Kidney, Salt Intake, and Na⁺,K⁺-ATPase Inhibitors in Hypertension

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In view of the finding by Mathews et al¹ that one of the circulating Na⁺, K⁺-ATPase inhibitors in humans is ouabain, I thought it would be useful to give a brief historical outline of the background to this subject and a tentative hypothesis that tries to explain how the concentration of such a substance comes to be raised in hypertension.

Historical Outline

In 1961 it was found that the natriuresis caused by acute volume expansion was due mainly to a change in the concentration of a circulating natriuretic substance.² About 10 years later it was noted that acute volume expansion was also accompanied by an increase in the ability of plasma to inhibit sodium transport³ ⁴ and that this was due to an inhibition of Na⁺,K⁺-ATPase.⁵ It was automatically assumed that the increased natriuretic capacity of the plasma and its increased ability to inhibit sodium transport, both of which occurred with volume expansion, were due to a change in concentration of the same substance, which was named the natriuretic hormone.

The atrial natriuretic peptide was discovered in 1981.⁶ -⁷ To the surprise of many of us, the atrial natriuretic peptide had no effect on Na⁺,K⁺-ATPase. It was obvious, therefore, that the increased natriuretic capacity of the plasma and its increased ability to inhibit sodium transport were not necessarily due to the same substance. It followed that the structure of the substance responsible for the volume-controlled Na⁺,K⁺-ATPase inhibition still needed to be determined. Furthermore, we began to pay attention to the well-established but not so well-recognized fact that in a normal animal the natriuretic effect of certain well-known exogenous Na⁺,K⁺-ATPase inhibitors, such as ouabain and digoxin, is negligible. It was therefore ironic that at about this time the atrial natriuretic peptide (an unquestionably powerful short-acting natriuretic substance) was being closely scrutinized, and only slowly accepted, as a possible physiologically relevant natriuretic substance, while the title of “natriuretic hormone” continued to be bestowed on the circulating Na⁺,K⁺-ATPase inhibitor that some of us suspected might not be natriuretic. A further complication is the presence of an as-yet-unidentified long-acting natriuretic substance⁸ that may have a relatively large molecular weight.⁹ ¹⁰ Many of us have tried to edge away from the label “natriuretic hormone” and to describe endogenous Na⁺,K⁺-ATPase inhibitors as such. Definitions such as “endogenous digitalislike substance” or “ouabainlike factor” are in use and avoid the term “natriuretic.” Among other similarities to ouabain, most of the endogenous Na⁺,K⁺-ATPase inhibitors being investigated have been found to displace tritiated ouabain from its receptor. The analogy is obvious between the endogenous circulating Na⁺,K⁺-ATPase inhibitor and ouabain receptors and encephalin and morphine receptors.

It was then observed that the capacity of plasma to inhibit Na⁺,K⁺-ATPase was raised in hereditary and acquired forms of hypertension.¹¹ It was pointed out that inhibition of Na⁺,K⁺-ATPase should raise intracellular calcium and thus might cause peripheral vasoconstriction and hypertension.¹² Many laboratories therefore have searched for an endogenous Na⁺,K⁺-ATPase inhibitor that is involved in volume control and hypertension. Na⁺,K⁺-ATPase-inhibiting extracts have been prepared from a variety of sites, including the plasma,¹⁹ the hypothalamus,²⁰ ²¹ and the urine.²² ²³ The search has been hampered by two principal difficulties. The first is that more than 100 endogenous compounds are known to modify the activity of Na⁺,K⁺-ATPase and that the inhibitory activity of most of these is not digitalislike. It is therefore not surprising that the concentrating effect involved in purification procedures has already yielded some well-known, endogenous Na⁺,K⁺-ATPase inhibitors, including unsaturated fatty acids and steroids.²⁴ ²⁶ However, the free plasma concentration of these substances has been considered to be too low to be physiologically important or it has not changed with volume expansion or salt intake, or it has not been raised in hypertension. However, plasma concentrations may be irrelevant. One of these substances may have a relevant physiological role at its site of production. Unsaturated hydroxy fatty acids, for instance,
have a wide range of activity locally; for example, thromboxane $\text{B}_2$ and leukotriene $\text{B}_4$.

