COMMENTARY

Plasma sodium and hypertension

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Plasma sodium and hypertension. Dietary salt is the major cause of the rise in the blood pressure with age and the development of high blood pressure in populations. However, the mechanisms whereby salt intake raises the blood pressure are not clear. Existing concepts focus on the tendency for an increase in extracellular fluid volume (ECV), but an increased salt intake also induces a small rise in plasma sodium, which increases a transfer of fluid from the intracellular to the extracellular space, and stimulates the thirst center. Accordingly, the rise in plasma sodium is responsible for the tendency for an increase in ECV. Although the change in ECV may have a pressor effect, the associated rise in plasma sodium itself may also cause the blood pressure to rise. There is some evidence in patients with essential hypertension and the spontaneously hypertensive rat (SHR) that plasma sodium may be raised by 1 to 3 mmol/L. An experimental rise in sodium concentration greater than 5 mmol/L induces pressor effects on the brain and on the renin-angiotensin system. Such a rise can also induce changes in cultured vascular tissue similar to those that occur in the vessels of humans and animals on a high sodium diet, independent of the blood pressure. We suggest that a small increase in plasma sodium may be part of the mechanisms whereby dietary salt increases the blood pressure.

High blood pressure is now recognized as the major cause of cardiovascular disease worldwide. In England, high blood pressure, which is both a certified cause of death and a contributory factor in over 170,000 deaths, is the most common cause of death [1]. In 1998, the prevalence of hypertension (a blood pressure greater than 140/90 mm Hg) was 41% in males and 33% in females, rising in males from 16% at 16 to 24 years of age to 74% at 75 years, and in females from 4% to 78% [2]. The rise in arterial pressure is related to dietary salt [3, 4], and dietary salt also increases the mass of the left ventricular wall [5], stiffens conduit arteries [6], and thickens and narrows resistance arteries [7] independent of the blood pressure. The rise in arterial pressure and other harmful cardiovascular effects of dietary salt are related to the primary inadequacy of the kidney to excrete sodium [8, 9]. The impairment of the kidney’s ability to excrete sodium is either genetic, as in essential hypertension and the spontaneously hypertensive rat (SHR) [10], or it can be superimposed as in obesity [11], primary hyperaldosteronism, or renal disease. The primacy of the kidney’s control of sodium excretion in the regulation of the blood pressure has been confirmed by the finding that of 20 genes so far identified to be associated with essential hypertension or responsible for rare Mendelian forms of high and low blood pressure, all are involved in the regulation of sodium handling by the kidney [12].

Evidence for the role of dietary salt in the rise in arterial pressure in essential hypertension, the SHR, and in the other cardiovascular effects that dietary salt induces independent of the blood pressure, come from epidemiologic studies [13–15] within and between populations, experimental models, particularly in primates [16, 17], physiologic and biochemical studies [10], controlled clinical trials [18–20] in normotensive and hypertensive individuals, and familial [21, 22], genetic [23, 24], and mortality studies [25]. In spite of this accumulation of information, the connecting and causative links between dietary salt and the rise in arterial pressure in essential hypertension and the SHR, and the other harmful effects it causes independent of the blood pressure, are uncertain. This paper reviews the evidence that small changes in plasma sodium may play a role.

POSSIBLE INITIATING FACTORS RESPONSIBLE FOR THE PESSOR EFFECT OF DIETARY SODIUM

In the study of essential hypertension and the SHR, the relevant input of sodium chloride is that which is habitually consumed, which, in humans in developed countries, is subject to large day-to-day variations. Sodium balance is controlled almost entirely by the kidney’s ability to vary the urinary excretion of sodium. The immediate effects of dietary sodium are to alter plasma sodium and, consequently, the extracellular fluid volume (ECV). These
changes must therefore be primarily responsible for the subsequent alterations that affect the blood pressure.

The mechanisms that link the input of sodium chloride to the blood pressure have been studied mainly following acute changes. Their relevance to the search for the mechanisms responsible for the rise in blood pressure that develops in humans over many decades is questionable. There have been relatively few studies of the effect of prolonged changes in salt intake, particularly the effect of a prolonged increase. An acute increase in sodium input can induce a rise in blood pressure by either raising plasma sodium even when the ECV is falling [26, 27], or by increasing the ECV even when the plasma sodium is falling [28]. This would indicate that acute changes in both plasma sodium and ECV are each potentially capable of independently controlling the blood pressure. The sections which follow describe the evidence in support of a hypothesis which proposes that prolonged increases in salt intake, or when the habitual intake of salt is high, particularly when there is a diminished ability of the kidney to excrete sodium, as in essential hypertension and the SHR, the associated rise in arterial pressure is initiated and sustained in part by a persistent increase in plasma sodium.

SODIUM INTAKE, PLASMA AND CEREBRAL SPINAL FLUID (CSF) SODIUM, AND BLOOD PRESSURE

Acute changes in dietary salt intake on plasma sodium

In both normotensive and hypertensive humans, a large and sudden increase in dietary sodium usually causes a 2 to 4 mmol/L rise in plasma sodium [29–35] (Table 1). In a study of gradually increasing salt intake from 10 to 250 mmol/day by a daily amount of 50 mmol, there was an increase in plasma sodium of approximately 3 mmol/L [29]. There were also significant correlations between the increase in plasma sodium and the reduction in plasma renin activity and aldosterone, and the rise in atrial natriuretic peptide (ANP) [abstract; He FJ et al, *Am J Hypertens* 17:181A–182A, 2004]. In studies of salt reduction in humans, there are consistent falls in plasma sodium. For instance, in two acute studies of salt reduction from 350 mmol/day to 10 mmol/day for 5 days, a highly significant reduction in plasma sodium of approximately 3 mmol/L was found in both black and white hypertensives, and white normotensives [36, 37]. The fall in plasma sodium was closely related to the increase in plasma renin activity. In double-blind studies using Slow Sodium (Ciba) and placebo, a more modest reduction in salt intake from 175 to 95 mmol (10 to 5 g/day), there was a small but significant fall in plasma sodium [abstract; He FJ et al, *Am J Hypertens* 17:181A–182A, 2004].

