Novartis Lecture

Neural Control of the Kidney
Past, Present, and Future

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Abstract—This article provides a chronological perspective on the development of knowledge concerning the neural control of renal function and is divided into three parts: the past, the present, and the future. (Hypertension. 2003; 41(part 2):621-624.)

Key Words: kidney ▶ renal function ▶ neuroregulators

The Past
Research in the area of the neural control of renal function was not very active for the first half of the 20th century. This can be attributed to 2 factors. First, the renowned renal physiologist, Homer Smith, rendered an opinion that the renal nerves were of little functional consequence.1–3 This was based on his interpretation of experiments involving renal denervation in anesthetized and surgically operated animals. He criticized this approach, as he believed that the starting level of renal sympathetic nerve activity (RSNA) would be quite elevated, owing to the associated stress, so that “denervation hyperemia and diuresis appear to be a release from enhanced vasoconstriction engendered by anesthesia and traumatic operative procedures.”4 Second, there was a lack of convincing evidence that the renal innervation extended beyond the renal vasculature to either the tubules or the juxtaglomerular apparatus.

The demonstration by Luciano Barajas4 that all segments of the renal tubule (as well as the juxtaglomerular apparatus) were innervated by noradrenaline-containing renal sympathetic nerve terminals that make contact with the renal tubular epithelial cell basement membrane paved the way for increased research activity in this area. This critical observation reconfirmed once again the important relationship between structure and function.

Given the powerful influence of changes in renal hemodynamics (ie, arterial pressure, glomerular filtration rate [GFR] and renal blood flow [RBF]) on urinary sodium excretion (UNaV), it was evident that the influence of changes in RSNA on UNaV must be examined in experimental protocols in which these variables remained constant. By using electrical stimulation of the efferent renal sympathetic nerves at frequencies just subthreshold for decreases in RBF, it was shown that a reversible decrease in UNaV occurred in the absence of changes in GFR (ie, filtered sodium load), RBF, and arterial pressure.5 These results indicated that low-frequency renal sympathetic nerve stimulation increased overall renal tubular sodium reabsorption via a direct action on the renal tubule, independent of changes in renal hemodynamics. Additional experiments demonstrated that this effect occurred in the proximal convoluted tubule, the thick ascending limb of Henle’s loop, the distal convoluted tubule, and the collecting duct.6–7 Subsequent work (reviewed in DiBona and Kopp8) showed that this was owing to the release of noradrenaline from renal sympathetic nerve terminals with stimulation of postsynaptic α1-adrenoceptors located on the basolateral membrane of renal tubular epithelial cells throughout the nephron. Subsequent intracellular signaling events resulted in an increase in activity of the sodium pump (Na+,K+-ATPase), with increased transepithelial sodium transport.

Even with growing evidence of a direct effect of RSNA on renal tubular sodium reabsorption, there was lingering skepticism related to the concerns initially raised by Homer Smith. However, experiments in conscious chronically instrumented rats and dogs, in the absence of anesthesia and surgical stress, put these concerns to rest. Conscious rats with unilateral renal denervation exhibit a higher rate of sodium excretion from the denervated kidney than from the contralateral innervated kidney.9 Conscious dogs subjected to head-out water immersion exhibit an increase in cardiac filling pressure that produces a sustained reflex decrease in RSNA, leading to a natriuresis in the absence of changes in GFR or RBF; the natriuresis is abolished by renal denervation.10 Conscious dogs subjected to head-up tilt exhibit a decrease in both arterial and cardiac filling pressure that produces a sustained reflex increase in RSNA, leading to an antinatriuresis in the absence of changes in GFR or RBF; the antinatriuresis is abolished by renal denervation.11

It also became evident from observations in humans that intact renal sympathetic innervation was important in ensuring a normal renal response to dietary sodium restriction.
Patients with systemic autonomic failure of the Shy-Drager type are unable to lower $U_{NaV}$ sufficiently to match a 17 mEq/day dietary sodium intake. Negative sodium balance ensues with decreased arterial pressure and GFR. As in rats with chronic renal denervation, these results demonstrated that intact renal sympathetic innervation is essential for the full expression of the maximal ability of the kidney to conserve sodium when faced with sufficiently severe dietary sodium restriction.