The lack of a specific or even a highly selective assay with which to distinguish a relevant substance has also been crippling. Researchers have had to make agonizing choices, based on differing assumptions when deciding which of several fractions, all of which inhibit $\text{Na}^+,\text{K}^+$-ATPase, should be the one to purify. The most widely held assumption has been that the relevant functional substance should closely resemble ouabain or digitalis: in other words, that it should 1) selectively inhibit $\text{Na}^+,\text{K}^+$-ATPase, 2) inhibit sodium, potassium, or rubidium transport, 3) displace $[^3\text{H}]$ouabain from surface receptors, 4) be ionotropic, 5) increase vascular tone, 6) increase intracellular calcium, and 7) cross-react against antibodies raised against digoxin. This certainly narrows the field, but choices still have had to be made between digitalislike substances that satisfy most of these criteria. Other investigators, while agreeing that the relevant substance may share some properties with ouabain, have thought it safer to assume that any substance that inhibits $\text{Na}^+,\text{K}^+$-ATPase, the concentration of which is controlled by volume changes or salt intake and is raised in hypertension, is potentially relevant.

**Hypothesis to Explain the Rise in $\text{Na}^+,\text{K}^+$-ATPase Inhibitor in Hypertension**

There is still no firm evidence that an endogenous $\text{Na}^+,\text{K}^+$-ATPase inhibitor or inhibitors have an etiologic role in hypertension. Assuming that they have, one still needs to understand how their concentration comes to be raised in hypertension. The following hypothesis, which tries to explain this, stems from the observation that the concentration of $\text{Na}^+,\text{K}^+$-ATPase-inhibiting activity in the plasma and the hypothalamus in the normal animal rises with an increase in salt intake. The hypothesis substantiates a particular aspect of one first put forward in 1980 and serves as a kind of functional infrastructure for any volume-controlled hypertensinogenic mechanism. Irrespective of the hypothesis proposes that most forms of hypertension share a single triggering mechanism, it is not "mosaic friendly." It is proposed that in most forms of hypertension there is one initiating factor, an abnormal kidney, the functional hypertensinogenic expression of which is a restricted ability to excrete sodium. This sustained restraint on sodium excretion stimulates a sustained activity of volume-controlled mechanisms, including an increase in $\text{Na}^+,\text{K}^+$-ATPase inhibitory activity in the plasma and hypothalamus. It is these that raise the blood pressure.

**Renal Abnormality**

The evidence that in most forms of hypertension the kidney is abnormal is discussed first, followed by evidence suggesting that the abnormality is the kidney's difficulty in excreting sodium.

**Acquired hypertension.** In most models of acquired hypertension, it is self-evident that the kidney initiates the hypertensive process. Most forms of experimental hypertension involve either some surgical interference to the kidney or its vascular supply or the administration of antinatriuretic agents. In humans, there is the association of renal disease and hypertension.

**Hereditary hypertension in animals.** The evidence that the initiating hypertensinogenic trigger resides in the kidney in hereditary hypertension has been obtained by cross-transplantation experiments. These experiments have been performed with hypertensive rat strains and their normotensive controls, the recipients having been bilaterally nephrectomized. Sometimes an F$_1$ recipient has been used. Variations on this experiment have been carried out by six different groups, with four different rat strains.

In all four hypertensive strains, cross-transplantation of kidneys has demonstrated that the blood pressure follows the kidney. It has been found that transplanting a kidney from a hypertensive-strain rat to a normotensive-strain rat raises the blood pressure of the normotensive-strain rat. To avoid the possibility that preexisting hypertensive vascular changes in the graft might have induced the rise in pressure in the recipient, the grafts have been taken either from 7-week-old or 20-week-old rats, the blood pressure of which has been kept within normal limits with a converting enzyme inhibitor from the age of 4 weeks. In the reverse set of experiments, a kidney from a normotensive-strain rat, when placed into a young hypertensive-strain rat before the onset of hypertension, prevents the onset of hypertension. If placed into an older rat with established hypertension, it lowers the blood pressure.