In normal dogs (weight 15 kg), plasma sodium after 24 hours on a high sodium diet (82.0 mmol/day) was 145.7 ± 1 mmol/L, and on a low sodium diet (7.5 mmol/day) was significantly lower, 142.8 ± 0.4 mmol/L [38]. In the Dahl SS rat, a high sodium diet for 4 days significantly raised plasma sodium from 142.2 mmol/L to 145.2 mmol/L [39]. In the normal rat there is a report [40] that, when measured during the night, plasma sodium rose from 137 to 142 mmol/L on the first night of an increase in salt intake, and remained raised thereafter for one week. Others [41], however, have found that an acute increase in salt intake for 7 days in the Dahl salt-sensitive and resistant rat, and the Sprague-Dawley rat did not raise plasma sodium of blood obtained during the day.

### Table 1. Changes in plasma sodium with alterations in salt intake

<table>
<thead>
<tr>
<th>Participant</th>
<th>Change in salt intake</th>
<th>Duration</th>
<th>Change in plasma sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sagnella et al [29]</td>
<td>6 normotensives</td>
<td>10 to 250 mmol/day</td>
<td>5 days</td>
</tr>
<tr>
<td>Sullivan et al [30]</td>
<td>27 normotensives</td>
<td>10 to 200 mmol/day</td>
<td>4 days</td>
</tr>
<tr>
<td>19 hypertensives</td>
<td></td>
<td>10 to 200 mmol/day</td>
<td>4 days</td>
</tr>
<tr>
<td>6 normotensives</td>
<td></td>
<td>10 to 400 mmol/day</td>
<td>4 days</td>
</tr>
<tr>
<td>Roos et al [31]</td>
<td>8 normotensives</td>
<td>20 to 200 mmol/day</td>
<td>5 days</td>
</tr>
<tr>
<td>Heer et al [32]</td>
<td>32 normotensives</td>
<td>50 to 550 mmol/day</td>
<td>7 days</td>
</tr>
<tr>
<td>Johnson et al [33]</td>
<td>15 isolated systolic hypertensives</td>
<td>50 to 300 mmol/day</td>
<td>14 days</td>
</tr>
<tr>
<td>8 diastolic ± systolic hypertensives</td>
<td></td>
<td>50 to 300 mmol/day</td>
<td>14 days</td>
</tr>
<tr>
<td>17 normotensives</td>
<td></td>
<td>50 to 300 mmol/day</td>
<td>14 days</td>
</tr>
<tr>
<td>Kawano et al [34]</td>
<td>7 hypertensives (non–salt-sensitive)</td>
<td>20 to 300 mmol/day</td>
<td>7 days</td>
</tr>
<tr>
<td>8 hypertensives (salt-sensitive)</td>
<td></td>
<td>20 to 300 mmol/day</td>
<td>7 days</td>
</tr>
<tr>
<td>Luft et al [35]</td>
<td>14 normotensives</td>
<td>10 to 300 mmol/day</td>
<td>3 days</td>
</tr>
</tbody>
</table>

### Acute increases in dietary salt intake on CSF sodium

In 15 patients with essential hypertension, CSF sodium concentration was 147.7 ± 0.4 while on a high salt diet (16–18 g/day) for 7 days, and on a low salt intake (1–3 g/day), it was 145 ± 0.5 (P < 0.001) [34]. In another group of 24 hypertensives [42] who were given 7 g, 3 g, and 25 g of dietary salt for 7 days on each intake, in that order, the CSF sodium changes were related to the patients’ “salt sensitivity;” on 25 g of salt, the CSF sodium of the 13 salt-sensitive patients was 149.3 mmol/L, and in the salt-resistant group it was 143.5 mmol/L. On the 7 g of salt per day diet the CSF sodium concentrations were not different.
There is one report that a high sodium diet had no effect on CSF sodium in the Dahl salt-resistant rat and the Sprague-Dawley rat, but that a rise in CSF sodium occurred in the Dahl salt-sensitive rat [41]. Similarly, a high sodium diet raised CSF sodium in the SHR and the Dahl salt-sensitive rat, but had no effect on the Dahl salt-resistant and Wistar Kyoto (WKY) rat [43]. Others who obtained CSF from SHR and WKY rats on a high sodium diet at 3- to 4-day intervals only obtained a rise in CSF sodium on the third day in both the SHR and the WKY rats [44].

The effect of acute changes in dietary sodium intake on plasma sodium and blood pressure

In humans, the effect of an abrupt increase in sodium intake for 5 to 28 days on the blood pressure is related to age. In the young (below 26 years), blood pressure does not rise, although there may be an increase in plasma sodium, ECV, blood volume, and exchangeable sodium [29, 31, 32, 45, 46]. In two of these studies plasma sodium did not rise [32, 45]. In contrast, in individuals over 60 years of age, most of whom had a raised blood pressure, an acute increase in sodium intake was associated with a rise in both plasma sodium (+1.5 to 3 mmol/L) and blood pressure [33, 34]. In the earlier mentioned study of normotensives in whom salt intake was increased by 50 mmol/day in 50 mmol/day increments, there was an increase in plasma sodium, and a highly significant relationship between the increase in plasma sodium and an increase in pulse pressure. In the studies on the effect of an acute and large reduction of salt intake in black and white hypertensive individuals, there was a significant fall in blood pressure with salt reduction associated with a significant fall in plasma sodium [36, 37], but there was no significant relationship between the change in blood pressure and the change in plasma sodium [abstract; He FJ et al, Am J Hypertens 17:181A–182A, 2004]. In double-blind studies of more modest salt restriction, however, there were significant falls in blood pressure, and a small but significant reduction in plasma sodium [abstract; He FJ et al, Am J Hypertens 17:181A–182A, 2004]. This change in plasma sodium was weakly, but significantly, correlated with the change in blood pressure (r = 0.18, P = 0.047).

