Sympathetic Neural Contribution to Salt-Induced Hypertension in Dahl Rats

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The Dahl strain provides a model for examining mechanisms involved in the genetic sensitivity or resistance to salt-induced hypertension. Dahl salt-sensitive rats develop hypertension when fed a high salt diet; Dahl salt-resistant rats remain normotensive. Based on early experiments, it was thought that hypertension in Dahl salt-sensitive rats epitomized the overriding importance of renal and humoral mechanisms in salt-induced hypertension, but studies in the past 15 years have demonstrated that alterations in sympathetic neural mechanisms also participate critically in the genetic predisposition to salt-induced hypertension in Dahl salt-sensitive rats. This article briefly reviews sympathetic neural mechanisms in Dahl rats, including evidence for a role of afferent baroreceptor as well as central neural and peripheral adrenergic mechanisms in salt-induced hypertension in Dahl salt-sensitive rats.

Following Dahl's original studies, other investigators extended insight into the renal and humoral mechanisms that participate in salt-induced hypertension. For example, the kidneys of DS rats were shown to exhibit impaired intrinsic natriuretic capacity, fewer and sparsely granulated renomedullary interstitial cells, lower renal papillary blood flow, and less antihypertensive capacity than do kidneys from DR rats.

Rapp and Dahl identified genetic differences in adrenal secretion of mineralocorticoids in DS and DR rats. This difference was postulated to contribute to the abnormal control of blood pressure. Based on these studies, it was suggested that the Dahl strain was a model in which renal and humoral mechanisms exerted the critical influence in salt-induced hypertension.

In 1968-1969, deChamplain and colleagues demonstrated that altered sympathetic neural mechanisms contribute importantly to development of deoxycorticosterone acetate–salt hypertension in rats. These studies on the importance of sympathetic neural mechanisms in an experimental model of salt hypertension in rats prompted examination of the possible role of neural mechanisms in the Dahl strain of genetically hypertensive rats. I review briefly here evidence obtained during the past 15 years for the role and mechanisms of the sympathetic nervous system in the pathogenesis of salt-induced hypertension in DS rats.

Vascular Resistance and Arterial Pressure

Ganguli et al measured cardiac output and total peripheral resistance during low and high salt diets in...
DS and DR rats. During a low salt diet, cardiac output and peripheral resistance did not differ in DS and DR rats. With a high salt diet, cardiac output increased in both strains; indeed, if anything, there were slightly greater increases in DR rats. In contrast, there were striking differences in the vascular responses to the high salt diet in the two strains: the high salt diet produced vasodilation in DR rats and vasoconstriction in DS rats.

In 1978, Takeshita and I reported that sympathetic neural mechanisms contribute importantly to the salt-induced vasoconstriction in DS rats. Vascular resistance was calculated by obtaining pressure-flow curves in perfused hindquarters of rats fed a high (8% NaCl) or a low (0.4% NaCl) salt diet for 4 weeks. High salt intake significantly increased arterial pressure and hindquarter vascular resistance in DS rats but not in DR rats. The contribution of neurogenic mechanisms to the increase in hindquarter vascular resistance was studied by comparing pressure-flow curves before and after sympathetic denervation. Sympathetic denervation significantly decreased vascular resistance in DS rats fed high salt diets but not in DS rats fed low salt diets or in DR rats. Under the conditions of these experiments, elevated sympathetic neurogenic vasoconstrictor tone accounted for approximately 50% of the salt-induced increase in hindquarter vascular resistance in DS rats.

Salt-induced enhancement of sympathetic neural vasoconstriction in the hindquarters of DS rats may not apply to all vascular beds. Fink et al studied renal vascular responses to sympathetic denervation and sympathetic nerve stimulation. Changes in renal vascular resistance in response to sympathetic denervation and stimulation were similar in DS and DR rats. However, a high salt diet significantly decreased resting renal vascular resistance in DR rats but not in DS rats. The absence of renal vasodilation during a high salt diet in DS rats could not be attributed to abnormalities in neurogenic mechanisms and appeared instead to relate to abnormal local or humoral mechanisms.