Two disconcerting but logical conclusions emerge from these cross-transplantation experiments. The first is that in hereditary forms of hypertension in the rat, the primary genetic lesion that stimulates the mechanisms that eventually cause the rise in pressure resides in the kidney. In other words, hereditary forms of hypertension in the rat are renal diseases. It does not follow that the genetic fault that leads to the functional hypertensinogenic renal disturbance is only present in the kidney [e.g., an increase in membrane Na-H exchange or Na$^+\text{K}^+$ (2Cl) cotransport]. Nor does it follow that the same genetic abnormality is responsible for all forms of hereditary hypertension. The second conclusion that emanates from the cross-transplantation experiments is that the presence of genetic abnormalities in vascular smooth muscle (including the increase in permeability to sodium), the brain, or the sympathetic system in hereditary strains of hypertension do not cause hypertension per se, because the blood pressure of a bilaterally nephrectomized hypertensive-strain rat does not rise in the presence of a normal kidney. Conversely, of course, an imposed surgical procedure on a normal kidney induces hypertension in a normal animal, which has no genetic abnormalities of its vascular smooth muscle or nervous system.
**Essential hypertension.** In essential hypertension, the nearest equivalent to the cross-transplantation experiments in animals is the relation of the recipient's blood pressure, after renal transplantation, to the blood pressure of the donor and particularly the donor's parents. The available information is consistent with the notion that the kidney initiates the rise in blood pressure in essential hypertension. In one study of 50 recipients of cadaver kidneys, the investigators measured the blood pressure of both parents of the donor and of both parents of the recipient. Recipients from normotensive families who received a kidney from a donor from a hypertensive family needed significantly more hypertensive therapy than those who received a kidney from a normotensive family. In addition, there is a complementary study in six hypertensive black patients with terminal renal failure due to severe essential hypertension that showed that the patients' blood pressure fell to normal and remained normal thereafter without the need of antihypertensive treatment after they received a kidney from young normotensive donors. The average follow-up was 4.5 years. This study is not only consistent with the notion that essential hypertension primarily is due to an abnormal kidney, it also supports the conclusion that hereditary abnormalities associated with essential hypertension that are situated outside the kidney do not give rise to hypertension.

**Impaired Ability of the Kidney to Excrete Sodium**

**Acquired hypertension.** Multiple observations show that the renal abnormalities that cause blood pressure to rise in acquired forms of hypertension diminish the kidney's capacity to excrete sodium. These include the fall in perfusion pressure engendered by partial occlusion of the aorta or the renal artery, reduction in renal mass, or the effect of deoxycorticosterone acetate or aldosterone. All these maneuvers reduce the kidney's ability to excrete sodium, a disability often accentuated by the administration of large amounts of sodium.

**Hereditary hypertension in animals.** In the Dahl salt-sensitive hypertensive-strain rat, the onset of hypertension was originally contingent on the kidney's insufficient capacity to excrete the enormous intake of sodium associated with the administration of 8% saline. The plasma volume of the Dahl salt-sensitive rat is raised and the plasma renin activity is low, both consistent with a difficulty in sodium excretion. It is interesting that, in addition, though the kidney appears to be primarily responsible for the hypertension, there are also inbred extrarenal hypertensive factors that contribute to the rise in pressure. In the Milan and spontaneously hypertensive rat (SHR) strains, the suggestion that there is an impaired ability to excrete sodium is based in part on the observation that in both strains, as blood pressure rises, a transient fall in urinary sodium excretion occurs, associated with a positive sodium balance that, in the SHR, persists thereafter.

