Special Feature

Neural Control of Renal Function:
Cardiovascular Implications

Gerald F. DiBona

The innervation of the kidney serves to influence the function of its component parts, for example, the blood vessels, the nephron (glomerulus, tubule), and the juxtaglomerular apparatus. Alterations in efferent renal sympathetic nerve activity produce significant changes in renal blood flow, glomerular filtration rate, the reabsorption of water, sodium, and other ions, and the release of renin, prostaglandins, and other vasoactive substances. These functional effects contribute significantly to the renal regulation of total body sodium and fluid volumes with important implications for the control of arterial pressure. The renal nerves, both efferent and afferent, are known to be important contributors to the pathogenesis of hypertension. In addition, the efferent renal nerves participate in the mediation of the excessive renal sodium retention, which characterizes edema-forming states such as congestive heart failure. Thus, the renal nerves play an important role in overall cardiovascular homeostasis in both normal and pathological conditions. (Hypertension 1989;13:539–548)

Introduction

In 1988, the Program Committee of the Council for High Blood Pressure Research (CHBPR) of the American Heart Association (AHA) established the Lewis K. Dahl Memorial Lecture to be presented by a distinguished scientist at the Scientific Sessions of the AHA. The establishment of the Lewis K. Dahl Memorial Lecture is in the finest tradition of the CHBPR. Dahl was a gifted investigator who shaped immeasurably insight and research into the interaction between genetic and environmental factors in the pathogenesis of hypertension. Dahl’s work and influence were admirably reviewed in this journal in 1982 by his former colleague John P. Rapp. The Program Committee, chaired by Oscar A. Carretero, selected Gerald F. DiBona to present the first Dahl Lecture at the 61st Scientific Sessions of the AHA in November 1988. As Editor-in-Chief, I decided after consultation with Dr. Carretero and with Michael J. Brody, the chairperson of the CHBPR, to initiate a tradition of publishing the Dahl Lecture annually as a Special Feature in Hypertension. The following article entitled “The Neural Control of Renal Function: Cardiovascular Implications” by Dr. DiBona inaugurates this tradition. The editors of Hypertension join with the Council for High Blood Pressure Research in paying tribute to the legacy of Lewis K. Dahl through publication of the lecture named in his honor.

Allyn L. Mark
Editor-in-Chief

Reference


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Interest in the functional significance of the renal nerves has increased steadily since the application of ultrastructural, histofluorescent, and histochemical techniques provided a more definitive description of the intrinsic innervation of the kidney.\(^1,2\) It is now known that there is extensive and exclusive adrenergic innervation of the afferent and efferent glomerular arterioles, proximal and distal renal tubules, ascending limb of Henle’s loop, and juxtaglomerular apparatus. Within the nephron, the greatest relative density of innervation is in the thick ascending limb of Henle’s loop, followed by the distal convoluted tubule and the proximal tubule.

With this more complete understanding of the ultrastructure of the intrinsic renal innervation, there was a growing interest in the effects of alterations in efferent renal sympathetic nerve activity (ERSNA) on various aspects of overall renal function. From an extensive body of experimental evidence, derived largely from studies in animals,\(^3-5\) it is known that renal sympathetic nerve activity significantly influences many important aspects of renal function (Table 1). With direct electrical renal nerve stimulation, application of graded frequencies produces frequency-dependent changes in renal blood flow and glomerular filtration rate, renal tubular sodium and water reabsorption, and renin secretion. In general, the frequency-response relation for increases in renin secretion rate is to the left of the frequency-response relation for increases in renal tubular sodium and water reabsorption, which in turn is to the left of the frequency-response relation for decreases in renal blood flow and glomerular filtration rates.

In mammalian species, the effect of increases in ERSNA that cause frequency-dependent decreases in renal blood flow and glomerular filtration rate, renal tubular sodium and water reabsorption, and renin secretion. In general, the frequency-response relation for increases in renin secretion rate is to the left of the frequency-response relation for increases in renal tubular sodium and water reabsorption, which in turn is to the left of the frequency-response relation for decreases in renal blood flow and glomerular filtration rates.

