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## CALL FOR PAPERS | *Molecular Mechanisms Linking Salt to Hypertension*

### Dietary salt and hypertension: new molecular targets add more spice

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BLOOD PRESSURE (BP) is timely controlled by several mechanisms. The neural and hormonal mechanisms react within seconds or minutes to change the diameter of the blood vessels and vascular resistance. The renal mechanisms react within hours or days and restore BP mainly by controlling the plasma volume. The role of the kidneys in BP regulation has been well-characterized by the elegant work of Guyton and colleagues (18, 19) on the pressure natriuresis and diuresis relationship. An increase in BP causes the kidneys to excrete more salt and water and thereby decreases the extracellular and plasma volume.

Hypertension involves abnormal and persistent changes in the BP control mechanisms. High dietary salt has long been associated with hypertension. In industrialized societies, the individual's average salt consumption is 10 g/day, and the incidence of hypertension is greater than in rural societies. A large body of evidence points to a link between dietary salt, kidney function, and hypertension (18, 19, 21, 32, 34, 36). Renal cross-transplantation experiments further emphasized the role of the kidneys in hypertension. Insertion of a kidney from young hypertensive rat into nephrectomized normotensive rat is associated with a rise in BP. Also, when a kidney from normotensive rat is inserted into young nephrectomized hypertensive rat, BP of the hypertensive rat does not rise. Similarly, the high BP of patients with hypertension and nephrosclerosis becomes normal when they are transplanted with a kidney from normotensive donor (36).

A decrease in the capacity of kidneys to excrete salt would cause salt and water retention, increased extracellular and plasma volume, and increased BP. The kidneys' ability to excrete sodium declines gradually with age, and smaller increases in salt intake induce a rise in BP. Also, with age, the glomerular filtration rate is reduced, accompanied by a decline in functioning nephrons and progressive glomerulosclerosis. If, with age, salt consumption is not reduced, sodium balance is maintained by raising fractional sodium excretion, which requires elevation of BP (9).

In some individuals of the same age, abrupt changes in salt intake or excretion induce large increase in BP and are called salt sensitive. However, salt sensitivity may not be reproducible in the same individual. Also, the individual's day-to-day variation in dietary salt intake and urinary salt excretion add to the complexity of defining salt-sensitivity (34, 36). Analysis of the genetic basis of salt sensitivity, which is likely related to the genetics of hypertension, has implicated over 20 genes in humans (11, 30, 31, 32, 34). Also, gene-targeting experiments

in mice have identified over 30 genes, for which inactivating or activating mutations trigger a chronic change in BP (36). Many of these genes encode proteins that control renal sodium channels and transporters.

The amiloride-sensitive epithelial Na channel (ENaC) contributes to sodium reabsorption in the distal nephron, and the genes encoding the  $\alpha$ -,  $\beta$ - and  $\gamma$ -subunits of ENaC may harbor mutations or polymorphisms that affect sodium excretion and BP (36). Activating mutations in  $\beta$ - and  $\gamma$ -subunits are associated with low renin salt-sensitive hypertension with suppressed aldosterone secretion (Liddle's syndrome). In mice, truncation of the  $\beta$ -subunit and high-salt diet may produce hypokalemic alkalosis and high BP mimicking the human syndrome.

Adducin, a cytoskeletal protein at the inner surface of plasma membrane, may modulate  $\text{Na}^+\text{-K}^+\text{-ATPase}$  activity in renal tubules, and the gene encoding  $\alpha$ -adducin may affect salt sensitivity and BP. Positive association was found in the frequencies of G460W polymorphism of  $\alpha$ -adducin gene in hypertensive patients and controls. Also, homozygous  $\beta$ -adducin-deficient mice display decreased  $\alpha$ -adducin levels and higher BP than wild-type controls. In Milan hypertensive rats, an increase in  $\text{Na}^+\text{-K}^+\text{-ATPase}$  activity may be related to aberrant adducin gene. Also, in Dahl salt-sensitive hypertensive rats, mutation of the  $\alpha_1$ -subunit of  $\text{Na}^+\text{-K}^+\text{-ATPase}$  in the form of leucine substitution for glutamine could lead to a 3:1  $\text{Na}^+\text{-K}^+$  transport ratio instead of the 3:2 ratio in normotensive salt-resistant rats and an excess of  $\text{Na}^+$  reabsorbed for each  $\text{K}^+$  transported (36).