In the Sprague-Dawley and Dahl salt-resistant rat, an acute increase in salt intake did not change plasma sodium or blood pressure, but in the Dahl salt-sensitive rat, in which the increase in salt intake was associated with a rise in plasma and CSF sodium, there was a rise in blood pressure [41]. Qi et al [39] measured the changes in blood pressure that occurred in inbred Dahl salt-sensitive rat (SS/JR) and salt-resistant rats (SR/JR) when the oral intake of salt was increased for 4 days, while body weight was maintained constant by a servo-control system. In the SS/JR rat, a change in the salt content of the food from 0.2% to 4% when there was no increase in body weight increased plasma sodium by 3.0 mmol/L, and blood pressure by 32.2 mm Hg. In another identical experiment in the SS/JR rat, except that body weight was not controlled and, therefore, body weight increased, there was a rise in plasma sodium of 1.5 mmol/L, and of blood pressure by 15 mm Hg. In contrast, in the inbred Dahl salt-resistant rat SR/JR, when body weight was controlled and the 4% salt diet was given, plasma sodium did not rise, and there was no change in blood pressure.

The effect of acute changes in salt input by intravenous or peritoneal dialysis on plasma sodium, ECV, and blood pressure

An increase in ECV associated with intravenous infusions of saline in animals can raise blood pressure, even if there is a fall in plasma sodium of 20 mmol/L [28, 47, 48]. The rise in pressure is associated with a rise in cardiac output [47, 48]. The predominance of ECV over plasma sodium in controlling the blood pressure following acute intravenous changes of sodium input was confirmed by Greene et al [49]. They used outbred Brookhaven National Laboratory, Upton, New York, Dahl S and Dahl R rats, the body weight of which was servo-controlled to be constant during the intravenous administration of either 1 mEq or 20 mEq of sodium per day for 4 days. When body weight was controlled, the intravenous administration of a high salt load did not cause the arterial pressure of the Dahl S or Dahl R rats to increase, although there was a rise in plasma sodium from 143.5 to 152.4 mmol/L. But if the high salt load was administered when the body weight was not controlled, there was an increase in body weight, plasma volume, and cardiac output, and a 2 mmol/L rise in plasma sodium in both the Dahl S and R, but only the Dahl S rat had a rise in arterial pressure. The unchanging arterial pressure of the Dahl R rat was associated with a fall in total peripheral resistance. The differences between these results and those of Qi et al [39], who increased salt intake orally, are discussed later.

Friedman et al [27] used intraperitoneal dialysis of saline solutions for 5 hours in the rat. Plasma sodium changes varied from ± 15 mmol/L, depending on the concentration of the dialysate. The systolic blood pressure rose or fell in direct relation to the plasma sodium. Associated changes in ECV could not explain the changes in blood pressure because they changed in the opposite direction to blood pressure.

Habitual salt intake, plasma sodium, and blood pressure in humans

In humans, there do not seem to be any direct measurements of plasma sodium in relation to the habitual intake
of sodium chloride, but there are some indirect observations which suggest that plasma sodium is directly related to the habitual intake. The first account [50] described three studies: the first study was in 634 patients with essential hypertension in whom there was a highly significant positive correlation between 24-hour urine volume and urinary sodium excretion \( (P < 0.001) \). The second was in 1731 hypertensive patients and 8343 nonhypertensive persons from 52 countries worldwide in the Intersalt Survey [51]. In within-sample analysis, 24-hour urine volume was significantly related to 24-hour urinary sodium excretion. Furthermore, this relationship was similar between the hypertensive patients and normotensive subjects; a reduction of 100 mmol/day in 24-hour urine sodium predicted a reduction in 24-hour urine volume of 379 and 399 mL, respectively. The conclusion that changes in urinary sodium excretion can control urine volume was strengthened by the third study [50], in which the sodium intake of 104 hypertensive patients was reduced from 350 mmol/day to 10 to 20 mmol/day. The regression line of relationship between the difference in urine volume and the decrease in urinary sodium excretion in this group, when superimposed on the results from the 2 previous studies, was similar.

As in normal circumstances, urinary sodium excretion is equivalent to sodium intake, and urine volume closely reflects fluid intake, these results show that dietary sodium intake controls fluid intake. But fluid intake is regulated by the activity of the thirst center, which is controlled by plasma osmolality and the blood volume. Thirst is stimulated by a rise in plasma osmolality, and depressed by an increase in blood volume [52]. Therefore, the control of fluid intake by the habitual dietary intake of sodium chloride appears to be due to the effect of the salt intake on thirst due to its effect on plasma sodium [53]. But hypertension is also related to a raised habitual intake of salt. Accordingly, hypertension should be associated with a rise in plasma sodium at least sufficient to stimulate the thirst center. The threshold of thirst in a normal rat being infused with 1 mol/L NaCl is a rise in plasma osmolality of 1.6 ± 0.11% mmol/kg [54], equivalent to a change of less than 1% in plasma sodium, which suggests that even large changes in sodium intake are likely to induce only minimal, and presumably, predominantly transient, changes in plasma sodium. It is also relevant that constant osmotic stimulation does not change the sensitivity of the thirst center [55, 56].

