The Sympathetic Nervous System and Long-Term Blood Pressure Regulation

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There is considerable evidence that activation of the sympathetic nervous system plays an important role in the pathogenesis of several cardiovascular diseases, including hypertension. However, the mechanisms that account for sympathetic activation and the precise mechanisms that mediate neurally induced hypertension are unclear. In large part, this is due to the difficulty in assessing sympathetic function under chronic conditions. Consequently, acute observations are often extrapolated to infer that similar neural mechanisms are operative under more long-term conditions, an unwarrantable assumption. Nonetheless, considerable theoretical and experimental evidence points to the renal sympathetic nerves as the critical link between the sympathetic nervous system and long-term arterial pressure control. Both chronic increases and decreases in renal adrenergic activity alter renal excretory function and produce sustained elevations and reductions in arterial pressure, respectively. Recent observations, including those in dogs with hemibladders and one denervated kidney, indicate that chronic suppression of renal sympathetic nerve activity and attendant natriuresis are long-term compensatory responses to excess body fluid volumes and hypertension. Furthermore, studies combining deafferentation of cardiac receptors and sinoaortic baroreceptors with the split-bladder preparation suggest that chronic renal sympathoinhibition is mediated by baroreflex mechanisms, an especially important finding given the technical limitations in determining whether baroreflexes completely reset and impact sympathetic activity in chronic hypertension. In contrast to the chronic inhibitory effects of baroreflexes on sympathetic activity, other studies indicate that angiotensin II (Ang II) has sustained renal sympathoexcitatory effects. The opposing long-term effects of baroreflexes and Ang II on renal sympathetic nerve activity support two major hypotheses for sympathetic activation in hypertension: baroreflex dysfunction and activation of the renin-angiotensin system, abnormalities often associated with clinical hypertension. Am J Hypertens 2001;14:147S–154S © 2001 American Journal of Hypertension, Ltd.

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Although it is well established that the sympathetic nervous system plays an important role in the acute regulation of arterial pressure, it is unclear whether changes in sympathetic activity contribute to long-term arterial pressure homeostasis. Nonetheless, it is widely believed that increased sympathetic activity contributes to the pathogenesis of chronic disease states associated with abnormal renal excretory function, including congestive heart failure and hypertension.1-5 However, the specific mechanisms whereby the sympathetic nervous system promotes sodium retention and the quantitative importance of neurally induced sodium retention to abnormal fluid retention in these disease states is unresolved. Furthermore, there is a rather poor understanding of the mechanisms that account for sympathetic activation in heart failure and hypertension. It is unfortunate that the role of the sympathetic nervous system in long-term arterial pressure homeostasis is often inferred from the results of acute studies. This is inappropriate because there is no scientific basis to assume that the neural mechanisms that dominate in rapid control of arterial pressure contribute to long-term arterial pressure regulation as well.

Role of the Kidneys in Long-Term Regulation of Arterial Pressure

Long-term regulation of arterial pressure is linked closely to volume homeostasis through the renal body fluid feedback mechanisms.6,7 A key feature of the renal body fluid feedback control system is pressure natriuresis or the abil...
ity of the kidneys to respond to changes in arterial pressure by altering the renal excretion of salt and water. Importantly, neurally induced changes in peripheral resistance and cardiac output, which are essential for rapid regulation of arterial pressure, do not alter arterial pressure chronically, unless they are also associated with sustained changes in renal excretory function.

The sensitivity of the pressure natriuresis mechanism can be modified by a number of extrarenal neurohormonal regulatory systems. For example, one hormonal system that is particularly important to arterial pressure homeostasis is the renin-angiotensin system. This is because the renin-angiotensin system is a nonadapting hormonal mechanism that chronically alters the sensitivity of pressure natriuresis. As arterial pressure or sodium intake increases, the renin-angiotensin system is suppressed, which enhances the ability of the kidneys to excrete salt and water. Conversely, when either arterial pressure or sodium intake is reduced, high endogenous levels of angiotensin (Ang) II decrease renal excretory function, which promotes sodium retention. In the absence of appropriate changes in the renin-angiotensin system, there is an abnormal shift in the pressure natriuresis relationship, resulting in sustained alterations in arterial pressure.