The renal sympathetic nerves can regulate urinary sodium and water excretion 1) by changing renal hemodynamics (e.g., renal blood flow and glomerular filtration rate) through changes in renal vascular resistance, 2) by changing renin release from the juxtaglomerular granular cells with increased formation of angiotensin II,\(^8\) or 3) through a direct effect on the innervated renal tubules. With respect to the influence of renal nerve stimulation on glomerular filtration rate, there is an additional contribution from the concomitant stimulation of angiotensin II production, which acts on glomerular mesangial cells to affect glomerular filtration rate through alterations in glomerular capillary ultrafiltration coefficient,\(^9\) which is the product of glomerular capillary surface area (regulated by mesangial cell contractility) and glomerular capillary hydraulic permeability.

Increases or decreases in ERSNA, which do not alter renal perfusion pressure, total renal blood flow or its distribution, or glomerular filtration rate, cause parallel changes in net renal tubular sodium and water reabsorption with reciprocal changes in urinary water and sodium excretion. That is, increases in ERSNA increase net renal tubular sodium and water reabsorption and decrease urinary water and sodium excretion, whereas decreases in ERSNA decrease net renal tubular sodium and water reabsorption and increase urinary water and sodium excretion. The changes in renal tubular sodium and water reabsorption occur throughout the nephron in rough proportion to the density of tubular innervation and are mediated by \(\alpha\)-adrenergic receptors located on the peritubular membranes in the dog,\(^10\) rat,\(^11,12\) and rabbit\(^13\) kidneys.

Evidence\(^14,15\) has been provided that demonstrates that the renal sympathetic nerves participate in the regulation of renal sodium handling in conscious animals during both acute and chronic changes in total body sodium content. During conditions of normal or increased dietary sodium intake, the renal contribution to the achievement of sodium balance is similar in intact innervated or denervated kidneys. However, when the organism is challenged by a sufficiently low dietary sodium intake that requires maximum activation of all participating mechanisms to maintain sodium balance, an important role of the renal nerves is revealed.\(^16,17\) Studies in conscious animals have provided conflicting results\(^18-21\) that, as discussed elsewhere,\(^22\) relate to differences in experimental design and the degree of severity of the dietary sodium restriction. The degree of dietary sodium restriction must be sufficiently severe so as to maximize the likelihood that other systems and mechanisms known to contribute to the renal regulation of sodium balance will have been maximally engaged and can no longer compensate for the loss of renal innervation. It is clear from studies in normal human subjects given guanethidine to effect autonomic blockade\(^23\) and in patients with idiopathic autonomic insufficiency\(^24\) that intact renal innervation is required for the

<table>
<thead>
<tr>
<th>Renal nerve stimulation frequency</th>
<th>RSR</th>
<th>(U_{\text{Na}V})</th>
<th>GFR</th>
<th>RBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 Hz</td>
<td>No effect on basal values; augments RSR mediated by nonneural stimuli</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.50 Hz</td>
<td>Increased without changing (U_{\text{Na}V}), GFR, or RBF</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.0 Hz</td>
<td>Increased with decreased (U_{\text{Na}V}) without changing GFR or RBF</td>
<td>↓</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2.50 Hz</td>
<td>Increased with decreased (U_{\text{Na}V}), GFR, and RBF</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

RSR, renin secretion rate; \(U_{\text{Na}V}\), urinary sodium excretion; GFR, glomerular filtration rate; RBF, renal blood flow.
normal renal adaptive response to dietary sodium restriction in humans. In both cases, daily urinary sodium excretion exceeded daily dietary sodium intake during dietary sodium restriction to less than 20 meq sodium/day. Thus, intact renal innervation appears to be an essential requirement for the normal renal adaptive response to dietary sodium restriction. Further, in response to acute intravenous isotonic volume loads, studies in rats, dogs, and monkeys demonstrate that the volume expansion–mediated decrease in ERSNA is an important contributor to the renal excretory responses to the volume load and that renal denervation attenuates the diuretic and natriuretic responses to the volume load. These and other studies indicate that the effluent renal sympathetic nerves contribute importantly to the regulation of renal sodium handling in conscious animals during both acute and chronic changes in total body sodium content.