There are few measurements on the relation of plasma sodium to blood pressure in essential hypertension. There are only 2 studies in which the sodium concentration in the blood has been measured in a large number of hypertensives and controls [57, 58]. Serum sodium was measured in 3222 normotensive normal subjects and 741 hypertensive patients in Japan [57]. Serum sodium concentration differed between the 2 groups. The serum sodium concentration distribution curve in the patients with essential hypertension was shifted by about 2 mmol/L toward the higher values. The prevalence of a serum sodium concentration greater than 147 mmol in 24% to 27% of hypertensives, regardless of age, was significantly greater than in the 4.6% of normotensive individuals in whom the sodium concentration increased with age. The difference in serum sodium concentration between the normotensive and hypertensive individuals was not related to a difference in blood urea and plasma creatinine. Some of this difference in serum sodium may be explained if some of the individuals with hypertension had mild primary aldosteronism, but it is unlikely to explain all of the difference.

Wannamethee et al [58] found a strong positive association between serum sodium and systolic blood pressure in 2297 hypertensives, and no relationship in 5393 normotensive subjects. In the hypertensive group there was also a slight, though not significant, tendency for the diastolic pressure to rise with increasing serum sodium. In the normotensives, there was a weak but significant inverse association between serum sodium concentration and diastolic pressure, but not in systolic blood pressure.

There is one study by Fang et al [59] on plasma sodium of 9-week-old SHR and WKY on their ‘normal’ basal diet, which contained 0.6 mol/L NaCl. Plasma sodium was measured at 1- to 2-hour intervals, and was about 1 to 3 mmol/kg greater in the SHR than in the WKY throughout the 24 hours. There was a profound diurnal rhythm, the pattern of which was similar in both strains. Plasma sodium concentration was highest during daylight, when the rats were asleep and blood pressure was at its lowest.

The pressor effect of plasma sodium on the brain, the blood vessels, and tissue angiotensin II activity

A rise in plasma sodium may affect blood pressure by a direct effect on the brain and the blood vessels, and it may also enhance the activity of the renin-angiotensin system.

Brain

Sodium concentration in the brain and blood pressure. Tobian and Ganguli found that the Na\(^+\) and K\(^+\) concentrations in the tissues surrounding the third ventricle of Sprague-Dawley rats on 8% NaCl were greater than in rats on a moderately low NaCl diet [60]. These observations suggest that a rise in plasma sodium may have an exaggerated effect on the sodium concentration of those areas surrounding the third ventricle, which control the blood pressure [61]. In the Dahl S and R rats placed on a high sodium diet, the rise in blood pressure in the Dahl S rat is associated with a substantially greater accumulation of \(^{22}\text{Na}^+\) in the CSF and brain of the Dahl S rat [62].

Wang and Leenen [63] found that the cascade of changes that take place in the hypothalamus of the Dahl 

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salt-sensitive rat on a high sodium diet, which leads to a rise in arterial pressure, can be prevented by the intracerebroventricular infusion of benzamil, which blocks certain sodium channels. This confirms earlier observations that the third ventricle periventricular tissues, which control the blood pressure, are particularly susceptible to changes in plasma sodium, and that such changes have a profound effect on the blood pressure [64]. In the adult hypertensive SHR, however, brain% water content and extracellular fluid NaCl sucrose volume of distribution are not significantly different from the levels in the WKY rat [65].

Increasing the concentration of CSF sodium by the administration of hypertonic saline centrally raises the blood pressure [66–68]. Initial studies on the conscious goat showed that infusions of solutions varying from 0.25 to 0.33 mol/L NaCl at 10 μL/min into the third ventricle increased the blood pressure by 15 to 30 mm Hg within 60 minutes. Subsequently, in studies in normal conscious rats, the CSF NaCl concentration has been raised by the continuous infusion of hypertonic NaCl, using 0.15 to 1.5 mol/L solution, into the third or lateral ventricle for 7 to 14 days at a pumping rate of 1 to 5 μL/hr [69–73]. In one experiment in Sprague-Dawley rats with an infusion of 0.8 mol/L NaCl [72], the systolic pressure did not rise significantly until the ninth day. In another experiment [73] in the same strain of rats on varying intakes of salt, a lateral ventricle infusion with the same concentration of NaCl, in rats on a normal intake of salt, increased the blood pressure on the 10th day, but if, in addition, the intake of NaCl was also raised, the rise in blood pressure occurred on the sixth day. In other experiments in which hypertonic saline was infused centrally, the sodium concentration of the CSF obtained from the cisterna magna was measured at the end of the experiment [69–72]. Kawano et al [70] infused 0.15 and 1.5 mol/L NaCl solutions at a rate of 5.5 μL/hr into the third ventricle for 7 days; the CSF sodium concentrations on the seventh day were 148.1 ± 0.55 and 153.2 ± 0.7 mmol/L, respectively. During the infusion of the 0.15 mol/L NaCl solution there was a progressive, though insignificant increase in systolic pressure, which plateaued on the fifth day. With the 1.5 mol/L NaCl solution there was a brisk and significant rise in blood pressure on the first day. Huang et al [69] infused either artificial CSF, 0.8 mol/L or 1.5 mol/L NaCl solution into the lateral ventricle at a rate of 5.0 μL/hr for 14 days; the CSF sodium concentrations at 14 days were 146 ± 2, 152 ± 2, and 160 ± 3 mmol/L, respectively. On the 14th day, there was a rise in blood pressure with both the 0.8 and 1.5 mol/L NaCl solutions. In a study by Katahira et al [71], though 0.15 mol/L, 0.8 mol/L, and 1.5 mol/L NaCl solutions were infused into the lateral ventricle at a rate of 1 μL/hr for 12 days, the CSF sodium concentrations on the 12th day were 153.4 ± 9, 152.5 ± 0.7, 153 ± 0.4 mmol, respectively. Although the CSF sodium did not appear to change, a sustained rise in blood pressure occurred on the eighth day in the rats receiving the 1.5 mol/L NaCl solution. Overall, these experiments demonstrate that a rise in CSF sodium concentration raises blood pressure and suggest that the rate of rise in pressure is directly related to the extent of the increase in CSF sodium.