Although the importance of the renin-angiotensin system in long-term regulation of arterial pressure is firmly established, it is unclear whether the sympathetic nervous system also plays a similar role in body fluid volume and arterial pressure homeostasis. One way in which the sympathetic nervous system could alter pressure natriuresis and contribute to long-term regulation of arterial pressure is through changes in renal sympathetic nerve activity. Indeed, there is considerable evidence from acute studies that baroreflex-mediated changes in renal sympathetic nerve activity influence pressure natriuresis and contribute to short-term regulation of body fluid volumes. However, it is not clear whether compensatory changes in renal sympathetic nerve activity are sustained chronically and alter pressure natriuresis during long-term perturbations in body fluid volumes and arterial pressure. This uncertainty is a result of technical limitations that prevent determination of both the long-term changes in renal sympathetic nerve activity and the sodium excretory responses to chronic alterations in renal adrenergic activity. Finally, although arterial and cardiac baroreflexes mediate changes in renal sympathetic nerve activity during acute perturbations in body fluid volumes and arterial pressure, it is also recognized that baroreceptors reset to the prevailing level of blood pressure. Consequently, if baroreflexes completely reset, then they could not possibly play a role in the long-term regulation of arterial pressure. Therefore, it is not clear what afferent mechanisms might detect chronic disturbances in body fluid volumes and arterial pressure and subsequently evoke sustained compensatory changes in renal sympathetic nerve activity.

**Chronic Changes in Renal Adrenergic Activity Do Have A Sustained Influence on Pressure Natriuresis**

Elegant studies in human subjects by Esler have demonstrated that renal norepinephrine overflow, an indirect index of renal sympathetic nerve activity, is increased in the early stages of obesity and essential hypertension. These findings are consistent with the hypothesis that increased renal sympathetic nerve activity plays an initiating role in the pathogenesis of these forms of hypertension. The fact that bilateral renal denervation delays the development or attenuates the severity of hypertension in some experimental models of hypertension provides further support for the participation of the renal nerves in the hypertensive process. However, equally important to this concept are experimental studies demonstrating that chronic renal adrenergic stimulation does have the capability of producing sustained hypertension.

One experimental approach to determine whether sustained renal adrenergic stimulation produces hypertension has been to chronically infuse norepinephrine directly into the renal artery of uninephrectomized dogs. In all of these studies, chronic hypertension occurred at infusion rates of norepinephrine infusion into the renal artery that produced little or no hypertension when administered systemically. Because sodium balance is achieved at an increased level of arterial pressure, these studies indicate that chronic renal adrenergic stimulation produces a hypertensive shift in pressure natriuresis.

Because increased renal nerve activity stimulates renin release, Reinhart et al investigated the role of the renin-angiotensin system in mediating the long-term hypertensive effects of renal adrenergic stimulation. The salient results of this study are illustrated in Fig. 1. In uninephrectomized dogs, chronic hypertension was achieved at a low rate of norepinephrine infusion into the renal artery, which did not produce sustained changes in renal hemodynamics. In addition, the hypertensive response to chronic renal adrenergic stimulation was associated with a sustained increase in plasma renin activity. Subsequently, the renal artery infusion of norepinephrine was repeated in a second group of dogs after first clamping circulating plasma Ang II concentration at control levels by systemic infusion of captopril and a low rate of Ang II. In marked contrast to control dogs in which the renin-angiotensin system was functional, chronic renal adrenergic stimulation failed to produce hypertension in the absence of an increase in plasma Ang II concentration. These results suggest that the tubular effects of Ang II to promote sodium reabsorption play an important role in mediating hypertension induced by low levels of renal adrenergic stimulation. These findings may be particularly relevant to the pathogenesis of essential hypertension in humans, a syndrome character-
ized by a high rate of renal norepinephrine spillover and increased plasma renin activity. These studies, using intrarenal infusion of norepinephrine, indicate that chronic renal adrenergic stimulation produces a hypertensive shift in pressure natriuresis. However, if the sympathetic nervous system is to function as an effective long-term controller of arterial pressure it is equally important that pressure natriuresis shifts to lower levels of arterial pressure when renal adrenergic stimulation is chronically suppressed. That decreased renal adrenergic stimulation increases renal excretory function is supported by a preliminary study in dogs in which arterial pressure was monitored 24-h/day before and after bilateral renal denervation. Under rigorously controlled experimental conditions, mean arterial pressure decreased by about 10% after renal denervation, indicating that chronic reductions in renal adrenergic activity do produce a hypotensive shift in pressure natriuresis. Thus, chronic decreases, as well as increases, in renal adrenergic stimulation have a sustained influence on pressure natriuresis.