Some evidence points to a relationship between the  $\text{Na}^+/\text{H}^+$  exchanger-3 in the proximal tubules and BP sensitivity to dietary salt. The  $\text{Na}^+/\text{H}^+$  exchanger activity is increased in erythrocytes and lymphocytes in essential hypertension but may not reflect genetic abnormality. Apical membrane vesicles from the kidney of young prehypertensive Milan rats and spontaneously hypertensive rats (SHR) show increased sodium uptake via  $\text{Na}^+/\text{H}^+$  exchange. Also, transgenic mice overexpressing the  $\text{Na}^+/\text{H}^+$  exchanger in renal tubules become hypertensive during salt loading (7, 33).

Several hormones/factors could affect the activity of renal tubular channels and transporters. The renin-angiotensin-aldosterone system plays a major role in control of sodium reabsorption and BP (20, 29, 30). Chronic increase in plasma angiotensinogen may increase ANG II and cause hypertension; however, analysis of the role of the angiotensinogen gene in essential hypertension has not shown consistent association. Also, although the ANG II receptor-1 ( $\text{AT}_1\text{R}$ ) mediates most

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effects of ANG II on sodium reabsorption and aldosterone secretion and is an obvious candidate gene in essential hypertension, the specific mutations in the coding region of the *AT<sub>1</sub>R* gene in hypertensive families are not fully delineated. However, genetically-altered mice clearly confirm the role of renin-angiotensin system in the control of BP. Mice strains with functional copies of the angiotensinogen gene demonstrate possible association between plasma angiotensinogen and BP. Also, in mice, a link between functional gene copies for the *AT<sub>1</sub>R* and BP is observed, and the expression of the *AT<sub>1</sub>R* gene in the brain, aorta, and kidneys is regulated by salt intake. The *AT<sub>2</sub>R* may have a hypotensive effect as suggested by the observed hypertension in homozygous *AT<sub>2</sub>R*-deficient mice. Interestingly, BP of homozygous *AT<sub>1</sub>R*-deficient mice is sensitive to dietary salt, whereas the hypertension in homozygous *AT<sub>2</sub>R*-deficient mice is not salt sensitive (36).

Mutations in the enzymes involved in aldosterone synthesis and in mineralocorticoid receptor function may also affect BP (29). Hyperaldosteronism may result from a chimera gene placing the aldosterone synthase *CYP11B2* normally expressed in the adrenal glomerulosa under the control of an adrenocorticotropic hormone-dependent promoter. As a consequence, adrenocorticotropic hormone-regulated *CYP11B2* is aberrantly expressed in the adrenal fasciculata where it continuously produces aldosterone, resulting in salt retention and hypertension. Mutations in the aldosterone-binding site of the mineralocorticoid receptor may also increase its affinity for steroids that normally bind, but not activate the receptor. 11-Hydroxysteroid dehydrogenase-II (*11-HSD2*) ensures the specificity of mineralocorticoid receptor to aldosterone by metabolizing excess cortisol to cortisone. Inactivating mutations in the *11-HSD2* gene lead to increased renal cortisol and corticosterone, which are more powerful agonists of the mineralocorticoid receptor than cortisone. Subjects with apparent mineralocorticoid excess have high a cortisol-to-cortisone ratio in plasma and urine and severe hypertension and hypokalemia. Homozygous *11-HSD2*-deficient mice, if they survive, are hypertensive and exhibit hypokalemia, polyuria, and apparent mineralocorticoid activity of corticosterone comparable to the mineralocorticoid excess syndrome in human (29, 36).

Renal nitric oxide (NO) contributes to the regulation of renal medullary flow and diuresis (10). Dietary sodium may inhibit L-arginine transport in the renal medulla and thereby renal NO production and medullary flow (49). High-salt diet may also increase renal medullary osmolality and decrease NO synthase expression (22), and reduced renal medullary NO synthase activity is associated with salt-sensitive hypertension (46). Additionally, salt intake may be associated with increased oxidative stress and renal expression of NADPH oxidase and decreased activity of superoxide dismutase (28). Other factors, such as epoxyeicosatrienoic acids and 20-HETE, may affect not only renal blood flow but also proximal tubule transporters and pressure natriuresis (13, 26). Dopamine may regulate sodium excretion by activating one of five receptors, D1-D5 (48). The D1 receptor inhibits  $\text{Na}^+\text{-K}^+\text{-ATPase}$  and  $\text{Na}^+\text{/H}^+$  exchanger, and activation of the D1 receptor stimulates natriuresis and diuresis, whereas its inhibition leads to sodium and water retention. D1-receptor deficiency in heterozygous and homozygous null mice is associated with hypertension. D2 receptors may also promote sodium excretion, and homozy-

gous D2-deficient mice fed a high-salt diet show sodium retention and increased BP (36).