There is little information on the effect of increasing dietary salt intake on CSF sodium and blood pressure [41, 44, 74]. In one study [41] in the Dahl salt-sensitive rat in which the CSF was only obtained during the day, the rise in blood pressure occurred on the first day, while CSF sodium rose on the fourth day. In another study [44] in the SHR-S on a high dietary intake of NaCl, an initial rise in CSF sodium for the first 3 days subsided to normal at 7 days, though the rise in plasma sodium and blood pressure continued thereafter [44]. It was concluded that alterations in CSF sodium do not contribute to the increase in arterial pressure induced by a high NaCl diet in SHR-S. In 1K1 wrap Grollman kidney hypertension given a diet rich in NaCl, CSF sodium only rose from the third to the seventh day, while the blood pressure rose on the sixth day and remained raised [74].

Sodium concentration, hypothalamic angiotensin II, and blood pressure

Intervention in the activity of the hypothalamic angiotensin system in various forms of hypertensive rats lowers blood pressure, but is without effect in the normal rat [88–95].

Andersson et al initially demonstrated that the pressor effect of angiotensin II was much reduced when infused centrally in a nonelectrolyte solution [66]. A quarter of a century later, Qadri et al [96] demonstrated in conscious rats that perfusion of the paraventricular nucleus by microdialysis with 0.3 mol/L and 0.6 mol/L NaCl elicited a concentration dependent increase in the release of angiotensin II from the nucleus. Huang et al’s [69] studies have demonstrated that the increase in hypothalamic angiotensin II activity, and the rise in blood pressure induced by an increase in CSF sodium, is secondary to a rise in the activity of an ouabain-like compound in the hypothalamus, and can be prevented or reversed by the intracerebroventricular administration of Fab fragments, which bind such compounds. The pressor effect and the increase in sympathetic activity induced by the central administration of hypertonic saline can also be largely prevented by the intracerebroventricular administration of losartan [67, 69]. Similarly, in the rat, saralasin injected into the third ventricle inhibits the response of paraventricular neurosecretory cells to an intracarotid infusion of 0.3 mol/L NaCl [97]. Chen et al [98] found that AT1a mRNA expression in the hypothalamus is significantly increased by loading mice with 2% saline for 5 days. There was no significant change in AT1b mRNA.
**Direct effect of sodium concentration on neuronal function**

The reduced hypothalamic sympathetic inhibition that is responsible for the rise in arterial pressure when the CSF sodium concentration rises may also be due in part to the direct effect of plasma sodium on neuronal activity for an increase in sodium concentration in neocortical and hippocampal slices diminishes synaptic transmission and neuronal excitability [99, 100], and a small rise in the sodium concentration in the anterior hypothalamus of the conscious rat reduces the local release of norepinephrine [101].

**VESSELS AND HEART**

There is direct evidence that a rise in plasma sodium in vivo can induce changes in the arteries which could contribute to the associated rise in blood pressure, and that, in vitro, a rise in sodium concentration can cause intracellular changes in the vessels and the heart that are similar to those found in vascular tissue from hypertensive individuals or animals.

There is indirect evidence that, independent of the blood pressure, a rise in plasma sodium in vivo induces structural hypertensive changes in the vessels and the heart, and that in both in vitro and in vivo, the vascular structural changes in hypertension may be due in part to an increase in tissue angiotensin II activity of unknown origin which, independent of the blood pressure, may be due in part to a raised plasma sodium.

**Direct in vivo evidence that an induced rise in plasma sodium causes arterial changes that may contribute to the associated rise in blood pressure**

In Friedman et al’s peritoneal dialysis experiments in rats with saline solutions of varying concentrations in which the resulting changes in blood pressure were directly related to the induced changes in plasma sodium, the transmembrane distribution of Na⁺, K⁺, and water was measured in rapidly excised tail arteries [26]. The intracellular sodium concentration was directly related to the systolic and diastolic pressures [26]. A rise in intracellular sodium increases muscle tone [102] due to the resultant increase in intracellular free Ca²⁺ concentration [103]. These studies were the first in vivo demonstration that an acute rise in plasma sodium, not accompanied by a rise in ECV, can raise blood pressure, and that such a rise in blood pressure is associated with an increase in the sodium concentration of smooth muscle.

**Direct in vitro evidence that a rise in plasma sodium induces multiple changes in vascular tissue similar to those that occur in hypertension**

The major structural changes in essential hypertension are reduced vessel lumen diameter and medial thickening due to hyperplasia, hypertrophy, reorganization of the cells around the lumen of the artery, and an increase in extracellular matrix and collagen [104]. In cultures of myocardial myoblasts and vascular smooth muscle cells, Gu et al [105] found that a change in sodium concentration from 146 mmol/L to 152 mmol/L for 5 days increased cell diameter, volume, and protein content of the cells. There was also a decrease in protein degradation, but no hyperplasia. In another experiment, increasing the sodium concentration by only 2 mmol/L above normal caused the cellular protein content of cultured coronary artery smooth muscle cells to increase by 84.5%. Similar results were obtained in cultured umbilical vein endothelial cells [106]. A 10 mmol/L increase in sodium concentration induced a transient rise in c-fos proto-oncogenic mRNA expression, which began at 2 hours. After 3 days there was an increased mRNA expression of many hypertrophy-related factors, including endothelin, IGF, FGF, TGF, and MIF. In isolated ventricular adult rat cardiomyocytes, increasing the sodium concentration of the bath fluid from 128 to 139 and 179 mmol/L, by adding hypertonic saline or increasing the osmolality by an equivalent amount with sucrose for 30 minutes, induced a dose-dependent increase in egr-1 and c-fos levels mRNA up to 4- and 5-fold, respectively [107]. Nickenig et al [108] found that an increase in the concentration of NaCl by 10 mmol/L in thoracic aorta and cultured rat vascular smooth muscle cells caused a time-dependent rise in AT₁ receptor mRNA levels that appeared at 12 hours, and was sustained for 48 hours when the experiment was ended.