Determination of the Long-Term Effects of the Renal Nerves on Sodium Excretion

Although chronic alterations in the degree of renal adrenergic stimulation in response to norepinephrine infusion and renal denervation have sustained effects on pressure natriuresis, this does not necessarily indicate that under either physiologic or pathophysiologic conditions changes in renal sympathetic nerve activity do occur that impact sodium excretion. Measurements of renal norepinephrine spillover in patients with advanced heart failure and in patients with obesity and essential hypertension provide strong evidence for increased renal sympathetic nerve activity in these disease states. However, the impact of increased renal sympathetic nerve activity on sodium excretory function cannot be discerned from these important observations.

An understanding of the role of the sympathetic nervous system in long-term control of sodium excretion and arterial pressure has been impeded by the difficulty in assessing the functional effects of the renal nerves under chronic conditions. The approach taken in many studies has been to produce chronic disturbances in body fluid volumes and arterial pressure and to compare long-term sodium excretory responses in animals with bilateral renal denervation to responses in controls with intact innervation. In many instances, the results have been conflicting. This is not surprising: a confounding factor in the interpretation of studies in which the renal nerves are totally removed is the possible compensatory mechanisms that may be activated to maintain sodium balance in the absence of the renal nerves. For example, in comparing animals with and without renal innervation, differential changes in arterial pressure might have a significant effect in masking the long-term influence of the renal nerves on sodium excretion.

To circumvent this confounding issue, we have used a split-bladder preparation in combination with unilateral renal denervation to elucidate whether chronic changes in renal sympathetic nerve activity have long-term effects on sodium excretion. In these studies, the urinary bladder of dogs was surgically divided and one kidney was denervated. Catheters exteriorized from each hemibladder permitted 24-h urine collection from both denervated and innervated kidneys. This is a powerful technique for exposing a functional role of the renal nerves because both kidneys are exposed to the same perfusion pressures and hormonal influences. Consequently, any differences in sodium excretion between the kidneys can be attributed to either the direct or indirect effects of the renal nerves on renal excretory function.

The Renal Nerves Chronically Promote Sodium Excretion During Long-Term Increments in Body Fluid Volumes or Arterial Pressure

Renal Nerves Promote Sodium Excretion in Norepinephrine Hypertension

Renal denervation is a widely used experimental approach for determining the role of the renal nerves in the regula-
tion of sodium excretion. However, a potential criticism of studies using renal denervation is that chronically denervated kidneys may be supersensitive to circulating levels of norepinephrine, a response that could mask the effects of renal denervation. To determine whether this might be a confounding factor in the interpretation of the sodium excretory responses in chronically denervated kidneys, dogs with split-bladders and one denervated kidney were subjected to chronic intravenous infusions of norepinephrine. Norepinephrine was infused for 5 days at rates of 25, 100, and 200 ng/kg/min to achieve physiologic, pathophysiologic, and pharmacologic plasma levels of norepinephrine. Results from this study are illustrated in Fig. 2.

During the control period (before norepinephrine infusion), denervated kidneys excreted slightly more sodium (5%) than intact innervated kidneys, as reflected by a relative 24-h excretion rate of sodium from denervated and innervated kidneys (Den/Inn) of 1.05 ± 0.05. During chronic infusion of norepinephrine up to a rate of 100 ng/kg/min, plasma norepinephrine concentration increased to as high as 3000 pg/mL, or to about 20 times normal (control, 145 ± 24 pg/mL), a level much higher than achieved in chronic pathophysiologic conditions including hypertension and heart failure. Nonetheless, there were no sustained changes in either the Den/Inn for sodium excretion or mean arterial pressure. In marked contrast, at the highest rate of norepinephrine infusion (200 ng/kg/min), which increased plasma norepinephrine concentration to 7000 pg/mL or to 50 times control levels, there was a significant increase in mean arterial pressure and a pronounced reduction in the Den/Inn for sodium excretion. This marked decrease in the Den/Inn for sodium excretion at pharmacologic levels of norepinephrine reflects a substantially lower rate of sodium excretion from denervated versus innervated kidneys.