Peptides synthesized in the heart, such as atriopeptin-A and -B, and the gastrointestinal tract, such as uroguanylin, may induce a natriuretic effect and decrease BP. These peptides are also produced locally in the kidneys where they could regulate tubular sodium transport. A linear relationship between functional natriuretic peptide receptor-A gene copies and BP is found in mice. Also, mice lacking atriopeptin-A develop hypertension when placed on high-salt diet. Interestingly, homozygous mice lacking uroguanylin have impaired capacity to excrete salt when subjected to oral salt load, suggesting an endocrine link in which uroguanylin is produced by the stomach/intestine and is released into the circulation when excess salt is ingested (36).

Thus many of the genes identified in human and mice as controllers of BP regulate renal sodium handling, further establishing renal sodium handling, which changes with dietary salt, as a central mechanism in long-term regulation of BP (31, 32). Mutations that decrease the ability of the kidney to excrete sodium would cause salt and water retention and thereby increase plasma volume, cardiac output, and BP. Interestingly, the cardiac output may be normal in essential hypertension, even when there is hypervolemia. Also, the cardiac output may not directly control BP, because dialysis patients loaded with saline show increased peripheral resistance but not cardiac output (36). It is possible that an increase in plasma volume and vascular wall stretch may induce autoregulation, vasoconstriction, and increased vascular resistance. An increase in plasma volume may also raise the pressure in the auricles, which induces afferent stimuli to the hypothalamus and leads to pressor increase in sympathetic activity and vascular resistance.

An important question is whether plasma sodium changes with dietary salt. In normotensive individuals, raising dietary salt acutely may transiently increase plasma sodium but not the BP. Effects of chronic high salt intake on plasma sodium and BP in normotensive humans are less clear. A small rise in plasma sodium may be difficult to detect, yet a rise in plasma osmolality equivalent to a change in plasma sodium <1% is significant enough to stimulate the thirst center in the hypothalamus. Also, in essential hypertension and SHR, both plasma and urinary arginine vasopressin are increased, suggesting a rise in plasma osmolality sufficient to affect the hypothalamus. Some studies suggest that plasma sodium is 2 mM higher in hypertensive patients than controls (21). Also, positive association between plasma sodium and systolic pressure has been shown in hypertensive but not normotensive subjects. In rats, when plasma sodium is measured at 1- to 2-h intervals for 24 h, it is 1–3 mmol/kg greater in SHR than Wistar-Kyoto rats (36).

A 1–3 mmol/kg rise in plasma sodium that may occur in hypertension is likely to increase plasma volume but may itself contribute to the pressor effect of dietary salt (36). In hypertensive humans, acute changes in salt intake may change sodium levels not only in the plasma, but also in the cerebrospinal fluid (CSF), suggesting central effects of sodium (23). For example, acute experimental increases in plasma or CSF sodium >5 mmol/kg raise BP independent of the extracellular fluid volume (36). Also, increased osmolality in water-deprived rats may support arterial pressure and sympathetic

activity via a central action (8). Acute sodium loading may also inhibit baroreflex-induced bradycardia (5). Small changes in plasma sodium may directly affect the hypothalamic control of BP through the local pituitary renin-angiotensin system. Additionally, high dietary salt may increase the synthesis of pro-opiomelanocortin by prohormone convertase 2 in the pituitary, which in turn increases melanocyte-stimulating hormone (MSH), a hormone that promotes salt excretion via melanocortin receptor-3 in the kidneys. The natriuretic role of MSH is supported by reports that homozygous mice lacking prohormone convertase 2 or melanocortin receptor-3 develop hypertension when fed a high-salt diet (25).

Increased plasma sodium may also initiate sodium-nucleic acid interaction in various cell types and increase the production of BP modulating hormones. In cultured vascular smooth muscle, an increase in sodium by 2–10 mM increases mRNA expression of hypertrophy-related factors and the number of AT<sub>1</sub> receptors (17). Interestingly, high-salt diet in normotensive rats is associated with increased expression of endothelin in the kidneys and perhaps in the blood vessels, yet the BP does not rise. This is likely because the vascular and renal pressor effects of ET<sub>A</sub> receptors are counterbalanced by ET<sub>B</sub> receptor-mediated vasodilation and sodium excretion. In support of this theory, chronic ET<sub>B</sub> receptor blockade in rats is associated with increases in BP particularly during a high sodium diet (3, 16, 38).