These changes are associated with a fall in plasma renin activity, which is transient in the Milan hypertensive-strain rat but is more prolonged in the SHR. Inspection of 12 reports leads to the conclusion that in the SHR the persistent increase in extracellular fluid volume is associated with a low plasma renin. In six reports, plasma renin activity of SHRs up to 15 weeks of age was lower than in control normotensive animals; in the other six, plasma renin activity was normal. The finding of low plasma renin activity was more frequent when blood was obtained by decapitation or under light ether anesthesia, rather than when blood was obtained from a conscious restrained animal either by cutting off part of its tail or from a previously inserted indwelling catheter. This suggests that plasma renin activity levels in the normal range are probably abnormal, having been raised by the SHR's increased sympathetic and behavioral response to environmental stress.

Three further observations support the conclusion that the true plasma renin activity in the SHR is low: renin release from kidney slices obtained from SHRs is less than that from slices obtained from Wistar-Kyoto rats; isolated perfused rat kidney releases significantly less renin at all perfusion pressures; and plasma renin levels fail to rise after volume contraction.

In addition, plasma and urinary aldosterone in 7- and 16-week-old SHRs are low. Furthermore, many observations obtained on brush border membrane vesicles, microdissected proximal tubules, and proximal tubules in situ demonstrate that the proximal tubule cells in the Milan hypertensive rat and the SHR have an increased capacity to absorb sodium.

**Essential hypertension.** The indication that essential hypertension is also due to a diminished capacity for sodium excretion comes from several sources. First is the relation between dietary sodium intake and blood pressure in population studies. Unfortunately, this subject has become something of a battlefield, now bedeviled by commercial interests, for both the appetizing taste and the weight of processed foods are related to their salt content. The results of a massive international epidemiological study, known as the INTERSALT Study, have recently been published. It was carried out in 10,079 men and women aged 20–59 sampled from 52 centers around the world and used a standardized protocol, central training, and a central laboratory. After standardization for age, sex, body mass index, alcohol intake, and potassium excretion, within-center analysis showed that sodium excretion is significantly related to systolic pressure in individuals. Cross-center analysis showed that sodium excretion is significantly related to the rise in arterial pressure with age. A conservative estimate of the size of the effect of sodium intake on blood pressure is that, on average, a reduction in sodium intake of 100 mmol/day, between the ages of 25 and 55, corresponds to a 9 mm Hg lower mean rise in systolic pressure.
Once again, this study demonstrated that in geographically isolated populations that have urinary sodium excretion rates of less than approximately 60 mmol/day, blood pressure does not rise with age. In the past, the applicability of such observations to other, particularly to Western, societies has tended to be dismissed on the assumption that the general health and daily life patterns of such isolated, unacculturated societies was probably more relevant to their low blood pressure than their sodium intake.58 But several observations suggest this assumption is unwarranted. The local organizers at each of the four INTERSALT centers that had sodium intakes of less than 60 mmol/day have reported that the participants were physically active, appeared healthy, and showed no sign of malnutrition or protein deficiency.60

Three studies, published previously, demonstrate that in contrast to sodium intake, the daily life patterns of unacculturated communities have little detectable effect on blood pressure.61-63 The first study was in six Solomon Island communities that shared similar unacculturated life patterns.61 The physical fitness of the participants in all six islands was “excellent.” In three of the communities, sodium intake was less than 30 mmol/day, and the prevalence of hypertension was less than 1%. In two communities, the inhabitants added salt to the cooking so that sodium intake varied between 50 and 130 mmol/day; the prevalence of hypertension was 3.4% and 2.7%. In the remaining site, where they cooked in “copious amounts of sea water,” the prevalence of hypertension was 7.8%.

The second study was carried out in two South American tribes living on the Amazon River.62 One tribe, under the care of missionaries, regularly used table salt. In the men of this tribe, there was a rising trend of arterial pressure with age; in the women, there was a similar but statistically unimportant rise. The other tribe, which ate native low sodium food, had no rise in blood pressure with age in either sex. The third study was made in an isolated nomadic tribe at a low level of acculturation in southern Iran.63 It again demonstrated that when salt is available, unacculturation does not protect against hypertension. The area the tribe has inhabited for approximately 400 years contains many natural surface deposits of salt, which the tribe uses liberally in the baking of bread and cooking, as well as at the table. The average urinary sodium excretion was 186 mmol/day in men and 141 mmol/day in women. The prevalence of hypertension in this unacculturated community in men and women aged more than 30 years was 12% and 18%, respectively, with no tendency for weight to increase with age.