Given the influence of nonvasoconstrictor intensities of RSNA on renal tubular sodium reabsorption, consideration was given to the effects of RSNA on renin secretion rate (RSR). In a series of studies, it was found that the effects of RSNA on RSR were graded with respect to the intensity of the RSNA that interacted with the level of engagement of the other mechanisms of renin secretion, ie, the renal arterial baroreceptor and the renal tubular macula densa receptor mechanisms. It was known that a denervated kidney had reduced RSR, both in the basal state and in response to stimuli. By using a frequency of renal sympathetic nerve stimulation that did not affect basal RSR (or $U_{NaV}$, GFR, or RBF), it was shown that this exerted a synergistic effect on the RSNA response to decreased renal arterial pressure (baroreceptor stimulus) and to furosemide administration (macula densa receptor stimulus). A slightly higher frequency of RNS, 0.5 Hz, increased RSR without affecting $U_{NaV}$, RBF, or GFR: this was attributed to direct activation of $\beta_1$-adrenoceptors on juxtaglomerular granular cells, as it was inhibited by $\beta_1$-adrenoceptor antagonists. At progressively higher frequencies of RNS, associated initially with antinatriuresis and then renal vasoconstriction, the macula densa receptor and baroreceptor mechanisms became engaged.

On examining the stimulus response curve of the frequency of RNS versus both renin secretion rate and RBF, it is important to note that a large portion of the maximum RSR response is achieved with frequencies of RNS that do not substantially affect RBF. It is over this range at which $\beta_1$-adrenoceptor blockade prevents the RSR response, reflecting its dominant dependence on $\beta_1$-adrenoceptors located on juxtaglomerular granular cells.

From these studies emerged the concept of the graded response of the 3 renal neuroeffectors to graded increases in the frequency of renal sympathetic nerve stimulation. At the lower frequency range ($\approx 0.5$ Hz), there is stimulation of RSR, without effects on $U_{NaV}$, RBF, or GFR. At slightly higher frequencies ($\approx 1.0$ Hz), there is both stimulation of RSR and a decrease in $U_{NaV}$, without effects on RBF or GFR. At higher frequencies ($\approx 2.0$ Hz), there is stimulation of RSR and a decrease in $U_{NaV}$ and renal vasoconstriction, with decreased RBF and GFR. The major implications of this quantitative relationship are (1) substantial stimulation of RSR and antinatriuresis can occur with intensities of RSNA that do not affect GFR or RBF, and (2) intensities of RSNA that decrease RBF and GFR will stimulate RSR and produce antinatriuresis.

At this point, RSNA was now known to have important effects on both renal tubular sodium reabsorption and RSR at intensities that did not affect RBF or GFR. This prompted the examination of pathophysiological conditions in which it had been long suspected that increased RSNA played an important role in the associated renal functional abnormalities via antinatriuresis and/or increased RSR. Hypertension and congestive heart failure (CHF) were important examples in this regard. However, as observations made in the early stages of these disease states often disclosed decreased $U_{NaV}$ and/or increased RSR, but normal or near normal values of GFR and/or RBF, it was deemed unlikely that increased RSNA was involved in the early pathogenetic or developmental stages of these conditions.

Two major observations significantly affected those views. First, it was demonstrated that renal denervation completely prevented, markedly attenuated the magnitude of, or delayed the development of experimental hypertension in a variety of animal models of experimental hypertension of diverse etiology. For example, renal denervation completely prevents the development of obesity-induced hypertension in the dog in association with a large reduction in cumulative sodium balance.

