Neurogenic Mechanisms and Salt Sensitivity

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The concept of salt sensitivity is based on the observation that some individuals respond to a high salt intake with a marked increase in blood pressure, whereas others experience little or no blood pressure changes. Salt sensitivity is found much more frequently in hypertensive than in normotensive subjects, and its presence predicts a significantly greater increase in blood pressure with age, suggesting that salt sensitivity plays some role in the pathogenesis of hypertension. In addition, the risk for the occurrence of cardiovascular events is >3-fold higher in salt-sensitive than in salt-resistant hypertensive subjects. In this issue of Hypertension, Coruzzi et al show that in individuals with essential hypertension, even modest levels of salt sensitivity are associated with alterations in autonomic cardiovascular control. Their study strongly supports the idea that neurogenic mechanisms are involved in the pathophysiology of salt sensitivity in essential hypertension.

Because the kidney is the primary site for the regulation of salt and water homeostasis, most of the previous search for mechanisms leading to salt sensitivity has focused on functional and genetic differences in renal sodium handling. In their classical analysis of long-term blood pressure control, Guyton et al predicted that any reduction of the steepness of the chronic pressure–natriuresis curve, such as a loss of kidney mass or an aldosterone-producing adenoma, will induce salt sensitivity of blood pressure. This proposal was confirmed by experimental and clinical observations, most elegantly in monogenic disorders, which functionally mimic aldosterone excess of aldosterone (glucocorticoid remediable aldosteronism, apparent mineralocorticoid excess, and Liddle’s syndrome). Other common findings in salt-sensitive individuals are a reduced renal blood flow but increased fractional sodium reabsorption in the proximal tubule in response to high salt, glomerular hyperfiltration, and an altered endocrine and paracrine control of tubular transport and the renal circulation. Together, these observations indicate that salt sensitivity reflects a physiological defect in the ability of the kidneys to excrete sodium chloride.

Several studies have also implicated sympathetic overactivity and an altered neurohumoral control of renal hemodynamics in the genesis of salt-sensitive hypertension, but their interpretation remained somewhat controversial. Direct intraneural recordings actually demonstrated an elevated central sympathetic neural outflow in young men with mild hypertension, but early hypertension is often salt resistant. Moreover, sympathetic activity was found to not be higher in salt-sensitive than in salt-resistant subjects. Similar observations were made when sympathetic activity was assessed by measuring urinary norepinephrine levels in salt-sensitive and salt-resistant individuals. Coruzzi et al now take a different approach to tackle the relationship between neural control and salt sensitivity. The authors ask whether an autonomic dysfunction may already be detectable in individuals with mild, salt-resistant essential hypertension. To quantify salt sensitivity in this range, they adopt the salt sensitivity index originally proposed by Kimura and Brenner. This index is defined as the ratio of the change in mean arterial pressure to the change in sodium excretion during a dietary salt challenge and exactly corresponds to the steepness of the chronic pressure–natriuresis curve. To assess autonomic cardiovascular control, they measure the spontaneous arterial baroreflex sensitivity using the sequence technique and calculate power spectra from their blood pressure and pulse interval recordings. The exciting main result of their analysis is shown in Figure 3; even in individuals conventionally regarded as salt resistant, spontaneous arterial baroreflex sensitivity progressively declines with increasing salt sensitivity. This effect is independent from age, body mass index, and the baseline 24-hour blood pressure levels and heart rates, and it is only moderately attenuated by reducing salt intake. Nearly identical alterations can be found for the spectral power of pulse interval in the high-frequency band (0.15 to 0.40 Hz). These data convincingly show that in essential hypertensive subjects, changes in salt sensitivity are specifically associated with alterations in autonomic cardiovascular control.

Are the alterations in neural control identified by Coruzzi et al primary or secondary to salt sensitivity, or do they only correlate with another yet unidentified factor? The sequence method used by Coruzzi et al to determine baroreflex sensitivity largely reflects baroreflex control of cardiac vagal drive, and the high-frequency band corresponds to respiratory sinus arrhythmia, which is also driven by vagal neurons. Accordingly, the autonomic alterations detected by Coruzzi et al will primarily affect cardiac function but not renal salt excretion or vascular tone. An interesting observation was made by Weinstock et al, who selectively bred rabbits for an impaired cardiac baroreflex. They generated normotensive but salt-sensitive rabbits that developed hypertension when fed a high-salt diet. However, although tempting, the conclusion that the altered baroreceptor reflex function is the cause of the salt sensitivity is not necessarily true because additional central sympathetic pathways may mediate the
salt-induced increase in sympathetic activity and the decrease in baroreflex gain. The same argument holds true for Dahl salt-sensitive (S) rats, which exhibit an impaired cardiac baroreflex sensitivity before they become hypertensive. In humans with essential hypertension, baseline sympathetic nerve traffic increased progressively from the normotensive to the moderate and more severe hypertensive group; in parallel, baroreflex control of the heart was progressively impaired, but baroreflex modulation of muscle sympathetic nerve activity remained entirely preserved even in the most hypertensive subjects.

Thus, whereas a direct mechanistic link between an impaired cardiac baroreflex and salt sensitivity is very unlikely, the association found by Coruzzi et al may be secondary to an altered regulation of sympathetic activity. The future identification of such a close relationship between subtle, subthreshold changes in salt sensitivity and sympathetic overactivity would be most interesting with respect to the recent idea that slowly accumulating acquired renal injury may be a common mechanism in the pathogenesis of salt-sensitive hypertension.

References

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