**Indirect in vivo evidence that a rise in plasma sodium is responsible in part for the increase in left ventricular mass and arterial thickness and stiffness in hypertension independent of blood pressure**

Earlier it was pointed out that sodium intake, which, in normal circumstances, is equivalent to sodium excretion, is directly related to urine flow, and that urine flow is directly related to thirst, which is controlled by plasma sodium. Therefore, alterations in dietary sodium intake appear to induce changes in plasma sodium. The following studies, which demonstrate that sodium intake (measured as urinary sodium excretion) is directly related to left ventricular mass and arterial thickening, therefore suggest indirectly that these vascular changes are associated with changes in plasma sodium.

In normotensive subjects, left ventricular mass and diastolic filling are positively correlated with urinary sodium excretion [109, 110]. Normotensive rats on 1% saline for several weeks develop an increase in heart weight due to an increase in left ventricle mass, without an increase in blood pressure [111, 112]. The increase in left ventricular mass, which accompanies an increased salt intake, is associated with an increase in noncollagen protein and total collagen content [112, 113]. An increase
in sodium intake in both humans and experimental animals increases the stiffness of conduit arteries and the activity of resistance arteries, and both become hypertrophied, independent of blood pressure [114]. A high salt intake in the rat induces structural alterations in the cerebral and renal vessels, independent of blood pressure [115], and in humans, an increase in salt intake increases the stiffness and thickness of arterial walls, independent of blood pressure [6].

In vivo and in vitro evidence that structural changes in hypertension are due in part to an increase in tissue angiotensin II activity in the vessels and the heart, independent of blood pressure, and that these may be due to an increase in plasma sodium

Epidemiologically, as the blood pressure rises with age there is an inverse association between plasma renin activity and systolic pressure [116], yet the administration of angiotensin inhibitors to patients with essential hypertension lowers their blood pressure, which suggests that such patients have an increase in angiotensin activity in the tissues, due possibly to an increase in sensitivity to angiotensin [117], perhaps related to dietary sodium. Genetically manipulated mice that have no tissue-bound angiotensin-converting enzyme (ACE), but a normal plasma ACE, have a low blood pressure [118], which also suggests that, in contrast to tissue angiotensin II, circulating angiotensin II plays only a minor role in the control of the blood pressure.

Arterial and cardiac changes in hypertension that appear to be due to increased angiotensin II activity. There is evidence of increased angiotensin II activity in the vessels of patients with essential hypertension. The gluteal muscle of patients with essential hypertension has been studied before, and after, one year’s treatment with either losartan or atenolol. The fall in blood pressure in the 2 groups was comparable, but the width-to-lumen ratio of the subject on losartan was significantly reduced, whereas there was no change in those on atenolol [119]. The distensibility of the common carotid artery in 41 patients with essential hypertension was enhanced by the administration of an ACE inhibitor for 6 months, but it was not altered by the administration of amiloride and hydrochlorothiazide, though the fall in blood pressure was not significantly different [120]. The relatively acute vascular changes which are associated with an infusion of angiotensin II do not occur when the blood pressure is raised by some other pressor agent, such as noradrenaline [121].

Experimental studies in the SHR have revealed evidence of an increase in angiotensin II activity in the heart. Ohta et al [122] found that left ventricular mRNA levels for skeletal α-actin and for collagen types I and III in the SHR were higher, and α-myosin heavy chain (MHC) mRNA levels were lower than in the WKY. The administration of an ACE inhibitor attenuated the increase in collagen types I and III mRNA, and raised the α-MHC mRNA. These effects did not take place after the administration of a calcium channel blocker or an α-1 adrenergic blocker, although the reductions in blood pressure were comparable. Thus, in the SHR, cardiac gene programming can be attributed at least in part to angiotensin II. Similarly, in the SHRSP rat, losartan induced regression of left ventricular hypertrophy, and returned the altered expression of α-MHC to normal, skeletal actin, TGF-β1, and collagen type I and III to a greater extent than amiodipine, despite comparable hypotensive effects [123, 124].

Possible role of plasma sodium in the apparent increase in angiotensin II activity in vascular tissue in hypertension. The increase in angiotensin II activity in the vessels in essential hypertension, which appears to be due in part to an increase in sensitivity to angiotensin II, may be due in part to a raised plasma sodium. In cultures of vascular smooth muscle, and of endothelial cells, a rise in sodium concentration of the bath increases the number of AT1 receptors [108] and TGF-β production [106, 125], and the functional response of the cells to stimulation with angiotensin II [108]. Touyz and Schiffrin suggest that the increase in tissue angiotensin II activity in hypertension is due to augmented angiotensin II signaling at the postreceptor level [104].