Björn Folkow’s view that hypertension represents the interaction between genetic factors (hereditary disposition) and environmental factors, such as dietary sodium intake and environmental stress, is particularly relevant. It was found that high dietary sodium intake enhanced the pressor, tachycardic, renal sympathoexcitatory, and antinatriuretic responses to environmental stress (defense reaction) only in rats with a genetic hereditary predisposition to hypertension. In addition to the induction of hypertension, several phenotypes related to the abnormal regulation of RSNA were identified in borderline hypertensive rats (F1 [first generation offspring] of spontaneously hypertensive rats × Wistar-Kyoto rats) fed a high but not a normal dietary sodium intake. These findings pointed to a central nervous system abnormality in the regulation of RSNA that was inducible by increased dietary sodium intake in the presence of the proper genetic setting. In backcross populations fed a high dietary sodium intake, there is cosegregation of the magnitude of the environmental stress–induced increase in RSNA with the degree of hypertension, and preliminary genome-wide screening has identified several possible quantitative trait loci.

The second observation was that renal denervation markedly improved the abnormal sodium excretory response to acute oral or intravenous isotonic saline loading in rats with experimental CHF, as well as other sodium-retaining edema-forming conditions characterized by increased RSNA, such as cirrhosis and the nephrotic syndrome. In addition, in month-long metabolic balance studies in renal denervated rats, it was demonstrated that the renal sympathetic nerves accounted for $\approx 40\%$ of the cumulative sodium retention observed in these various models. These findings support the view that increases in RSNA, although not sufficient to affect RBF or GFR, can contribute to increased renal tubular sodium reabsorption, renal sodium retention, and edema formation in CHF, cirrhosis, and nephrotic syndrome.

**The Periphery**

Peripheral sympathetic neural outflow has come to be recognized as a regionally differentiated process wherein reflex stimuli can produce increases in sympathetic nerve activity to one or more organs or regions, as well as decreases or no change in sympathetic nerve activity to other organs or regions. This allows for much finer control and adjustment in
local organ or region function, and provides greater homeostatic effectiveness and efficiency. Such differentiation into functionally specific sympathetic nerve fibers is present within major sympathetic nerve structures. As shown by stimulation of the cervical sympathetic trunk of the cat, the fibers to the cutaneous arteriovenous anastomoses, the nictitating membrane, and the pupil have a lower threshold than that of the constrictor fibers to the ordinary vessels in the skin and tongue, whereas the sympathetic vasodilator fibers to the skeletal muscles had the highest threshold. By analogy with somatic nerves, this was explained by an inverse relationship between stimulation threshold and fiber diameter.

This raised the question of whether such functionally specific fiber groups existed in the renal sympathetic innervation that could provide selective and specific innervation and control of the 3 renal neuroeffectors: the vasculature, the tubules, and the juxtaglomerular granular cells. The critical evidence supporting the existence of such a system was the analysis of single renal sympathetic neural unit responses to a variety of reflex stimuli. If renal sympathetic nerve fibers were a homogeneous uniform population, then all single units should respond in a similar manner to all reflex stimuli. This was shown not to be the case in the rat because those units exhibiting spontaneous activity responded uniformly to baroreceptor, chemoreceptor, and peripheral thermal receptor stimulation, whereas those units that did not exhibit spontaneous activity responded only to peripheral thermal receptor stimulation. That this stimulus, peripheral thermal receptor stimulation, activates a functionally specific renal sympathetic nerve fiber group was further demonstrated when it was shown that the frequency information encoded in the RSNA response to this stimulus was unique and different from that produced by another stimulus (tail pinch) that increased overall RSNA to the same level. Functionally, this was reflected as a greater renal vasoconstriction with the peripheral thermal receptor stimulus than with the tail-pinch stimulus, despite a similar degree of increase in integrated RSNA voltage. Additional evidence for the existence of functionally specific renal sympathetic nerve fiber groups, also based on analysis of single renal sympathetic neural units to different reflex inputs, derives from studies in the cat.

