The Sympathetic Nervous System and Hypertension
Recent Developments

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Arterial Baroreflex Control of Renal Sympathetic Nerve Activity and the Renal Body Fluid Feedback Mechanism—A Revisionist View

A major hypothesis for the development of hypertension is that abnormal renal excretory function is critical for the initiation, development, and maintenance of primary hypertension. The renal body fluid feedback mechanism couples the long-term regulation of arterial pressure to extracellular volume (sodium and water) homeostasis via pressure natriuresis, whereby the kidneys respond to changes in arterial pressure by altering urinary sodium and water excretion. The obligatory requirement for maintenance of sodium and water balance by the kidneys is believed to be primary in the long-term control of arterial pressure. An increase in arterial pressure (via increases in total peripheral resistance or cardiac output or both) leads to an increased urinary sodium and water excretion via the pressure natriuresis mechanism, with consequent reduction in blood volume until arterial pressure is returned to normal. Thus, factors that decrease renal excretory function and disrupt the maintenance of sodium and water balance by the kidneys lead to an increase in arterial pressure, which is required to reestablish and maintain sodium and water balance. Based on computer modeling studies, a long-term increase in arterial pressure can only occur if there is a chronic and sustained decrease in renal excretory function.

Increased renal sympathetic nerve activity (RSNA) is known to be a factor capable of decreasing renal excretory function. The renal effects of increased RSNA include increased renal tubular sodium reabsorption leading to renal sodium retention; decreased renal blood flow and glomerular filtration rate with renal vasoconstriction and increased renal vascular resistance; and increased renin release leading to angiotensin II production. Each of these renal functional alterations can decrease renal excretory function.

The role of increased RSNA as being a critically important factor contributing to this renal excretory dysfunction in hypertension is strengthened by the fact that increased RSNA has been identified in hypertensive human subjects and in a variety of animal models of experimental hypertension.
carotid baroreceptors led to an immediate and sustained 7-day increase in arterial pressure in association with increases in heart rate and plasma renin activity and decreases in urinary sodium excretion, reflecting sustained increases in sympathetic nerve activity (with little to no resetting) to heart and kidneys.\(^9\) When hypertension was produced by 5 days of angiotensin II infusion, urinary sodium excretion from the innervated kidney increased compared with that from the denervated kidney.\(^10\) The suggestion that this was caused by an arterial baroreflex-induced sustained decrease in RSNA (with little to no resetting) and was confirmed by the finding that sinoaortic denervation decreased urinary sodium excretion from the innervated kidney. The ability of the arterial baroreflex to produce even longer sustained decreases in RSNA (with little to no resetting) was demonstrated by the fact that urinary sodium excretion from the innervated kidney remained increased throughout a 10-day pressor infusion of angiotensin.\(^11\) Collectively, these studies provided indirect evidence that alterations in RSNA in response to unloading or loading of arterial baroreceptors can be sustained for prolonged periods of time. This supports the suggestion that arterial baroreflex control of RSNA, and thus overall renal excretory function, contribute importantly to the long-term regulation of arterial pressure.

Direct recording of RSNA in conscious rabbits infused with angiotensin II for 7 days unambiguously support this view.\(^12\) The sustained increase of 18 mm Hg in arterial pressure was accompanied by a sustained decrease in RSNA, which was reduced by 56% and 50% on days 2 and 7 of angiotensin II infusion, respectively. Moreover, the arterial baroreflex relationship between arterial pressure and RSNA was not reset (no shift to either lower or higher arterial pressure) on either day 2 or day 7 of angiotensin II infusion. Compared with the basal state, the range of the arterial baroreflex was reduced, the gain was not changed, and the resting point was moved from the steepest part of the curve to the lower plateau portion of the curve. Thus, during angiotensin II infusion, further increases in arterial pressure from the resting point did not produce further decreases in RSNA. Overall, it appears that suppression of RSNA serves a compensatory role in decreasing the magnitude of the hypertension by increasing renal excretory function and shifting the pressure natriuresis relationship to a lower arterial pressure. These results clearly demonstrate that arterial baroreflexes regulate RSNA during long-term changes in arterial pressure and suggest that arterial baroreflex control of RSNA, and thus overall renal excretory function, is critical in the short-term and long-term regulation of arterial pressure.