DISCUSSION

It is probable that one of the principal reasons why it took about 100 years for the connection between dietary salt and hypertension to be generally accepted was the absence of a satisfactory explanation. On a high salt intake a defect in the kidney’s ability to excrete sodium will give rise to a greater retention of sodium, and thereby, a tendency for volume expansion. There are several hypotheses on the nature of the pressor mechanisms, which are induced by the combined effect of an impaired ability to excrete salt, and a raised intake of dietary salt. All incorporate the concept that this results in a tendency for the extracellular volume to be increased. Based on experiments in 70% nephrectomized dogs given large amounts of saline intravenously daily for 2 weeks, Guyton [126] suggested that volume expansion raises the blood pressure by the autoregulatory effect on resistance vessels of the increase in blood flow that accompanies the associated persistent increase in cardiac output, even if this slight increase in cardiac output is usually unmeasurable [127]. But cardiac output in essential hypertension is normal, even when there is hypervolemia [128, 129]. Admittedly, this does not exclude essential hypertension from being caused by intermittent small increases in cardiac output, but there are several observations that demonstrate that cardiac output does not control blood pressure. Dialysis patients loaded with saline develop a rise in
peripheral resistance without an increase in cardiac output [130]; hypertension can occur in a patient with mitral stenosis and a low cardiac output [131]; and after raising the blood pressure of a dog for 6 weeks with metaprine, there was no evidence of circulatory autoregulation [131]. Others [132] have proposed that among the multiple changes that counter the kidney’s impaired ability to excrete sodium, and the resultant tendency to volume expansion, there is an increase in the plasma’s capacity to inhibit Na-K-ATPase, which not only increases sodium excretion, but also raises blood pressure by inhibiting the sodium-calcium pump in vascular smooth muscle [133]. This hypothesis was based on the demonstration that in normal dogs acute volume expansion increases the plasma’s capacity to inhibit Na-K-ATPase. Such an increase is detectable in essential hypertension, the SHR, and the Milan hypertensive rat. The nature of the substance responsible for the Na-K-ATPase inhibition has been difficult to elucidate. One study in 27 untreated patients with essential hypertension has demonstrated that plasma marinobufagenin immunoreactivity, which rises with acute volume expansion [134], is raised in essential hypertension [135]. A variable increase in plasma ouabain immunoreactivity [135], and of ouabain extracted from plasma [136], has also been reported in essential hypertension, although volume expansion does not raise plasma ouabain [136]. A third hypothesis on the pressor mechanism induced by dietary salt suggests that the tendency for an increase in extracellular fluid volume is responsible for the documented increase in right and left (wedge) pressures in the auricles. It is proposed that the resultant increase in vagal afferent stimulation is responsible for the observed hypothalamic pressor changes [61].

In view of the impaired ability to excrete sodium evident in the normotensive children of hypertensive parents [137], and in young prehypertensive genetically hypertensive rats [138], the premise that the increase in blood pressure in these forms of hypertension is associated with some increase in the extracellular fluid volume, however difficult to detect, is theoretically reasonable. Studies of the extracellular volume, exchangeable sodium, and of the natriuretic response to a rapid infusion of saline, suggest that in hypertension there exists a state of continuous correction of a slightly expanded extracellular fluid volume. Mullins [139] and Harrap [140] found the extracellular volume and exchangeable sodium in the SHR was significantly larger than in the WKY. In humans, one group [141] found that in a total of 211 hypertensive men there was a significant correlation between exchangeable sodium, related to body surface and arterial pressure, but not in women [142]. In hypertensive men below the age of 35 years, however, exchangeable sodium was significantly decreased. Simon et al [143] also found that the extracellular volume in hypertension was not increased. Nevertheless, both groups [141, 143] found that the extracellular fluid volume correlated with the blood pressure. Subsequently, Berreta-Piccoli [144] reported that exchangeable sodium was unrelated to arterial pressure in both normotensive and hypertensives. A striking functional signal of the existence of a controlled state of volume expansion is the syndrome of accelerated natriuresis, which is elicited by a rapid infusion of saline. This response occurs in primary hyperaldosteronism [145] in normal subjects given aldosterone [146], even when, as in essential hypertension, it may not be possible to detect an increase in extracellular fluid volume. It is also elicited in the SHR [147, 148], particularly those with a low plasma renin, and in normotensive children of hypertensive parents [21]. Other indications that hypertension is probably associated with a tendency to volume expansion include the reduced level of plasma renin [116], the raised levels of atrial natriuretic hormone [137], and the increase in the plasma’s capacity to inhibit Na-K-ATPase [132]. There is agreement that plasma and total blood volume in essential hypertension and hypertensive strains of rats are either normal or decreased [129, 142, 143, 149–151].

The possible role of prolonged small (<5 mmol) changes in plasma sodium on blood pressure has not been studied. The concentration of sodium in plasma is closely and rapidly controlled by the movement of fluid between the intra- and the extracellular fluid space, changes in sodium excretion, and by the activity of the thirst center, which, in the rat, is influenced by changes in plasma sodium of under 1% [54]. Such small but still potent changes in plasma sodium are technically difficult to detect. Burtis and Ashwood [152] state that the coefficient of variation for contemporary methods of detection of sodium is less than 1.5%. The conclusion that, in essential hypertension and the SHR, there is a small and persistent rise in plasma sodium and osmolality, at least sufficient to affect the hypothalamus, is consistent with the finding that in both of these forms of hypertension, in which there is evidence to suggest that there is a state of continuous correction of a slightly expanded extracellular fluid volume [which would tend to reduce arginine vasopressin secretion (AVP)], both plasma and urinary AVP are raised [61].

In humans, we have not been able to find observations on plasma sodium in large groups of normal or hypertensive individuals, whose habitual intake of salt is known. It would also be interesting to know if there are diurnal changes in plasma sodium, and the effect of meals. Dogs have a substantial transient postprandial rise in plasma sodium [153]. The close relation that exists between dietary sodium and urine volume in normal and hypertensive humans [50] suggests that the habitual dietary intake of sodium controls plasma sodium—in other words, that the raised thirst engendered by an habitually raised intake of sodium, which is evident as a raised 24-hour urine
volume, is due to stimulation of the thirst center by an increase in plasma sodium. It follows that in essential hypertension, the incidence of which is also related to a high intake of salt, plasma sodium should be slightly raised.