ERSNA influences renin secretion rate from the kidney by a variety of mechanisms, directly or by interacting with the renal tubular macula densa and vascular baroreceptor mechanisms for renin secretion (Tables 1 and 2). Frequencies of renal sympathetic nerve stimulation (0.25 Hz), which themselves do not affect renal hemodynamics, urinary sodium excretion, or renin secretion rate, are capable of augmenting the renin secretion rate response to nonneural stimuli for renin secretion. This important interaction functions so that when there is strong stimulation to the renal vascular baroreceptor (markedly reduced renal arterial pressure), augmentation of the renin secretion rate response is achieved with very low frequencies of renal sympathetic nerve stimulation, and when there are lesser degrees of renal vascular baroreceptor stimulation (lesser decreases in renal arterial pressure), higher frequencies of renal sympathetic nerve stimulation are required. At slightly higher frequencies of renal sympathetic nerve stimulation (0.5 Hz), renin secretion rate is increased without alterations in renal hemodynamics or urinary sodium excretion and, thus, without change in input stimuli to the baroreceptor or macula densa receptor mechanisms for renin secretion. This increase in renin secretion rate is due to direct stimulation of β-adrenergic receptors located on juxtaglomerular granular cells. At a frequency of renal sympathetic nerve stimulation (1.0 Hz), which increases renal tubular sodium reabsorption (lowers urinary sodium excretion) without changing renal hemodynamics, renin secretion rate is further increased. This occurrence possibly reflects an interactive contribution from the tubular macula densa receptor mechanism.

At frequencies of renal sympathetic nerve stimulation (>2.0 Hz) that produce renal vasoconstriction with decreases in renal blood flow, glomerular filtration rate, and urinary sodium excretion, the increase in renin secretion rate derives from a complex interaction between all three mechanisms involved in the regulation of renin secretion and involves both β- and α-adrenergic receptors, with renal prostaglandins coupled in series to the α-adrenergic receptor–mediated renal vasoconstriction.

As is evident, the renal sympathetic nerves participate in the regulation of several renal functions that are felt to be importantly involved in hypertension and edema-forming conditions; among these functions are the control of renal hemodynamics (renal blood flow, vascular resistance, and glomerular filtration rate), renal tubular reabsorption of sodium and water, and renin secretion rate.

**Role of Renal Nerves in Hypertension**

A major hypothesis for the development of hypertension is that abnormal renal function is critical for the initiation, development, or maintenance of primary hypertension. The maintenance of sodium and water balance by the kidneys is believed to be primary in long-term control of arterial pressure. An increase in arterial pressure leads to an increased urinary sodium and water excretion with consequent reduction of blood volume until arterial pressure is returned to normal. In hypertension, it is hypothesized that factors disrupt the maintenance of sodium and water balance by the kidneys in such a way that an elevated arterial pressure is required to reestablish and maintain normal sodium and water balance. Several types of renal dysfunction could contribute to the hypertensive state; these types include increased renal vascular resistance, increased renal retention of sodium and water, and increased release of renin, catecholamines, or other vasoactive substances. As outlined above, the extensive sympathetic innervation of the kidney is known to be important in the physiological regulation of these renal functions.

Although difficult to obtain, there is clear evidence that ERSNA is increased in human essential hypertension. Hollenberg demonstrated that the increase in renal blood flow in response to the renal arterial administration of the α-adrenergic receptor antagonist, phentolamine, was significantly greater in human subjects with essential hypertension than in normotensive control subjects. This finding indicates that in human essential hypertension there is increased sympathetic vasoconstrictor influence on the renal vasculature. Esler et al have demon-

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**Table 2. Neural Control of Renin Secretion Rate**

<table>
<thead>
<tr>
<th>Renal nerve stimulation frequency</th>
<th>Mechanism of increase in renin secretion rate</th>
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<tbody>
<tr>
<td>0.25 Hz</td>
<td>Modulation of nonneural mechanisms</td>
</tr>
<tr>
<td>0.50 Hz</td>
<td>Direct neural release from juxtaglomerular granular cells without alterations in stimuli to macula densa receptor or baroreceptor</td>
</tr>
<tr>
<td>1.0 Hz</td>
<td>Alteration in stimulus to macula densa receptor</td>
</tr>
<tr>
<td>2.5 Hz</td>
<td>Alteration in stimulus to baroreceptor</td>
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</tbody>
</table>

Effects become additive as frequency of renal nerve stimulation increases.
that delays the development of the hypertension in example, the effect of complete renal denervation and that this derives in large part from the process was associated with changes in renal function characteristic of decreases in ERSNA. For the most severe forms of hypertension in animals in which renal innervation was intact. Thus, the increased levels of ERSNA known to occur in human subjects with essential hypertension produce renal functional effects that can significantly contribute to several mechanisms known to participate in initiation, development, and maintenance of hypertension. In addition, these physiological effects of increased ERSNA can interfere with the normal adaptive response of the kidney in the regulation of blood volume and contribute further to the hypertensive process.

