Interactions Between Angiotensin II and Baroreflexes in Long-Term Regulation of Renal Sympathetic Nerve Activity

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There is considerable evidence that the sympathetic nervous system plays an important role in the pathogenesis of hypertension. However, the factors that chronically influence sympathetic activity and the precise mechanisms that mediate neurally induced hypertension are unclear. Topics of long-standing interest, but of considerable uncertainty, relate to the potential impact of the renin-angiotensin system and baroreflexes on sympathetic activity in hypertension. Numerous studies have demonstrated that baroreflex function is impaired in hypertension and that angiotensin II (Ang II) acutely stimulates the sympathetic nervous system. Despite this wealth of information, it is still unclear whether baroreflex dysfunction and elevated plasma levels of Ang II lead to chronic increases in sympathetic activity that promote hypertension. This uncertainty, in large part, has been due to technical limitations that prevent determination of long-term changes in sympathetic activity, particularly sympathetic activity to the kidneys (as discussed below). In this regard, the study by Barrett et al in this issue of Circulation Research is especially important for two reasons. First, it establishes a novel experimental technique for directly monitoring renal sympathetic nerve activity, 24 hours per day. Thus, for the first time, an experimental tool has been developed for assessing the critical neural signal from the brain to the kidneys that leads to long-term changes in body fluid volumes and arterial pressure. Second, by clearly establishing the time-dependent changes in renal sympathetic nerve activity during the induction of Ang II hypertension, this study brings to focus the complex interactions between Ang II and the sympathetic nervous system that are important in the long-term regulation of arterial pressure. Clearly, these interactions cannot be predicted from acute studies. Indeed, the most important finding in this study—that renal sympathetic nerve activity is chronically suppressed in Ang II hypertension—is diametrically opposite to what one might predict from the acute sympathoexcitatory effects of Ang II and the prevailing notion that baroreflexes reset in hypertension. Therefore, it is not surprising that extrapolation of the results from acute studies has led to erroneous conclusions regarding the role of the sympathetic nervous system in mediating Ang II hypertension.

As Barrett et al recognize, the kidneys play a preeminent role in long-term control of arterial pressure and, for that reason, these investigators have focused on changes in renal sympathetic nerve activity to understand the influence of the nervous system in the genesis of Ang II hypertension.

Long-term regulation of arterial pressure is closely linked to extracellular volume homeostasis through the renal body fluid feedback mechanism (blocks with darkened borders in the Figure). A key feature of the renal body fluid feedback control system is pressure natriuresis (crosshatched blocks in the Figure) or the ability 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 function, which are essential for acute regulation of arterial pressure, do not alter arterial pressure chronically, unless they are associated with sustained changes in renal excretory function. For example, in the absence of an effect on renal excretory function, an increase in total peripheral resistance and/or cardiac pumping would increase pressure natriuresis. In turn, increased fluid excretion would decrease extracellular fluid volume until cardiac output and arterial pressure returned to normal and fluid balance is reestablished. Unfortunately, this concept is not widely appreciated by researchers investigating mechanisms of neurogenic hypertension. Indeed, as Barrett et al have indicated, a fairly popular indirect approach for inferring the importance of the sympathetic nervous system in mediating hypertension has been to determine the hypotensive response to pharmacological autonomic blockade. An accentuated reduction in arterial pressure with ganglionic blockade in hypertension is assumed to indicate a role for the sympathetic nervous system in the genesis of the hypertension. However, this is an inappropriate assumption for at least two reasons. First, it fails to consider the fact that sympathetic activity is differentially regulated. Accordingly, it provides no insight into the level of renal sympathetic activity, a critical determinant of chronic neurally induced changes in arterial pressure. Second, as the impact of neurally induced changes in pressure natriuresis on arterial pressure takes days to be fully manifested, the role of the nervous system in the genesis of hypertension cannot be predicted from acute changes in arterial pressure during ganglionic blockade. As Barrett et al have emphasized, techniques for direct assessment of renal sympathetic activity are needed to clearly elucidate the role of the sympathetic nervous system in the pathogenesis of hypertension. The new methodology described by Barrett et al for continuous monitoring of renal sympathetic nerve activity provides a novel approach for understanding neural mecha-
nisms that chronically influence the regulation of body fluid volumes and arterial pressure.