Thus, these studies provide no support for the notion that chronically denervated kidneys are supersensitive to either physiologic or pathophysiologic plasma levels of norepinephrine. Consequently, denervation supersensitivity does not appear to be a confounding issue in studies using chronic renal denervation to elucidate the role of the renal nerves in the regulation of sodium excretion in either physiologic or pathophysiologic states. On the other hand, the marked decrease in the Den/Inn for sodium excretion at plasma levels of norepinephrine that chronically increase arterial pressure is consistent with previous findings that exaggerated antinatriuretic responses occur in denervated kidneys when pharmacologic doses of norepinephrine are administered. Alternately, the higher excretion rate of sodium in innervated versus denervated kidneys at plasma levels of norepinephrine that increase arterial pressure raises the intriguing possibility that chronic renal sympathoinhibition and attendant loss of sodium may be a long-term compensatory response to the hypertension.

Renal Nerves Promote Sodium Excretion During Chronic Increases in Sodium Intake

In light of the evidence that excess salt intake may play a major role in causing hypertension, there has been considerable interest in identifying the physiologic mechanisms that prevent excessive increments in arterial pressure at high levels of salt intake. It is well established that reflexes, especially those initiated by activation of cardiac receptors, inhibit renal sympathetic nerve activity and contribute to the elimination of sodium after an acute salt load. However, it is not known whether reductions in renal sympathetic nerve activity persist and whether cardiorenal reflexes contribute importantly to the chronic regulation of sodium excretion during sustained increments in salt intake.

To determine whether the renal nerves contribute to sodium homeostasis during long-term increments in sodium intake, studies were conducted in conscious dogs with split-bladders and unilateral renal denervation. During eightfold increases in sodium intake (control, 60 mEq/day), there were no significant long-term changes in mean arterial pressure, and sodium balance was achieved within 48 h. Moreover, throughout the entire 5-day period of increased sodium intake, there were persistent reductions...
in the Den/Inn for sodium excretion, indicating that sustained renal sympathoinhibition promotes sodium excretion during long-term increments in sodium intake. It is of interest that baroreflex dysfunction has been reported in a number of disease states associated with increased renal nerve activity and impaired renal excretory function, including heart failure and some forms of hypertension.\textsuperscript{1–5,17} However, the extent to which impaired baroreflex suppression of renal sympathetic nerve activity contributes to activation of the renal sympathetic nerves and salt sensitivity in hypertension remains to be elucidated.

**Renal Nerves Promote Sodium Excretion in Angiotensin Hypertension**

Because numerous acute studies have shown that Ang II stimulates sympathetic activity by both central and peripheral actions, it has been proposed that the sympathetic nervous system may play a role in mediating the long-term hypertensive actions of Ang II.\textsuperscript{7,18,19} On the other hand, our findings during norepinephrine hypertension and high salt intake, discussed above, are consistent with the hypothesis that suppression of renal sympathetic nerve activity is a long-term compensatory response that promotes sodium excretion when there are sustained increments in body fluid volumes or arterial pressure. Consequently, if renal sympathoinhibition were a dominant long-term response in Ang II hypertension, one would expect the sympathetic nervous system to attenuate, not exacerbate the severity of Ang II hypertension. Chronic studies designed to discern the role of the sympathetic nervous system in mediating the long-term hypertensive actions of Ang II have produced inconsistent results.\textsuperscript{7,18,20,21}

To determine whether the sympathetic nervous system contributes to the hypertension induced by pathophysiologic increments in plasma Ang II concentration, Ang II was infused intravenously for 5 days at 5 ng/kg/min in dogs with split-bladders and unilateral renal denervation.\textsuperscript{13,15} This rate of Ang II infusion produces about a fivefold increase in plasma Ang II concentration.\textsuperscript{22} As illustrated in Figs. 3 and 4 (intact condition), intravenously infused Ang II caused sodium retention for several days before sodium balance was achieved at a sustained increase in mean arterial pressure of 30 to 35 mm Hg. There were no significant changes in heart rate during Ang II hypertension. Moreover, in contrast to the control period when approximately equal amounts of sodium were excreted by both kidneys (Den/Inn = 1.04 ± 0.04), throughout Ang II infusion there was about a twofold greater rate of sodium excretion from innervated versus denervated kidneys (day 5 Den/Inn = 0.51 ± 0.05). The marked and sustained decrease in the Den/Inn for sodium excretion during Ang II hypertension was comparable to that achieved during norepinephrine hypertension (Fig. 2) and suggests chronic suppression of renal sympathetic nerve activity during Ang II hypertension. Indeed, this functional response is entirely consistent with our earlier measurements of renal norepinephrine spillover in chronically instrumented dogs subjected to long-term Ang II infusion.\textsuperscript{20} In that study, renal norepinephrine spillover was markedly suppressed after 6 days of Ang II hypertension. More recently, Cox and Bishop\textsuperscript{21} directly recorded renal sympathetic nerve activity in conscious rabbits subjected to Ang II hypertension. They reported that renal sympathetic nerve activity was depressed after 10 days of Ang II infusion. Taken together, these studies suggest that suppression of renal sympathetic nerve activity is a long-term compensatory response that shifts pressure natriuresis to lower arterial pressure levels and opposes the antinatriuretic and hypertensive actions of Ang II.