Pressor effects of dietary salt in hypertension may be, in part, due to an increase in a plasma factor that inhibits Na<sup>+</sup>-K<sup>+</sup>-ATPase (2, 14, 15, 24, 47). Acute volume expansion in dogs increases the capacity of plasma to inhibit Na<sup>+</sup>-K<sup>+</sup>-ATPase, and this increase is also observed in essential hypertension, SHR, and Milan hypertensive rat (36). The nature of the substance responsible for Na<sup>+</sup>-K<sup>+</sup>-ATPase inhibition in hypertension is not clear. One study (2) suggests that plasma marinobufagenin immunoreactivity, which rises with acute volume expansion, is raised in essential hypertension. A cross-sectional study of 369 individuals has shown positive association between plasma sodium and ouabain (15). Also, in rats, the rise in BP induced by an increase in CSF sodium may be secondary to increased ouabain in the hypothalamus, as it is prevented by intracerebroventricular administration of Fab fragments, which bind ouabain. Ouabain is also released from the adrenal gland and may affect sodium homeostasis by exerting direct actions on Na<sup>+</sup>-K<sup>+</sup>-ATPase in renal tubules, the heart, and the vasculature. Studies from Lingrel's group (14) have examined the role of  $\alpha_2$ -isoform of Na<sup>+</sup>-K<sup>+</sup>-ATPase in mediating the pressor effects of ouabain in mice. They analyzed the effects of ouabain on BP in wild-type mice expressing ouabain-sensitive  $\alpha_2$ -isoform and genetically engineered mice expressing ouabain-insensitive  $\alpha_2$ -isoform. Because  $\alpha_1$ -isoform is more resistant to ouabain in rodents, the ouabain response in the two genotypes can be only attributed to  $\alpha_2$ -isoform. Administration of ouabain increased ouabain in serum of both wild-type and  $\alpha_2$ -resistant mice, but hypertension developed only in wild-type mice. Also, in vitro, ouabain increased vascular tone and phenylephrine-induced contraction in aorta of wild-type but not  $\alpha_2$ -resistant mice, suggesting that the  $\alpha_2$ -Na<sup>+</sup>-K<sup>+</sup>-ATPase mediates the ouabain-induced increase in vascular contraction and hypertension (14).

Studies in Blaustein's laboratory (51) have further examined the role of Na<sup>+</sup>-K<sup>+</sup>-ATPase in hypertension. BP and vascular function were compared in wild-type mice and mice with a null

mutation in one gene of low ouabain affinity  $\alpha_1$  ( $\alpha_{1+/-}$ )-subunit or high affinity  $\alpha_2$  ( $\alpha_{2+/-}$ )-subunit of Na<sup>+</sup>-K<sup>+</sup>-ATPase. BP was elevated in  $\alpha_{2+/-}$  but not  $\alpha_{1+/-}$  mice. Small mesenteric arteries from  $\alpha_{2+/-}$ , but not  $\alpha_{1+/-}$ , had enhanced myogenic tone and vascular reactivity, confirming that  $\alpha_2$ -Na<sup>+</sup>-K<sup>+</sup>-ATPase plays a key role in the control of vascular tone and BP. Interestingly, low-dose ouabain (1–100 nM), which inhibits only  $\alpha_2$ , elevated intracellular Ca<sup>2+</sup> concentration ([Ca<sup>2+</sup>]<sub>i</sub>) and constricted arteries of mice. Thus nanomolar increase in plasma ouabain may increase BP by inhibiting  $\alpha_2$ -Na<sup>+</sup>-K<sup>+</sup>-ATPase, which in turn affect the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger (NCX), and thereby promote Ca<sup>2+</sup> entry into vascular smooth muscle and vasoconstriction. Arnon et al. (1) also suggested that sodium entry into vascular smooth muscle via store-operated Ca<sup>2+</sup> channels may influence Na<sup>+</sup>-K<sup>+</sup>-ATPase activity, NCX, and [Ca<sup>2+</sup>]<sub>i</sub> signaling. In support of this hypothesis, small increases in extracellular sodium may promote vascular contraction, and NCX inhibitors, particularly those inhibiting the reverse mode of the exchanger, prevent the effects of extracellular sodium on vascular contraction (4).