The effect of imposed changes in sodium intake on the blood pressure of patients suffering from essential hypertension also supports the conclusion that such patients have a difficulty with sodium excretion. A review of 61 studies published between 1947 and 198664 and three subsequent studies65-67 have shown that prolonged salt restriction reduces blood pressure in patients with severe, moderate, and mild hypertension. In addition, there is considerable heterogeneity, there is an overall increase in the hypertensive population’s response to sudden changes in sodium status.68 In other words, hypertensive patients have an increased sodium sensitivity; a sudden increase in sodium, for instance, will cause an exaggerated rise in blood pressure. In some patients, this is related to a detectable impairment in their ability to excrete an acute sodium load.69 There is also the significant negative correlation between blood pressure and plasma renin activity that has been observed in the men of an epidemiological study.70 In a smaller number of women, the drift downward in plasma renin activity with blood pressure was not significant.

Effect of Induced Changes in Dietary Salt Intake in Normal Animals and Humans

The apparent connection between salt intake and hypertension appears to be a manifestation of a normal phenomenon demonstrable in normal animals and humans. The prolonged ingestion of increased quantities of salt causes hypertension in the dog,71 chicken,72 rabbit,73 baboon,74 and rat.75

Unfortunately, in normal humans there are no studies comparable to those made in animals of the effect on blood pressure of a prolonged and modest increase in salt intake. Certainly, intakes greater than 600 mmol/day for 2–3 weeks increase blood pressure.76 And in older subjects in whom it is known that the ability to dispose of sodium is reduced, an increase in salt intake up to only 340 mmol/day for 4 weeks can cause the blood pressure to rise.77,78

It would appear, therefore, that the hypertensogenic effect of stressing the capacity of the normal kidney to excrete sodium by raising sodium intake is analogous to the hypertensogenic effect of a normal sodium intake stressing the impaired ability of abnormal kidneys to excrete sodium in acquired and hereditary hypertension.

The opposite is also true; diminishing the demand on the normal kidney to excrete sodium by reducing salt intake lowers arterial pressure. For obvious reasons, such studies have been easier to carry out than those studying the effect of raising sodium intake. Relatively small reductions in sodium intake have been studied over several months, including one study in neonates,79 four in school children,80-83 and one in adults.84 And, of course, there is the well-established observation that a persistent renal difficulty in retaining sodium, due to disease, can cause a fall in blood pressure.

Comments

How blood pressure is affected by stressing and relaxing the demand on the kidney’s ability to excrete sodium is problematical. It seems reasonable to propose that when the demand on the kidney’s capacity to excrete sodium is altered, there is an alteration of volume-controlled phenomena. One of
these is the plasma's capacity to inhibit Na⁺,K⁺-ATPase, which, as pointed out above, is related directly to induced changes in volume and sodium intake. It is therefore suggested that in acquired and hereditary hypertension, the sustained restraint on the ability of the kidney to excrete sodium leads to a sustained rise in the activity of volume-controlled systems. This would account for the sustained rise in concentration of Na⁺,K⁺-ATPase-inhibitory activity in the plasma and the hypothalamus.

In summary, normal plasma and hypothalamic extracts contain volume-controlled Na⁺,K⁺-ATPase-inhibitory activity. The intensity of this activity in the plasma and hypothalamic extracts is raised in acquired and essential hypertension. This change in inhibiting activity may be due to several substances. It is proposed that the rise in Na⁺,K⁺-ATPase-inhibiting activity in acquired and hereditary hypertension is due to a renal defect in excreting sodium. The role of Na⁺,K⁺-ATPase-inhibiting substances in hypertension is not known. Theoretically, they could be hypertensinogenic.

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