In humans, there are only 2 relatively substantial studies in patients with essential hypertension in which plasma sodium has been published [57, 58]. In both, the rise in arterial pressure is significantly related to a small (~2 mmol) rise in plasma sodium. In the SHR, Fang et al [59] found that on a normal intake of salt, plasma sodium, measured at 1- to 2-hour intervals, was about 1 to 3 mmol/L greater throughout the 24 hours than in the WKY rat. Because the pronounced and parallel diurnal changes in plasma sodium in both strains were not synchronous with the diurnal rhythm of the blood pressure, Fang et al were reluctant to relate the hypertension to the raised plasma sodium. But the plasma sodium concentration in the SHR was greater than in the WKY throughout the 24 hours, as was blood pressure. In keeping with the evidence discussed below, a small rise in plasma sodium appears to be more likely to raise the blood pressure if it is prolonged. Accordingly, the persistent small rise in plasma sodium concentration in the SHR is likely to be relevant to that strain's persistently higher blood pressure, whereas the short-term superimposed diurnal fluctuations in plasma sodium in both the SHR and WKY are unlikely to be responsible for diurnal changes in blood pressure.

The evidence available suggests that the temporal relationship between a rise in sodium concentration and the effect such a rise produces is such that small changes of 2 to 5 mmol/L take some days to have an effect, whereas larger changes (e.g., of 15 mmol or more) may induce a change within an hour. For instance, a rapid infusion of hypertonic saline into the third ventricle increases blood pressure within an hour [66], whereas a prolonged infusion of a lower concentration of saline, which only raises CSF sodium by 4 to 5 mmol/L, may take 6 to 10 days to raise the blood pressure [73]. In essential hypertension and the SHR, there appears to be a rise in CSF sodium concentration that is less than 4 mmol/L [34, 43], so that any effect such a rise would have on blood pressure might take even longer. Similarly, in vivo, a rise of 15 mmol/L in plasma sodium induces certain arterial changes and a rise in blood pressure within hours [27], but, in vitro, a rise of only 5 mmol/L takes 3 to 6 days to induce changes in arterial segments [105, 106]. It is possible that the considerable time it appears to take for a modest rise in sodium concentration to affect the blood pressure is the reason why the blood pressure did not rise in the study by Greene et al [49] in rats which lasted 4 days, and in which the weight of the rat was kept constant while plasma sodium was raised from 143.5 to 152.4 mmol/L by a continuous intravenous infusion of salt solution. Accordingly, the pressure response obtained with 4 days by a rise in plasma sodium of 3.2 mmol/L by Qui et al [39], using a similar protocol, but in which the input of salt was raised by increasing the dietary salt intake, is anomalous.

It is interesting in contrast to individuals over 30 years of age, a large increase in salt intake, including intravenous infusions of saline for 8 to 30 days in young men below the age of 26 years, does not raise the blood pressure, in spite of increases in plasma sodium, extracellular fluid volume, blood volume, and exchangeable sodium. In the young, therefore, none of those primary disturbances that are induced by an increase in salt intake are effective in raising the blood pressure. Presumably, this is due to the potency of counter mechanisms. Similarly, a fall in pressure induced by a reduction in dietary salt appears to be related to the extent of the compensatory change in plasma renin activity and angiotensin II [36].

The evidence that the increase in angiotensin II activity in hypertensive vessels is in part secondary to a rise in plasma sodium is suggested by the in vitro experiments which demonstrate that an increase in sodium concentration of the bath solution increases the number and activity of AT1 receptors in vascular tissue [108], and promotes metabolic changes which are similar to those induced by angiotensin II [154]. These include increases in the size and protein content, and a decrease in protein degradation, of cultured cardiac myoblasts and vascular smooth muscle cells [104, 105]. This suggests that a rise in plasma sodium could be responsible in part, not only for the rise in arterial pressure, but also for the increase in ventricular mass [5] and thickening of the arteries [7], both of which are related to the intake of dietary salt and, independent of the blood pressure [3, 4], are responsible for certain changes in the pressure, such as an increase in pulse pressure. Furthermore, Gu et al’s [105] signal observation on the influence of sodium concentration on cell metabolism may also explain some of the deleterious effects attributed to DOCA and aldosterone. Somers et al [155] reported that rats given DOCA and water to drink instead of 1% saline not only fail to develop hypertension, but in contrast to rats given 1% saline, aortic superoxide production and relaxation of vascular segments to acetyl choline are unaffected.

**CONCLUSION**

Accumulating evidence suggests that for a given salt intake, those individuals who develop a rise in blood pressure have a reduced ability to excrete sodium. This results in a barely perceptible rise in plasma sodium of 1 to 3 mmol/L, which is responsible for the tendency for an increase in extracellular volume. Experimental increases in plasma and CSF sodium concentrations greater than 5 mmol/L can increase the blood pressure independent of the extracellular volume. In these studies, the time of onset of the rise in arterial pressure appears to be related
to the extent of the increase in sodium concentration, so that the delay may take several days. With 1 to 3 mmol/L increases in sodium concentration that occur in hypertension, but that have not been studied experimentally, the delay is likely to be considerably longer. We suggest that a small increase in plasma sodium (1 to 3 mmol/L) not only tends to increase the extracellular fluid volume, but may itself be a primary factor in the pressor effect of dietary salt (Fig. 1). In other words, plasma sodium drives the system. This hypothesis suggests the need for well-controlled studies of careful measurement of plasma sodium and urinary sodium excretion on normotensive and hypertensive individuals on their habitual intake of salt, and when salt intake is changed. In animals, much longer studies should be carried out on the effect of prolonged 1 to 3 mmol/L increases of sodium concentration on the blood pressure. There is also a need to study the effect of prolonged similar increases in sodium concentration on cultures of vascular tissue.

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Fig. 1. The greater rise in plasma sodium that occurs in hypertensive prone subjects is due to a defect in the kidney’s ability to excrete salt, and is responsible for the rise in blood pressure.


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