The sensitivity of pressure natriuresis can be altered by a number of extrarenal factors, including circulating Ang II and the level of renal sympathetic nerve activity (Figure). Inappropriately high plasma levels of Ang II impair pressure natriuresis, necessitating an increased level of arterial pressure for the establishment of fluid balance. Further, it is well established that the hypertension induced by Ang II is a result of its antinatriuretic effects, which are mediated both directly and indirectly by stimulation of aldosterone secretion. In addition, it has been hypothesized that the sympathetic nervous system contributes to Ang II hypertension. This hypothesis is based on a large number of acute studies indicating that Ang II acts centrally (and peripherally) to stimulate the sympathetic nervous system. Increases in renal sympathetic nerve activity, as well as increases in plasma levels of Ang II, decrease sodium excretion and impair pressure natriuresis (Figure). Therefore, if the sympathetic nervous system contributes to Ang II hypertension, one would expect increased circulating levels of Ang II to induce renal sympathoexcitation. However, a number of recent studies in chronically instrumented animals suggest just the opposite. In a study by Carroll et al., renal norepinephrine overflow, an indirect index of renal sympathetic nerve activity, was markedly reduced after 6 days of Ang II hypertension, suggesting inhibition (not activation) of the renal sympathetic nerves. Additionally, a series of experiments in dogs with surgical division of the urinary bladder into hemibladders and denervation of one kidney clearly demonstrated a relative increase in the daily rate of sodium excretion in innervated versus denervated kidneys during Ang II hypertension. Therefore, these results also indicate that high circulating levels of Ang II induce sustained renal sympathoinhibition and are entirely consistent with the direct 24-hour recordings of renal sympathetic nerve activity reported by Barrett et al. In Barrett’s study, renal sympathetic nerve activity was suppressed throughout the entire 7-day period of Ang II hypertension. Taken together, the above experimental studies suggest that suppression of renal sympathetic nerve activity plays a compensatory role in attenuating the severity of Ang II hypertension by increasing renal excretory function and shifting the pressure-natriuresis relationship to lower levels of arterial pressure. Further, these studies provide no support for the notion that the sympathetic nervous system contributes to the genesis of hypertension induced by high circulating levels of Ang II. However, as discussed next, suppression of renal sympathetic nerve activity during Ang II hypertension may be critically dependent on the integrity of the baroreflex.

As suppression of renal sympathetic nerve activity is associated with Ang II hypertension, another goal of Barrett’s study was to investigate the afferent mechanisms that might account for chronic renal sympathoinhibition during Ang II hypertension. A logical possibility is that this response is mediated by baroreflexes. On one hand, a major argument against the role of baroreflexes in the chronic regulation of body fluid volumes and arterial pressure is that they reset in the direction of the prevailing level of arterial pressure. Consequently, if baroreflexes completely reset in hypertension, renal sympathoinhibition could not be sustained through this mechanism and, therefore, baroreflexes could not possibly play a role in the chronic regulation of sympathetic activity and arterial pressure. On the other hand, although chronic resetting is a universal finding, the magnitude and time course of baroreflex resetting is not clearly established. Moreover, recent observations in chronically instrumented dogs indicate that baroreflex resetting is incomplete in Ang II hypertension. In dogs with hemibladders and one denervated kidney, the usual relative increase in the rate of sodium excretion in innervated versus denervated kidneys during Ang II hypertension in intact dogs was abolished following deafferentation of sinoaortic and cardiopulmonary receptors. In fact, after sinoaortic and cardiopulmonary deafferentation, there was a reversal in the relative rates of sodium excretion between the kidneys. That is, in the absence of baroreflexes, innervated kidneys excreted less sodium (not more as before) than denervated kidneys during Ang II infusion. This suggests that Ang II does have sustained (central?) effects to increase renal sympathetic nerve activity, but that this action of Ang II is chronically counteracted by the baroreflex (Figure). Further support for the hypothesis that the baroreflex is chronically activated in Ang II hypertension comes from a study using Fos-Li immunohistochemistry to determine activation of neurons in the central baroreflex pathway. During both acute and chronic Ang II infusion, increased arterial pressure was associated with increased Fos-Li staining in both the nucleus tractus solitarius and the caudal ventrolateral medulla, neurons that mediate baroreflex suppression of sympathoexcitatory cells in the rostral ventrolateral medulla. The concept that baroreflex suppression of renal sympathetic activity is a long-term compensatory response in Ang II hypertension receives further support from the study by Barrett et al. Temporal assessment of baroreflex function during chronic Ang II infusion demonstrated that there was no resetting of the baroreflex curves, depicting the acute relationship between changes in arterial pressure and renal sympathetic nerve activity. That is, during Ang II hypertension, the resting point of the baroreflex curve lay close to the lower plateau for renal
sympathetic nerve activity and further acute increases in arterial pressure did not result in further renal sympathoinhibition. Although these acute baroreflex curves provide only indirect evidence that baroreflexes account for the reported sustained suppression of renal sympathetic nerve activity observed during Ang II hypertension, Barrett and associates now have the tools to directly test this hypothesis. Indeed, their preliminary studies indicate that sinoaortic denervation greatly attenuates the chronic suppression of renal sympathetic nerve activity normally present in Ang II hypertension.14

The importance of Barrett’s study goes far beyond elucidating the neural mechanisms that influence Ang II hypertension. With the ability to directly monitor chronic changes in renal sympathetic nerve activity, these investigators now have unique methodology to more clearly determine the role of the nervous system in the pathogenesis of multiple forms of hypertension. It will be especially important to determine whether baroreflex suppression of renal sympathetic nerve activity is a compensatory mechanism that is prevalent in other forms of hypertension, as well as hypertension induced by Ang II. If so, this would lend credence to the notion that progressive baroreflex dysfunction during the evolution of hypertension is a ubiquitous mechanism that contributes to sustained increments in sympathetic activity and arterial pressure.

References

KEY WORDS: angiotensin ▪ hypertension ▪ baroreflex ▪ sympathetic nervous system ▪ renal nerves
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