Strong evidence for the participation of the renal nerves in hypertension derives from the studies\(^ {34,35} \) of complete renal denervation in several experimental forms of hypertension in animals. For the most part, the technique that was used produced a combined surgical-pharmacological disruption of the entire renal nerve population, both afferent and efferent; this disruption is referred to as complete renal denervation. Table 3 shows the various experimental forms of hypertension in animals in which complete renal denervation delayed the development or attenuated the magnitude of the hypertension.\(^ {34} \) In several of the models, the effect of the complete renal denervation on the hypertensive process was associated with changes in renal function characteristic of decreases in ERSNA. For example, the effect of complete renal denervation that delays the development of the hypertension in spontaneously hypertensive rats (SHR)\(^ {35} \) was associated with an increase in the fraction of the ingested sodium excreted in the urine (denervation natriuresis, more negative sodium balance), and the subsequent development of hypertension was paralleled by a return of renal tissue norepinephrine content toward normal (evidence of renal reinnervation) and a decrease in the fraction of the ingested sodium excreted in the urine (more positive sodium balance). The uniform effect of complete renal denervation on the hypertension in such a diverse group of experimental forms of hypertension would seem to indicate a universally important role for the renal nerves in hypertension.

The issue of whether the effect of complete renal denervation, with section of both afferent and efferent renal neural pathways, is mediated by interruption of afferent or efferent renal nerve activity has been studied by more direct techniques involving selective interruption of the afferent renal neural pathways. Thoracolumbar dorsal rhizotomy to produce selective afferent renal denervation attenuated the severity of hypertension in rats with one-kidney, one clip and two-kidney, one clip Goldblatt hypertension and in dogs with chronic aortic coarctation hypertension, but severity of hypertension was not attenuated in SHR.\(^ {35} \) Similarly, complete renal denervation did not affect the hypertension in Dahl salt-sensitive (DS) rats.\(^ {36} \) The effect of selective afferent renal denervation is mediated by a central feedback mechanism that involves a reduction in hypothalamic norepinephrine stores and results in a decrease in peripheral sympathetic nervous system activity; thus, arterial pressure is reduced. These results indicate that afferent renal nerves, conveying information from renal sensory receptors to the neuraxis, are important modulators of central integrative centers involved in the regulation of peripheral sympathetic nervous system activity. Kopp et al\(^ {37} \) have recently demonstrated that renorenal reflexes, which are important in the coordination of renal excretory activity between the two kidneys and are mediated by both renal mech-

### Table 3. Animal Models of Experimental Hypertension in Which Complete Renal Denervation Delays or Prevents Development of Hypertension

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
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<tbody>
<tr>
<td>Spontaneously hypertensive rat (SHR)</td>
<td></td>
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<tr>
<td>Stroke-prone SHR</td>
<td></td>
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<tr>
<td>New Zealand spontaneously hypertensive rat</td>
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<tr>
<td>Goldblatt one-kidney, one clip (rat)</td>
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</tr>
<tr>
<td>Goldblatt two-kidney, one clip (rat)</td>
<td></td>
</tr>
<tr>
<td>Aortic coarctation (dog)</td>
<td></td>
</tr>
<tr>
<td>Aortic nerve transection (rat)</td>
<td></td>
</tr>
<tr>
<td>DOCA-NaCl Rat</td>
<td></td>
</tr>
<tr>
<td>Grollman renal wrap (rat)</td>
<td></td>
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<tr>
<td>Low sodium, one kidney (rat)</td>
<td></td>
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<tr>
<td>Angiotensin II (rat)</td>
<td></td>
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</tbody>
</table>

Animal models table was adapted from Reference 34.
anoreceptors and chemoreceptors, are abnormal in SHR. They further report that this abnormality is related to the effect of arterial pressure on the kidney since the abnormality is not present in young prehypertensive SHR or in treated SHR that are normotensive.