Because salt-induced augmentation of sympathetic neural vasoconstrictor tone was not observed in all vascular beds, it was important to examine whether the sympathetic nervous system contributed importantly to the salt-induced hypertension. This was tested in three ways. The first test involved chemical sympathectomy with 6-hydroxydopamine; the second involved interruption of peripheral adrenergic function with guanethidine; and the third involved ganglionic blockade with chlorisondamine. Takeshita et al demonstrated that chemical sympathectomy completely prevented the development of salt-induced hypertension and eliminated increased neurogenic vasoconstrictor tone in the hindquarters in DS rats without altering sodium excretion and weight gain. Contemporaneously, Friedman et al reported that interruption of peripheral adrenergic function with guanethidine also prevented the development of salt-induced hypertension in young DS rats. Gordon et al subsequently evaluated the neural contribution to hypertension in conscious intact Dahl rats by using ganglionic blockade. After 4 weeks of high salt diet, DS rats had significantly higher arterial pressure than DR rats. When neurogenic vasoconstrictor tone was removed by ganglionic blockade, arterial pressure fell to levels that were not different in the two strains. These studies indicate that 1) the integrity of the sympathetic nervous system appears to be essential for the development of salt-induced hypertension in the Dahl strain and 2) the elevated arterial pressure of DS rats depends on neurogenic mechanisms.

There is evidence that the abnormalities in sympathetic neural mechanisms involve peripheral adrenergic, central nervous system, and afferent baroreceptor mechanisms.

**Peripheral Adrenergic Mechanisms**

Peripheral adrenergic mechanisms were evaluated by comparing hindquarter vasoconstrictor responses produced by electrical stimulation of the lumbar sympathetic nerves and by local administration of norepinephrine. A high salt diet potentiated vasoconstrictor responses to sympathetic nerve stimulation in DS rats but did not augment responses to norepinephrine. A high salt diet did not alter vascular responses to either stimulus in DR rats. These observations suggest that a high salt diet in DS rats either facilitates release of norepinephrine from peripheral adrenergic nerve endings or increases sympathetic innervation of blood vessel.

Studies from three laboratories indicate that DS rats have abnormal responses of catecholamine-forming enzymes and of norepinephrine turnover in response to a high salt diet. Saavedra et al found that a high salt diet decreased activity of tyrosine hydroxylase and dopamine β-hydroxylase in the adrenal glands of DR but not of hypertensive DS rats. Subsequently, Racz et al observed that DS rats fed high salt diets had a higher adrenal synthesis of norepinephrine and a higher adrenal content of norepinephrine and epinephrine compared with DR rats. Genain et al reported that in the heart and intercapsular brown fat, norepinephrine turnover was decreased by high dietary salt in DR but not in DS rats. Taken together these neurochemical studies are consistent with the concept that the predisposition of the DS rats to salt-induced hypertension may be related in part to an inability of dietary salt to inhibit sympathetic nervous system activity.

**Central Nervous System Mechanisms**

Central neural mechanisms in the pathogenesis of salt-induced hypertension in DS rats have been implicated by several lines of evidence. Lesions in the anteromedial hypothalamus, the paraventricular nuclei, or the anteroventral third ventricular region prevent or minimize salt-induced hypertension in DS rats. In addition, pressor and splanchnic sym-
pathetic nerve responses to electrical stimulation of the ventromedial hypothalamus are exaggerated in DS compared with DR rats on either low or high salt diets. Further intracerebroventricular injection of hypertonic NaCl solution or angiotensin II produces greater pressor responses in DS than DR rats even before the development of hypertension. Koepke et al have identified an important interaction between environmental factors (such as stress and dietary salt) and genetic factors in the central nervous system control of renal function in DS rats. These investigators have performed a series of studies that indicate that an acute behavioral stress increases renal sympathetic nerve activity and decreases urinary flow rate and urinary sodium excretion. The increases in renal sympathetic nerve activity and the decreases in urinary sodium excretion with acute stress were greater in DS than in DR rats. Moreover, a high salt diet augmented the sympathoexcitatory and antinatriuretic responses to stress in DS but not in DR rats. These investigators concluded that a main locus of action of the high salt diet in DS rats is the central nervous system. Specifically, it was proposed that the interaction between dietary salt and genetic factors may lead to enhanced responsiveness of renal sympathetic nerves to environmental stress and consequently to renal sodium retention.

Afferent Baroreceptor Mechanisms

Pressor responses to vasoconstrictor stimuli depend on the balance between direct vasoconstrictor effects and the buffering action of baroreceptor reflexes. Thus, an augmentation in pressor responses to a vasoactive stimulus could result from increased vascular reactivity or, alternatively, from impairment in baroreceptor reflex buffering. Hypertension is associated with abnormalities in baroreceptor reflex control. These have been thought to be the result of hypertension, but there is emerging evidence that abnormalities in baroreceptor reflex function may precede and contribute to hypertension.