Thus, defective arterial baroreflex control of RSNA and overall renal excretory function could contribute to altered regulation of arterial pressure. In support of this are the findings in rats that arterial baroreceptor denervation (1) impairs the ability to establish sodium balance during low-sodium dietary intake and high-sodium dietary intake and that chronic sinoaortic denervation is exhibited and (2) leads to the development of increased arterial pressure during high-sodium dietary intake in association with increased renal sodium retention.\(^13\) It appears that arterial baroreflex-mediated suppression of RSNA is present in other forms of hypertension, also. Chronic nitric oxide synthase blockade with \(L\)-NAME in rabbits with sinoaortic denervation failed to produce a chronic sustained increase in arterial pressure.\(^14\) These results confirm that arterial baroreflexes are importantly involved in the long-term regulation of arterial pressure and that one mediator of this regulation is nitric oxide.

Thus, progressive dysfunction of the arterial baroreflex during the development of hypertension may be a uniform mechanism that contributes to sustained increases in activity of the sympathetic nervous system (including RSNA) and arterial pressure.

Although mean arterial pressure is not substantially altered by arterial baroreceptor denervation, arterial pressure variability is significantly increased. This is most notable in response to ordinary environmental and alerting stimuli that, although eliciting only modest changes in arterial pressure in intact animals, result in striking hypertensive increases after arterial baroreceptor denervation. By way of clinical analogy, Sharabi et al have presented 3 patients with arterial baroreflex failure as a late sequela of neck irradiation.\(^15\) Arterial baroreflex (cardiovagal portion) gain was zero, and the patients exhibited orthostatic intolerance. During ambulatory blood pressure monitoring, each patient exhibited highly labile blood pressure (increased standard deviation of systolic and diastolic blood pressures) with sudden pressor (>200 mm Hg) and depressor episodes. Thus, chronic arterial baroreflex denervation results in labile hypertension in association with orthostatic intolerance.

There is evidence for chronic activation of the arterial baroreflex in hypertension. In angiotensin II and obesity hypertension, activation of neurons in the central arterial baroreflex pathway has been identified using Fos-Li immunohistochemistry. In the case of angiotensin II hypertension,\(^16\) there was activation of neurons in the nucleus tractus solitarius (NTS) and in the caudal ventrolateral medulla (CVLM) that mediate arterial baroreflex suppression of sympathoexcitatory neurons in the rostral ventrolateral medulla (RVLM). In obesity hypertension,\(^17\) there was activation of neurons in NTS, CVLM, and RVLM.

Impairment in other reflex mechanisms that tonically regulate RSNA can also result in sustained higher levels of RSNA, leading to increased renal sodium retention and a shift of the pressure-natriuresis relationship to a higher arterial pressure. In otherwise normal rats, selective afferent renal denervation by \(T_{\gamma}L_1\) dorsal rhizotomy results in NaCl-sensitive hypertension in association with impaired pressure natriuresis.\(^18\) When challenged with a 4-fold increase in dietary sodium intake, sodium balance was achieved in sham afferent renal denervated rats with an approximate 10-mm Hg reduction in mean arterial pressure, whereas afferent renal denervated rats required a 30-mm Hg increase in mean arterial pressure.

### A View from the Patient: Interaction of the Renin–Angiotensin System and the Sympathetic Nervous System With Hypertension, Congestive Heart Failure, and Chronic Renal Failure

The central regulation of sympathetic nervous system activity is complex, comprising multiple reflex pathways and neural
connections involving an expanding number of neurotransmitters and neuropeptides. Although an interaction between the renin–angiotensin system and sympathetic nervous system activity has been long-appreciated in animals, there is growing evidence for the importance of this interaction in human subjects. Patients with renal artery stenosis and hypertension (ie, renal vascular hypertension) have increases in both sympathetic nervous system activity (muscle and renal) and activity of the renin–angiotensin system.19 When arterial pressure was lowered to the same level in such patients with either dihydralazine (vasodilator) or enalaprilat (angiotensin-converting enzyme inhibitor), different responses occurred. In the dihydralazine group, a typical response to acute arterial baroreceptor unloading occurred with increases in muscle sympathetic nerve activity (MSNA), heart rate, total body norepinephrine spillover, and plasma angiotensin II concentration. However, in the ACE inhibitor group with a similar decrease in arterial pressure, plasma angiotensin II concentration decreased and there was no change in MSNA, heart rate, or total body norepinephrine spillover. Thus, interruption of the renin–angiotensin system led to a resetting of the arterial baroreflex control of MSNA (ie, similar level of MSNA at a lower arterial pressure). The results also demonstrate a tonic action of the renin–angiotensin system to increase MSNA and to affect arterial baroreflex regulation of MSNA. One central site of this interaction is the RVLM, wherein microinjection of the angiotensin II type 1 receptor (AT1) antagonist candesartan decreased RSNA and arterial pressure only in rats whose renin–angiotensin activity was physiologically increased by dietary sodium restriction.20