Folkow has identified three major interdependent causative elements in the physiology of primary hypertension: hereditary predisposition (genetic factor), environmental influences, and structural cardiovascular adaptations to the increase in arterial pressure. Of the environmental influences, two major factors are distinguished: excitatory environmental (psychoemotional) stress and dietary salt (NaCl) intake. Environmental stress may be translated into increased sympathetic nervous system activity by way of the limbic-hypothalamic-bulbar autonomic centers. Increased dietary NaCl intake can augment sympathetic nervous system activity responses to environmental stress. The development of hypertension in rats with a genetic predisposition to hypertension is accelerated by high dietary NaCl intake alone or by environmental stress alone; however, the combination of genetic predisposition, high dietary NaCl intake, and environmental stress results in more severe hypertension than any factor alone. Complete renal denervation delays the onset of chronic stress hypertension; thus, the important role of the renal nerves in the pathophysiology of hypertension is emphasized.

To examine the interaction between genetic predisposition to hypertension, environmental stress, and dietary NaCl in the hypertensive process, we have used an acute environmental stress intervention in SHR, which are genetically destined to become hypertensive. Chronically instrumented SHR are studied in the conscious state. The acute environmental stress is air jet stress, as adapted from Lundin and Thorén. A jet of air is directed to the dorsum of the rat’s head; this air jet elicits a prompt and sustained response that resembles the classic defense reaction: increase in arterial pressure and heart rate, renal and mesenteric vasoconstriction, hindquarters vasodilation, and an increase in ERSNA. The renal response to the increase in ERSNA consists of a decrease in urinary flow rate and sodium excretion, but there is no change in renal plasma flow or glomerular filtration rate. The environmental stressor, that is, air jet stress, produces no effect in the normotensive Wistar-Kyoto control rats. The antidiuresis and antinatriuresis that are related, in part, to significant decreases in renal plasma flow and glomerular filtration rate (i.e., marked renal vasoconstriction). These renal responses were not observed in SHR on a normal dietary NaCl intake. When dietary NaCl intake is increased by allowing SHR to drink 0.9% NaCl as drinking fluid for 4 weeks (no effect on basal arterial pressure), the responses to acute environmental stress are amplified over those seen in SHR on a normal dietary NaCl intake (see Figure 1). Although the heart rate and arterial pressure responses are similar, the renal responses demonstrate a greater (p<0.01) antidiuresis and antinatriuresis that are related, in part, to significant (p<0.01) decreases in renal plasma flow and glomerular filtration rate (i.e., marked renal vasoconstriction). These renal responses were not observed in SHR on a normal dietary NaCl intake. When dietary NaCl intake is increased by allowing SHR to drink 0.9% NaCl as drinking fluid for 4 weeks (no effect on basal arterial pressure), the responses to acute environmental stress are amplified over those seen in SHR on a normal dietary NaCl intake (see Figure 1). Although the heart rate and arterial pressure responses are similar, the renal responses demonstrate a greater (p<0.01) antidiuresis and antinatriuresis that are related, in part, to significant (p<0.01) decreases in renal plasma flow and glomerular filtration rate (i.e., marked renal vasoconstriction). These renal responses were not observed in SHR on a normal dietary NaCl intake.
dietary NaCl intake. Again, bilateral renal denervation abolished the renal responses to acute environmental stress in SHR on a high dietary NaCl intake. The augmented renal hemodynamic and excretory responses to acute environmental stress in SHR on a high dietary NaCl intake compared with SHR on a normal dietary NaCl intake were causally related to a proportionally greater increase in ERSNA in response to the acute environmental stress. Thus, increased dietary NaCl intake resulted in a centrally mediated increase in the ERSNA response to acute environmental stress. In addition, high dietary NaCl intake appears to result in an increase in neurotransmitter release per nerve impulse compared with normal dietary NaCl intake.\(^{49}\) This high dietary salt intake would also result in augmented renal sodium and water retention. The resultant expansion of the blood volume would require an elevation in arterial pressure to increase renal sodium and water excretion in an attempt to restore blood volume and, thereby, arterial pressure to the prior level.