Recalling that the sodium-retaining edema-forming disease states are characterized by increases in both RSNA and renin-angiotensin system activity, the possible interaction between the 2 systems was examined. In rats with CHF, intracerebroventricular losartan had no effect on arterial pressure but decreased the basal level of RSNA and improved both the arterial and cardiopulmonary baroreflex control of RSNA, and chronic intraperitoneal losartan administration produced an improvement in the ability to excrete both acute and chronic sodium loads. This led to an examination of the effect of physiological changes in the renin-angiotensin system on arterial baroreflex control of RSNA in normal rats by using the intervention of alterations in dietary sodium intake. Intracerebroventricular losartan, although not affecting arterial pressure, decreased the basal level of RSNA and shifted the arterial baroreflex control of RSNA to a lower arterial pressure in proportion to the degree of activation of the renin-angiotensin system. Thus, the greatest effect was seen in low dietary sodium intake rats with increased plasma renin activity and the least effect was seen in high dietary sodium intake rats with suppressed plasma renin activity. This effect could be further localized to the rostral ventrolateral medulla, an important cardiovascular regulatory nucleus, wherein rostral ventrolateral medulla microinjection of losartan or candesartan (angiotensin type 1 receptor antagonists) decreased arterial pressure and RSNA in rats on low dietary sodium intake but not in rats on normal or high dietary sodium intake. Furthermore, candesartan injected into the rostral ventrolateral medulla decreased the basal level of RSNA and improved the arterial baroreflex control of RSNA in CHF rats. These studies focus on an important action of locally produced angiotensin in critical cardiovascular regulatory regions of the brain, which influence both the basal level of RSNA and its arterial baroreflex control.

The Future

It remains a significant challenge to further define and functionally characterize renal sympathetic nerve fiber groups that specifically and selectively innervate and control the function of the 3 renal neuroeffectors: the vessels, the tubules, and the juxtaglomerular granular cells. Current efforts involve a more precise analysis of the frequency response of the renal vasculature, comparing the dual inputs of arterial pressure and RSNA. Additional control and fine-tuning would be conferred on the relationship between single renal sympathetic neural units and the vasculature they innervate, if the vasculature was tuned to respond in a specific manner to certain frequencies encoded within the RSNA signal. It is apparent that the renal vasculature deals with the frequencies encoded within the arterial pressure input in a different manner than with the frequencies encoded within the RSNA input. This is not surprising as, in the case of the arterial pressure input, the renal vasculature is responding by using a myogenic (autoregulatory) mechanism, whereas in the case of the RSNA input, the renal vasculature is responding by using a mechanism that involves binding of ligand (norepinephrine) to a specific receptor (α1-adrenoceptor) followed by activation of an intracellular signaling cascade.

Over the course of the evolution of our knowledge in these several areas, it has become apparent that a potentially beneficial therapeutic approach for patients with hypertension or CHF would be the ability to antagonize α1-adrenoceptors selectively within the kidney. This would relieve the kidney from the adverse effects of RSNA, ie, increased renal tubular sodium reabsorption and RSR at lower frequencies and vasoconstriction with decreased RBF and GFR at higher frequencies. In addition, it would avoid the offsetting antinatriuretic influence of the decrease in arterial pressure that occurs with blockade of systemic α1-adrenoceptors. This recapitulates the important experiment of Barger, in which unilateral renal denervation in CHF dogs resulted in an ipsilateral diuresis and natriuresis without changes in RBF, GFR, or arterial pressure. It also focuses on increased RSNA as one of the contributing factors to the defect in renal sodium excretory capacity so fundamental to a prevailing concept of the development of hypertension. Before the availability of effective antihypertensive medications, bilateral lumbar sympathectomy was used for the treatment of patients with severe malignant hypertension. This denervated the
kidneys and permitted the survival of patients otherwise doomed to die but was complicated by the fact that much of the visceral and lower-extremity vasculature was also denervated, so that postural hypotension was a common and debilitating side effect.

How can renal-selective α1-adrenoceptor blockade be achieved? Much thought has been given to examination of the various subtypes of adrenergic receptors in the kidney in the hope that their distribution would be sufficiently different from other parts of the body so as to enable the systemic function and body fluid volume homeostasis. In addition, its postural hypotension was a common and debilitating side effect.

perspectives

Knowledge concerning the neural control of renal function has expanded to a level at which it joins other control mechanisms that are involved in the regulation of renal function and body fluid volume homeostasis. In addition, its recognition as a significant contributor to the pathophysiology of clinically important disease states such as hypertension and sodium-retaining edema-forming conditions (eg, CHF) gives promise of future therapeutic interventions.

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