Pathways by Which Dietary Salt Affects Blood Pressure and the Nervous System

J. Michael Wyss

In their article in this edition of *Hypertension*, O’Donobaugh and Brooks address a double controversy, that is, salt-sensitive hypertension and the role of the nervous system in long-term blood pressure control. Although both of these areas of research have avid opponents and proponents, there is an emerging understanding of the multifaceted mechanisms that underlie hypertension in humans and the importance of both dietary NaCl and the nervous system in hypertension.

The role of dietary salt intake in hypertension has been widely debated in both the lay and scientific literature for over a half century, and the view of its role has shifted during that period. Much of the evidence against the pathogenic role of salt in hypertension is based on epidemiological and dietary interventional studies that did not discriminate between putative salt-sensitive and salt-resistant individuals. More selective studies have established that salt-sensitive changes in arterial pressure exist in many individuals and that these changes can result in significant health risks. Furthermore, recent studies have demonstrated that salt sensitivity is present more frequently in hypertensive than in normotensive humans and that “normotensive” salt-sensitive individuals have a greater risk of developing hypertension with increasing age. Also, given the latest downward adjustment of the threshold for hypertension by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), even modest dietary salt-related increases in arterial pressure will thrust into the hypertension category many more individuals than anticipated previously. Thus, salt sensitivity in blood pressure control is real and important.

The mechanisms underlying hypertensive responses to chronic high-salt diets have been as hotly debated as the existence of salt sensitivity itself. Much of the human literature assumed that alterations in renal function were the primary proximate cause of arterial pressure increases. Guyton and his associates detailed an elegant model that indicated long-term blood pressure increases in arterial pressure control was primarily dependent on the ability of the kidney to regulate fluid volume. When that volume was chronically increased, the kidney would demand an increase in systemic pressure to maintain fluid homeostasis. Many forms of human hypertension support this model, arguably the most exciting of which has been the discovery of the gene mutation in ENaC in Liddle’s disease that causes the collecting duct to avidly retain sodium. However, it is clear that such monogenic forms of hypertension are very rare and that renal abnormalities do not appear to underlie salt-sensitive hypertension in many individuals.

Several lines of evidence over the past 40 years have suggested that chronic neurohormonal abnormalities contribute to salt-sensitive hypertension. However, the importance of these mechanisms was dismissed by many, because neurogenic mechanisms were considered to be active only in the acute and not chronic regulation of blood pressure. This assumption is grounded in the fact that the best known neural regulator of blood pressure, that is, the baroreflex, was known to rapidly reset after sustained alterations in arterial pressure. Furthermore, studies using relatively nonselective methods to assess sympathetic nervous system activity were inconsistent in their support of the importance of a neural component. In contrast, studies using more selective techniques indicate that sympathetic nervous system activity increases during the progressive development of hypertension in many individuals and that impairments in the regulation of the sympathetic nervous system are selective. For instance, baroreflex regulation of sympathetic nervous system activity to the heart (but not to the skeletal muscles) is composed of salt-sensitive hypertension in some humans. Although many mechanisms for salt-sensitive hypertension have been suggested by human studies, it is unlikely that human studies will quickly resolve the relative importance of these mechanisms.

In their study, O’Donobaugh and Brooks use the deoxycorticosterone acetate (DOCA)-NaCl rat model to test the hypothesis that supplemental dietary salt raises plasma concentrations of NaCl and that this contributes to the rise in arterial pressure in the DOCA-NaCl model of hypertension. The results demonstrate that chronic, high dietary NaCl raises plasma concentrations of NaCl by ≥3 mEq/L in DOCA-treated rats. The rise in plasma NaCl is associated with a rise in arterial pressure and sympathetic nervous system activity in the DOCA rats. Furthermore, treatment with either DOCA or NaCl alone does not significantly alter blood pressure, plasma NaCl concentration, or sympathetic nervous system activity. This confirms that a synergistic interaction exists between the mineralocorticoid and dietary NaCl excess. More importantly, the authors test whether the small change in plasma NaCl was responsible for the elevated arterial pressure and sympathetic activity. The authors infused SDW to dilute the plasma NaCl concentration. The dilution resulted in a fall in arterial pressure and sympathetic nervous system activity in the DOCA-NaCl group but not in the control or...
DOCA-only groups. Together, this strongly supports the idea that small changes in plasma NaCl concentration can lead to relatively large increases in sympathetic nervous system activation and a resulting increase in arterial pressure.

Similar, relatively small increases in plasma and/or cerebrospinal fluid Na⁺ or NaCl have been observed in other models of hypertension, and they also appear to be linked to activation of the sympathetic nervous system.6–7 However, if and how these small changes can chronically cause rises in blood pressure or changes in the nervous system remains debated. One obvious place for an interaction between circulating NaCl and the nervous system is in the organum vasculosum of the stria terminalis, an area of the hypothalamus that lies outside of the blood-brain barrier and is, thus, readily exposed to ionic changes in the plasma. Neurons in this region are very responsive to changes in plasma NaCl that are >1 mEq/L,8 and the neurons respond to such changes with an alteration in neurotransmitter delivery to the hypothalamus.8 Furthermore, long-term elevations of dietary NaCl can activate hypothalamic neuroendocrine neurons through this circumventricular organ.10

Other circumventricular areas of the brain may also play a role in detecting small increases in plasma NaCl, for example, the subfornical organ, which contains neurons that are very sensitive to circulating angiotensin II, an indirect surrogate for plasma NaCl. Furthermore, dietary NaCl has been shown to alter the firing rate of peripheral neurons in visceral organs, for example, the liver; however, the importance of these pathways in long-term blood pressure regulation is less clear.11

In some models of salt-sensitive hypertension, excess dietary NaCl appears to directly increase the concentration of NaCl to which neurons in the hypothalamus and brain stem are exposed, and such changes can increase sympathetic nervous system activity. The effects of increased NaCl on brain neurons may also be mediated by intermediaries, like ouabain, and in some models appear to involve stimulation of mineralocorticoid and angiotensin receptors in the brain. Ongoing studies of long-term regulation of hypothalamic/artrial-pressure-relevant neurons should greatly elucidate the role that they play (for example, see Reference 12).

Examples of other recent exciting discoveries concerning the mechanisms that may link the brain to salt-sensitive hypertension include overexpression of angiotensin III and aminopeptidase A,13 underexpression of γ adducin,14 and genes that regulate the protein kinase cascade.

O’Donoughy and Brooks1 have taken an important step in elucidating the mechanisms of NaCl-sensitive hypertension in the DOCA-NaCl rat. Although their findings will likely facilitate the understanding of the pathogenesis of salt-sensitive hypertension in some individuals, it is probable that there are other important mechanisms than salt-sensitive hypertension in animal models and human cohorts. Additional research is needed to uncover the full panoply of these mechanisms. Although it is unlikely that humans will revert to the hunter-gatherer diets that were low in salt (~1 g/day versus current 6 to 12 g/day), a full understanding of the causes of salt-sensitive hypertension may lead the way to better protect humans from the adverse effects of their dietary salt choices.

References


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