We subsequently explored central nervous system centers responsible for the responses to air jet stress. By using a combination of intracerebroventricular injections and microinjections in specific brain areas, we identified two brain regions that were involved. Microinjection of the \(\beta_2\)-adrenergic receptor antagonist ICI 118,551 into the posterior hypothalamus\(^{50}\) or the \(\alpha_2\)-receptor agonist guanabenz into the central amygdaloid nucleus\(^{51}\) abolished the increase in ERSNA and the antidiuretic and antinatriuretic responses to acute environmental stress. Of interest, the pressor and heart rate responses were not affected. These anatomic areas are known to contain populations of \(\beta_2\)- and \(\alpha_2\)-adrenergic receptors and to participate in the conversion of cortically perceived environmentally stressful stimuli into altered sympathetic nervous system activity. These observations suggested that there might be a differentiated distribution of sympathetic outflow during environmental stress inasmuch as the increases in ERSNA were abolished whereas the pressor and tachycardiac responses were preserved. We investigated these differences with conscious SHR instrumented with Doppler flow probes for the measurement of regional blood flows and vascular resistances. During acute environmental stress, intracerebroventricular administration of guanabenz abolished the increase in ERSNA, but the pressor response was unaffected. This outcome was possibly due to reciprocal alterations in regional vascular resistances that occurred when the inhibition of the mesenteric vasoconstriction was offset by the conversion of the hindquarters vasodilation to vasoconstriction.\(^{47}\) These results suggest that the central nervous system regulation of environmental stress–stimulated peripheral sympathetic neural outflow to regional vascular beds may be selectively and differentially altered by activation of central nervous system \(\alpha_2\)-adrenergic receptors.

The clinical relevance of an important interaction between dietary NaCl intake and stimuli that cause reflex activation of the sympathetic nervous system in hypertension is illustrated by a recent study by Lawton and colleagues.\(^{52}\) The arterial pressure, renal blood flow, and renal vascular resistance responses of borderline hypertensive and normotensive subjects when changing from supine to upright posture were measured during consumption of both low and high dietary NaCl intakes. This orthostatic stress is known to produce reflex sympathetic activation. In the normotensive subjects, the decreases in diastolic arterial pressure and the increases in renal vascular resistance with assumption of upright posture were similar on both low and high dietary NaCl intakes. However, in the borderline hypertensive subjects, the results were different. On low dietary NaCl intake, diastolic arterial pressure did not decrease, and the increase in renal vascular resistance with assumption of upright posture was greater (not significant) than that observed in normotensive subjects on low dietary NaCl intake. On high dietary NaCl intake, diastolic arterial pressure increased, and the increase in renal vascular resistance with assumption of upright posture was significantly greater than that observed in normotensive subjects on high dietary NaCl intake. Therefore, a high dietary NaCl intake produced an augmented renal vasoconstrictor response to orthostatic stress in borderline hypertensive subjects. Because orthostatic stress is known to produce reflex activation of the sympathetic nervous system and borderline hypertensive subjects may be conjectured to have a genetic predisposition to hypertension, the congruence of these findings in human subjects with those of SHR given a high dietary NaCl intake and subjected to acute environmental stress is noteworthy. Therefore, in a setting of genetic predisposition to hypertension, there is an interaction between dietary NaCl intake and stimuli that reflexively activate the sympathetic nervous system, which elicits targeted responses in the kidney. The renal responses are mediated by increases in ERSNA.

Hypertension in the DS rat is dependent on a combination of genetic and environmental factors. The DS rat is genetically predisposed to become hypertensive, and the Dahl salt-resistant (DR) rat is genetically predisposed to resist hypertension when exposed to a high dietary NaCl intake.\(^{53}\) In addition, the sympathetic nervous system contributes to the pathogenesis of hypertension in DS rats.\(^{53}\) Thus, the Dahl rat provides a unique model of hypertension to further characterize the interaction of genetic predisposition to hypertension with environmental stress and dietary NaCl intake in the neural control of renal function. Dr. Dahl described his research in his curriculum vitae as an "interrelationship of environmental factors (in particular, dietary NaCl) and genetic constitution in the etiology and pathogenesis of clinical and experimental hypertension."\(^{54}\) In early studies\(^{54}\) on stress interventions in DS and
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RESPONSE TO AIR STRESS
DAHL R and S on low and high NaCl

A RENAL NERVE ACTIVITY. resets/min

L H L H

DAHL R
DAHL S

FIGURE 2. Bar charts of absolute changes in urinary sodium excretion and renal nerve activity in response to environmental stress (air jet) in Dahl salt-resistant (R) and Dahl salt-sensitive (S) rats consuming low (L) and high (H) dietary NaCl intakes.

