely commercial reasons continue to add large amounts of salt to processed food, is now causing much unnecessary cardiovascular disease. Law calculated in his summary of the evidence about salt that a 50 mmol (3 g) reduction in salt intake in the UK would reduce strokes by 22% and heart attacks by 16% [32]. This reduction of 3 g salt per day from an average of 9 to 6 g is exactly that recommended in the UK as part of a dietary strategy to reduce the number of heart attacks and strokes. However, following financial and political pressure from the food industry, these recommendations were not implemented, and similar events have occurred in almost all developed countries.

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