**Baroreflexes Prevent Neurally Induced Sodium Retention in Angiotensin Hypertension**

Having established from the above three split bladder studies that suppression of renal sympathetic nerve activity and concomitant increases in renal excretory function are sustained responses to increments in body fluid volumes and hypertension, we investigated whether barore-
pressure. Consequently, if baroreflexes do completely undergo rapid resetting in response to changes in arterial pressure, it is well established that arterial baroreceptors unilaterally impair pressure natriuresis during Ang II hypertension. On the other hand, baroreceptors there was a sustained tachycardia throughout Ang II hypertension, Ang II was infused chronically in the same dogs, before (intact) and after deafferentation of cardiopulmonary receptors and sinoaortic baroreceptors (CPD + SAD). Results from this study are illustrated in Figs. 3 and 4. Deafferentation of cardiopulmonary and sinoaortic baroreceptors was achieved by stripping the vagus in the thorax and the adventitia in the area of the carotid bifurcation. Several weeks after CPD + SAD, BP variability was increased about twofold, but there were no persistent increments in either mean arterial pressure or the Den/Inn for sodium excretion, 24-h responses indicating little or no sustained increase in sympathetic activity after baroreceptor denervation. As expected, however, basal values for heart rate were elevated due to elimination of cardiac vagal innervation.

Baroreceptor denervation did alter the hemodynamic responses to chronic Ang II infusion. The on and off transient responses to Ang II were more pronounced after CPD + SAD than in the intact state, although the final increments in mean arterial pressure were the same in both conditions. In addition, CPD + SAD had a sustained influence on the heart rate response to Ang II infusion. In contrast to the intact state in which heart rate tended to decrease during Ang II hypertension, in the absence of baroreflexes there was a sustained tachycardia throughout Ang II infusion, suggesting prolonged activation of cardiac sympathetic nerves.

More importantly to the focus of this article, CPD + SAD had a substantial influence on the relative excretion rates of sodium from denervated and innervated kidneys during Ang II infusion (Fig. 4). In contrast to the marked reduction in the Den/Inn for sodium excretion during Ang II infusion in the intact state, this ratio actually increased substantially during Ang II hypertension after CPD + SAD (Fig. 4). On day 5 of Ang II infusion, the Den/Inn for sodium excretion was 2.02 ± 0.14, indicating that innervated kidneys were excreting only approximately half as much sodium as denervated kidneys. Most significantly, the increase in the Den/Inn for sodium excretion during Ang II infusion suggests that Ang II chronically increased renal sympathetic nerve activity, a response exactly opposite to that achieved when all baroreflexes were intact.

The increase in the Den/Inn for sodium excretion during Ang II infusion in the absence of baroreflexes indicates that Ang II can chronically promote sodium retention in part by activation of the renal nerves. However, the quantitative importance of the direct versus the indirect neurally induced antinatriuretic effects of Ang II in chronically impairing pressure natriuresis remains to be established. This is a particularly intriguing question in light of our findings during chronic intrarenal norepinephrine infusion (Fig. 1) indicating that the long-term hypertensive effects of renal adrenergic stimulation are greatly dependent on the generation of Ang II. This would suggest that the direct renal actions of Ang II to promote sodium retention are far more important than the indirect effects mediated by the activation of the renal nerves.

To determine whether cardiac reflexes with vagal afferents or arterial baroreflexes mediate chronic suppression of renal sympathetic nerve activity during Ang II hypertension, Ang II was infused chronically in the same dogs, before (intact) and after deafferentation of cardiopulmonary receptors and sinoaortic baroreceptors (CPD + SAD). Results from this study are illustrated in Figs. 3 and 4. Deafferentation of cardiopulmonary and sinoaortic baroreceptors was achieved by stripping the vagus in the thorax and the adventitia in the area of the carotid bifurcation. Several weeks after CPD + SAD, BP variability was increased about twofold, but there were no persistent increments in either mean arterial pressure or the Den/Inn for sodium excretion, 24-h responses indicating little or no sustained increase in sympathetic activity after baroreceptor denervation. As expected, however, basal values for heart rate were elevated due to elimination of cardiac vagal innervation.