DR rats, electric shocks were administered independent of the rats' behavior, and no elevations in arterial pressure occurred. However, with the appropriate chronic conflict between the necessity to obtain food and to avoid electric shock, DS rats responded with increases in arterial pressure that were greater than those in DR rats. By using the acute environmental stress paradigm described above, Koepke et al observed that DS and DR rats (mean arterial pressure 119±7 and 117±4 mm Hg, respectively) on low dietary NaCl intake had only small increases in ERSNA and decreases in urinary sodium excretion during acute environmental stress. However, DS and DR rats (mean arterial pressure 154±5 and 114±3 mm Hg, respectively) on high dietary NaCl intake had significantly (p<0.01) greater increases in ERSNA and decreases in urinary sodium excretion, and the responses of DS rats were greater (p<0.05) than those of DR rats (Figure 2). The antinatriuretic responses in both DS and DR rats were abolished by prior bilateral renal denervation. With this acute environmental stress intervention, there were only small changes in mean arterial pressure, which were not significant. For the entire group, DR and DS rats on both low and high dietary NaCl intake, there was a significant inverse correlation between the environmental stress–induced increase in ERSNA and the decrease in urinary sodium excretion (Figure 3). Thus, in DS and DR rats, acute environmental stress produces centrally mediated changes in the neural control of renal function. These changes result in renal sodium retention and are enhanced in hypertensive DS rats with a high dietary NaCl intake.

Thus, in two rat models of genetic predisposition to hypertension with two different environmental interventions, dietary NaCl intake and psychoemotional stress interacted to produce centrally mediated changes in the neural control of renal function. These changes can result in renal vasoconstriction and sodium retention. This interaction reinforces the separate effect of each intervention as demonstrated by the increased renal sympathoexcitatory responses to psychoemotional stress when dietary NaCl intake is increased. The resultant alterations in renal function are known to be capable of contributing to the initiation, development, and maintenance of the hypertensive process.

Role of Renal Nerves in Edema-Forming States

In the common clinical presentations of edema, congestive heart failure, cirrhosis with ascites, and the nephrotic syndrome, there is accumulating evidence of a generalized activation of the sympathetic nervous system with specific activation of ERSNA. With respect to congestive heart failure, the early study of Barger and colleagues is especially illuminating. They studied conscious dogs with congestive heart failure produced by a combination of tricuspid insufficiency and pulmonary stenosis. Unilateral renal arterial administration of phenoxybenzamine, a nonselective α-adrenergic receptor antagonist, elicited an ipsilateral diuresis and natriuresis in the absence of substantial changes in glomerular filtration rate and renal plasma flow. These observations indicated that the avid sodium retention of the kidney in heart failure is due to excess renal α-adrenergic receptor activation by means of augmented ERSNA or increased circulating concentrations of norepinephrine. The studies of Hasking et al in human subjects with congestive heart failure.
heart failure demonstrated an increase in total norepinephrine spillover to plasma. This increase supported a generalized increase in sympathetic nervous system activity and was derived mainly from increases in cardiac and renal norepinephrine spillover, which reflected selective increases in efficient sympathetic nerve activity to the heart and the kidney, respectively. Recent direct microneurographic studies in human subjects with congestive heart failure indicate that muscle sympathetic nerve activity is increased and that the increase is proportional to the severity of the congestive heart failure, taken as the magnitude of the increase in left ventricular end-diastolic pressure. Early clinical observations by Brod et al. indicated that the intravenous administration of an α-adrenergic receptor antagonist had a beneficial effect on renal hemodynamics and urinary sodium excretion in patients with congestive heart failure of diverse etiologies.