Iwamoto and colleagues (26a) further investigate the relationship between salt-sensitive hypertension and [Ca<sup>2+</sup>]<sub>i</sub> entry via NCX type-1 in vascular smooth muscle. SEA0400, specific inhibitor of [Ca<sup>2+</sup>]<sub>i</sub> entry via NCX1, has been shown to lower BP in salt-sensitive hypertensive but not normotensive rats. Infusion of SEA0400 into the femoral artery of salt-sensitive hypertensive rats increased blood flow, indicating peripheral vasodilation. SEA0400 reversed ouabain-induced [Ca<sup>2+</sup>]<sub>i</sub> elevation and vasoconstriction in pressurized arteries. Also, heterozygous NCX1-deficient mice have low salt sensitivity, whereas transgenic mice expressing the vascular NCX1.3 are salt hypersensitive, and SEA0400 lowered BP in mice expressing NCX1.3. These findings suggest that salt-sensitive hypertension may be related to Ca<sup>2+</sup> entry via NCX1 in vascular smooth muscle, and NCX1 inhibitors might be useful in salt-sensitive hypertension.

The identification of several molecular mechanisms linking dietary salt and hypertension confirm that salt sensitivity and the BP are not determined by a single gene but rather by the combined action of a number of genes. Each of these genes may affect one or more channel, transporter, or enzyme associated with the neural, hormonal, vascular, and renal control mechanisms of BP. For example, salt-sensitive hypertension may be associated with changes not only in vascular but also renal NCX (6). High-salt diet may affect cellular mechanisms not only in vascular smooth muscle, but also in the endothelium. Studies of Lingrel's group (14) show an increase in aortic basal tone in  $\alpha_2$ -Na<sup>+</sup>-K<sup>+</sup>-ATPase deficient mice that is dependent on the endothelium. Also, homozygous 11-HSD2-deficient mice that exhibit impaired renal sodium excretion may have an additional endothelial dysfunction demonstrated by enhanced norepinephrine-induced vascular contraction, which may contribute to hypertension (29, 36). In Dahl salt-sensitive rats, hypertension may be related to decreased availability of vasodilatory NO leading to increased vasoconstrictive response to norepinephrine and ANG II. The high-salt-induced decrease in NO availability and vascular relaxation could be due to inhibition of NO synthase or increased superoxide production (39, 50). This is supported by reports that arginase inhibition restores arteriolar endothelial function in Dahl rats with salt-sensitive hypertension (27).

An individual's sensitivity to dietary salt may also be related to ethnic background, gender, and other environmental factors. For example, the decline in glomerular filtration rate with age is more marked in blacks (36). Also, in a series of more than 400 hypertensive subjects, seven missense mutations were found in the gene coding for the  $\beta$ -ENaC subunit, most of them in patients of African descent. Some of the ENaC polymorphisms might be associated with greater ENaC activity in vivo and contribute to ethnic differences in sodium retention and the risk of low renin hypertension (36). This is supported by a randomized control trial in which modest salt reduction decreases BP and urine protein excretion in black hypertensives (44). Obesity is also a major factor that may influence salt sensitivity and BP via central and peripheral mechanisms (12, 45). Gender differences in the vascular control mechanisms of BP and the expression of vascular NCX have also been suggested (4). Estrogen receptors in the central nervous system may be regulated by hypertonicity and may play a role in central osmotic regulation (40, 41). Also, salt appetite in rats is inhibited by central oxytocin (42). Finally, dietary salt should be carefully monitored during pregnancy because it may affect the mother in the form of hypertension/preeclampsia or may initiate in utero programming leading to hypertension in growth-restricted offspring when placed on high-salt diet (37, 43).

Thus the relationship between dietary salt and hypertension has evolved from a possible association to the identification of specific mutations in BP-controlling genes and measurable alterations in the expression/activity of distinct ion channels, transporters, and enzymes. Future research should further isolate, analyze, and characterize each of these molecular mechanisms. Yet, evidence suggests complex interaction between the various BP-controlling mechanisms in vivo. For instance, the arterial baroreceptors long known for short-term control of BP may play a role in controlling the level of sympathetic nerve activity to the kidneys and thereby the long-term control of plasma volume and BP (35). As hypertension is a multifactorial disorder, an integrative approach will help to examine the combined effects of multiple molecular targets on the neural, hormonal, vascular, and renal control mechanisms of BP. Likewise, it is important to consider the contribution of ethnic background, gender, and other dietary and environmental factors to the individual's sensitivity to dietary salt and susceptibility to hypertension.

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