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In summary, these data indicate that cardiac or arterial baroreceptors chronically inhibit renal sympathetic nerve activity during Ang II hypertension and that in the absence of these reflexes Ang II has sustained renal sympathoexcitatory effects. A corollary of these studies is that Ang II hypertension should be more severe in the absence of baroreflex-mediated suppression of renal sympathetic nerve activity. This notion could not be tested in the study illustrated in Figs. 3 and 4 because pressure natriuresis in the denervated kidney would be expected to attenuate the severity of Ang II hypertension. In this regard, it will be important in future studies to determine whether deafferentation of cardiac or sinoaortic baroreceptors exacerbates the severity of Ang II hypertension in dogs with intact renal innervation to both kidneys.

**Perspectives**

The studies discussed using the split-bladder preparation in combination with unilateral renal denervation indicate that suppression of renal sympathetic nerve activity plays a compensatory role in the chronic regulation of body fluid volumes and arterial pressure in states of volume excess and hypertension. In addition, these studies identify two mechanisms that have opposing long-term effects on renal sympathetic activity in hypertension: the baroreflexes and the renin-angiotensin system. Furthermore, unpublished observations from our laboratory indicate that both baroreflexes and Ang II have sustained effects on renal sympathetic nerve activity for up to 2 weeks of hypertension, the longest duration of our experiments. Taken together, these findings lend credence to two major hypotheses for sympathetic activation in hypertension: baroreflex dysfunction and activation of the renin-angiotensin system.

But are sympathetic responses lasting up to 2 weeks relevant to chronic hypertension in humans? Given the caveat that there are regional differences in sympathetic activation in pathophysiologic states including hypertension, direct recordings of skeletal muscle sympathetic nerve activity by microneurography suggest that they are relevant to chronic hypertension in humans. Although the mechanisms that stimulate the sympathetic nervous system are unclear, both muscle and renal (renal norepinephrine spillover) sympathetic activity are elevated in patients with obesity and essential hypertension. In contrast, patients with pheochromocytoma and primary aldosteronism have suppressed muscle sympathetic nerve activity compared with normal subjects. These clinical observations of chronic sympathoinhibition in patients with secondary hypertension are consistent with our findings indicating that baroreflex suppression of renal sympathetic nerve activity is a chronic compensatory response in hypertension.

On the other hand, muscle sympathetic nerve activity appears to be more variable in another form of secondary hypertension, renovascular hypertension. An early report indicated that muscle sympathetic nerve activity is elevated in patients with relatively severe renovascular hypertension and substantial increases in plasma renin activity. In contrast, more recently it was reported that muscle sympathetic nerve activity is normal in patients with more moderate renovascular hypertension and presumably less activation of the renin-angiotensin system (plasma renin activity was not measured in this study). However, in either case, these measurements of muscle sympathetic nerve activity, whether elevated or normal, differ from our findings indicating sustained suppression of renal sympathetic nerve activity in Ang II hypertension. It is not clear whether these disparate findings reflect either differences in muscle versus renal sympathetic nerve activity or differences in the sympathetic responses to different plasma levels of Ang II. Alternately, as our studies indicate opposing effects of baroreflexes and Ang II on renal sympathetic nerve activity, the inconsistent sympathetic responses in renovascular hypertension may reflect a time dependency in the manifestation of the sympathoexcitatory effects of Ang II. The sympathoexcitatory effects of Ang II may become more evident in time as baroreflex suppression of sympathetic activity wanes, due either to chronic baroreflex resetting or to progressive baroreflex dysfunction. In regard to the latter possibility, it is of interest that the evolution of obesity hypertension is associated with progressive increments in both muscle sympathetic nerve activity and progressive impairment of baroreflex-mediated suppression of sympathetic discharge. Clearly, time-dependent studies are needed to further elucidate the chronic interactions among the renin-angiotensin system, cardiac reflexes, and arterial baroreflexes that impact renal sympathetic nerve activity, the critical link between the sympathetic nervous system and long-term BP regulation. Additional studies are also needed to determine the quantitative importance of neurally induced alterations in pressure natriuresis to the pathogenesis of disease states associated with sympathetic activation and impaired renal excretory function.

**References**