To pursue the role of increased ERSNA in congestive heart failure, a chronic animal model of low output congestive heart failure due to contractile dysfunction of the left ventricle was needed. The left coronary artery ligation model of myocardial infarction in the rat was suitable for this purpose. Within 1–4 weeks after left coronary artery ligation, surviving rats with elevated left ventricular end-diastolic pressure (>15 mm Hg) had reduced cardiac output and failed to increase cardiac output in response to intravenous volume expansion-induced increases in cardiac filling pressure. They exhibited cardiac hypertrophy, hydrothorax, ascites, and peripheral edema. With respect to renal sodium and water handling, they had a defect in the ability to excrete an acute oral or intravenous isotonic saline load which was proportional to the severity of the congestive heart failure.

We measured the contribution of ERSNA to the renal response to acute or intravenous administration of a standard isotonic saline load in control unoperated rats and in two groups of rats with both left coronary artery ligation and congestive heart failure. The latter two groups consisted of those with bilateral renal denervation and those with sham bilateral renal denervation. When the renal response (fraction of the administered isotonic saline load that was excreted as either water or sodium over the ensuing 2 hours) was analyzed, the rats with congestive heart failure and sham bilateral renal denervation excreted only 20–35% of the load compared with control rats that excreted 65–75% of the load. However, prior bilateral renal denervation corrected the renal excretory defect of the rats with congestive heart failure so that they excreted 60–65% of the load; this percentage was not different from control rats. These observations suggested that bilateral ERSNA was elevated in congestive heart failure and this high value of basal ERSNA was restraining the ability of the kidney to excrete the acute isotonic saline load. It is known that the decrease in ERSNA that occurs during volume expansion in normal animals contributes to the renal excretory response to the volume load; that is, the diuretic and natriuretic responses to volume expansion are diminished by renal denervation in conscious rats, dogs, and monkeys. Therefore, these results further suggested that the elevated basal ERSNA was not appropriately suppressed during the volume expansion. When direct measurements of ERSNA were made in conscious congestive heart failure rats that received an acute intravenous isotonic saline load, it was found that the decrease in ERSNA was significantly attenuated in congestive heart failure rats compared with normal control rats. Furthermore, the attenuated renal sympathetic inhibition by volume expansion in the congestive heart failure rats was proportionally more severe with longer duration of congestive heart failure; the defect was greater in rats 21 days after left coronary artery ligation than in rats 14 days after left coronary artery ligation. The basal levels of ERSNA were higher in rats 14 days (131±20 units) and 21 days (166±29 units) after left coronary artery ligation than in control rats (88±10 units). Thus, the impaired ability of the kidney in congestive heart failure to excrete an acute sodium load is related to an increased basal level of ERSNA that fails to normally decrease in response to the volume load. In renal clearance and micropuncture studies in anesthetized congestive heart failure rats, acute unilateral renal denervation significantly increased ipsilateral urinary flow rate and sodium excretion by an amount that was greater than that seen when anesthetized control rats were subjected to acute unilateral renal denervation. In the congestive heart failure rats, these renal excretory responses to acute unilateral renal denervation were accompanied by increases in ipsilateral whole kidney and single nephron glomerular filtration rate and single nephron blood flow. Calculated fractional water and sodium excretion increased; this occurrence indicated that the increase in urinary flow rate and sodium excretion was in excess of that accounted for by the increase in whole kidney glomerular filtration rate (filtered load); thus a role is indicated for a renal denervation–induced decrease in net renal tubular sodium and water reabsorption.

In view of similar findings in animal models of cirrhosis with ascites (primary biliary cirrhosis due to common bile duct ligation) and nephrotic syndrome (adriamycin), it appears that an increased basal level of ERSNA that fails to decrease appropriately in response to a volume load represents one final common pathway by which these different underlying disease states produce avid renal sodium retention leading to edema formation. Sufficient information has accumulated concerning the important role of the renal nerves in the regulation of various aspects of renal function so that it is possible to revise the older view of H.W. Smith: "For the moment it may be said that substantial evidence of the neural control of either
the tubular excretion or reabsorption of any urinary constituent is lacking." In addition, it is now possible to respond in the affirmative to the more recent query of J.E. Norvell: "Renal nerves: Are they essential?" Future inquiry will delineate the precise participation of the renal nerves in cardiovascular disease states wherein the kidney contributes to the overall pathophysiology.

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