**It Is NO All Over Again**

The interaction between sympathetic nervous system activity and renin–angiotensin system activity has been expanded by consideration of the role of nitric oxide (NO). The increase in arterial pressure associated with intracerebroventricular angiotensin II (angiotensin-converting enzyme inhibitor), different responses occurred. In the dihydralazine group, a typical response to acute arterial baroreceptor unloading occurred with increases in muscle sympathetic nerve activity (MSNA), heart rate, total body norepinephrine spillover, and plasma angiotensin II concentration. However, in the ACE inhibitor group with a similar decrease in arterial pressure, plasma angiotensin II concentration decreased and there was no change in MSNA, heart rate, or total body norepinephrine spillover. Thus, interruption of the renin–angiotensin system led to a resetting of the arterial baroreflex control of MSNA (ie, similar level of MSNA at a lower arterial pressure). The results also demonstrate a tonic action of the renin–angiotensin system to increase MSNA and to affect arterial baroreflex regulation of MSNA. One central site of this interaction is the RVLM, wherein microinjection of the angiotensin II type 1 receptor (AT1) antagonist candesartan decreased RSNA and arterial pressure only in rats whose renin–angiotensin activity was physiologically increased by dietary sodium restriction.20

In contrast to control rats, l-NAME hypertensive rats have increased angiotensin-converting enzyme activity in the brain stem and a greater decrease in arterial pressure after hexamethonium administration, indicating increased sympathetic nervous system activity.22 Injection of an AT1 receptor antagonist into the depressor region of the NTS decreased mean arterial pressure, heart rate, and RSNA more in l-NAME hypertensive rats than in control rats. Thus, l-NAME hypertension is caused by increased sympathetic nervous system activity that is dependent on activation of the renin–angiotensin system in NTS-mediated by AT1 receptors.

**The Weight of It All**

Increased sympathetic nervous system activity is an important part of the hypertension associated with obesity.23 Sustained activation of central baroreceptor pathways has been identified in obesity hypertension in conscious dogs.17 Using Fos-Li immunoreactivity to identify neuronal activation, increased numbers of Fos-Li–positive cells were observed in the NTS, CVLM, and RVLM.

In rats, intravenous administration of leptin increases arterial pressure in association with increases in renal, lumbar, and adrenal sympathetic nerve activity. In mice, intracerebroventricular administration of leptin increases RSNA without affecting arterial pressure or heart rate; the increase in RSNA was prevented by intracerebroventricular administration of an inhibitor of phosphoinositol-3 kinase (PI3K).24 Microinjection of leptin into the ventromedial hypothalamus increased arterial pressure and RSNA, and into the dorsomedial hypothalamus it increased arterial pressure without affecting RSNA.25 These might be important central sites where leptin activation leads to the increase in peripheral sympathetic vasomotor activity and heart rate that are seen in the hypertension associated with obesity. In human subjects, plasma leptin concentration was observed to correlate with renal norepinephrine spillover, suggesting that leptin stimulates RSNA.26 However, plasma leptin concentration and total body norepinephrine spillover were increased in congestive heart failure patients, providing no support for the concept of regulatory feedback inhibition of leptin release by the sympathetic nervous system.

In conscious rats, chronic glucose infusion produces a mild hypertension that is not affected by combined α- and β-adrenoceptor blockade.27 However, concurrent nitric oxide synthase inhibition (l-NAME) enhances the hypertensive response to chronic glucose infusion in association with a marked tachycardia. The hypertensive and tachycardia responses are significantly attenuated by combined α- and β-adrenoceptor blockade in the combined glucose and l-NAME–infused rats. These results suggest that NO may protect against hypertension during chronic glucose infusion by suppressing sympathetic nervous system activity.

Hyperinsulinemia and increased sympathetic nervous system activity have been proposed as pathophysiological links between obesity and hypertension. Pima Indians have a high prevalence of obesity and hyperinsulinemia but a low prevalence of hypertension associated with obesity.28 The lack of an increase in muscle sympathetic nerve activity with increasing adiposity and insulinemia in Pima Indians may contribute to the low prevalence of hypertension in this population.

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**References**