Gordon and colleagues demonstrated that prehypertensive DS rats fed low salt diets exhibit impaired arterial baroreceptor reflex control of heart rate and vascular resistance compared with DR rats. Miyajima and Bunag subsequently demonstrated that prehypertensive DS rats also exhibit impaired inhibition of renal and splanchnic sympathetic nerve activity during phenylephrine-induced increases in arterial pressure. Interestingly, both groups of investigators found that baroreceptor reflex responses did not differ in DR and prehypertensive DS rats during nitroprusside-induced decreases in arterial pressure. In other words, prehypertensive DS rats have an abnormality in buffering responses to hypertensive but not to hypotensive stimuli. These and subsequent studies also demonstrated that there was an impairment in arterial baroreceptor discharge in prehypertensive DS rats during increases in arterial pressure but not during decreases in arterial pressure. The finding that abnormalities in afferent baroreceptor firing paralleled the abnormalities in baroreceptor reflex control of sympathetic nerve activity, vascular resistance, and arterial pressure suggested that the defect in the baroreceptor reflex in prehypertensive rats related primarily to abnormalities in afferent baroreceptor function. This view was supported by the observation that decreases in sympathetic nerve activity and arterial pressure elicited by electrical stimulation of the aortic depressor nerve did not differ in DR and prehypertensive DS rats. However, Miyajima and Bunag observed that, whereas the sympathetic nerve and blood pressure responses to aortic nerve stimulation are not reduced in prehypertensive DS rats, the heart rate responses are weaker in DS compared with DR rats fed a low salt diet. These workers concluded that there is an abnormality in central neural integration that involves selectively the baroreceptor reflex control of heart rate in prehypertensive DS rats. In contrast, the abnormal baroreceptor reflex control of sympathetic nerve activity and blood pressure appears to relate instead to afferent mechanisms. Because these differences in baroreceptor function are evident before any elevation in arterial pressure, it was suggested that they may reflect genetic abnormalities in afferent baroreceptor function, which may contribute to the propensity to salt-induced hypertension in DS rats.

Ferrari et al subsequently demonstrated that there is also impairment in cardiopulmonary (low pressure) baroreceptor reflex inhibition of sympathetic nerve activity during acute volume expansion in prehypertensive DS rats. Because this reflex participates in the control of renal sodium and water excretion, as well as renin release, this abnormality could contribute to salt-dependent hypertension in DS rats.

Thus, these studies suggest that in Dahl rats, underlying differences in baroreceptor function, which reside in large part at the afferent level and are presumably genetically determined, may contribute to the contrasting responses of DS and DR rats to a high salt diet.

A second concept regarding baroreceptor reflexes in Dahl rats relates to the interaction between dietary salt intake and baroreceptor properties. Several studies have demonstrated that changes in dietary salt intake can modulate baroreceptor reflex control of sympathetic nerve activity. This modulation has usually been attributed to alterations in central neural or efferent components of the baroreceptor reflex or to interactions with other reflexes. My colleagues and tested the concept that changes in dietary salt might alter afferent baroreceptor discharge properties. This hypothesis was prompted by evidence that ion and humoral factors, which may be altered by changes in dietary salt, have important influences on afferent baroreceptor mechanisms. Ferrari and observed that the slopes relating aortic baroreceptor discharge to mean arterial pressure were significantly steeper in DR rats fed a high
salt than in DR rats fed a low salt diet. This phenomenon did not appear to result from changes in vascular distensibility. Thus, a high salt diet augmented arterial baroreceptor function in DR rats, probably by sensitizing baroreceptor endings. The mechanism by which a high salt diet might sensitize arterial baroreceptors is not clear but could conceivably involve ionic or humoral adjustments that attend high dietary salt.

Interestingly, a high salt diet did not augment baroreceptor function in DS rats even when the salt-induced hypertension was prevented by chemical sympathectomy. In other words, a high salt diet failed to sensitize baroreceptors in DS rats, presumably because of an underlying abnormality in baroreceptor function in DS rats.

Victor et al. found that a high salt diet sensitizes cardiopulmonary baroreceptor reflex modulation of sympathetic nerve activity in DR but not in DS rats. Thus, the phenomenon of salt-induced augmentation of baroreceptor function in DR rats appears to involve both arterial and cardiopulmonary baroreceptor reflexes.

We speculated that salt-induced augmentation of baroreceptor reflex restraint of sympathetic nerve activity in DR rats would exert a protective effect against the development of salt-induced hypertension. Conversely, the absence of this compensatory augmentation in baroreceptor reflex function in DS rats might contribute to their salt sensitivity.

In conclusion, in the DS rat, the genetic propensity to salt-induced hypertension was initially thought to involve primarily renal and humoral factors. I have reviewed evidence derived during the past 15 years that abnormal control of the sympathetic nervous system also contributes critically to the propensity to salt-induced hypertension. Further insight into the mechanisms of salt-induced hypertension in Dahl rats will probably require understanding of the interactions among neural, renal, and humoral mechanisms.

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