There has been a long-standing interest in the possibility that activation of the sympathetic nervous system may contribute to the hypertension induced by angiotensin II (Ang II). This hypothesis is commonly assessed by chronically infusing Ang II and using various tests to determine the sympathetic component to the increase in arterial pressure. Despite a multitude of studies, it is still unclear whether the sympathetic nervous system plays an important role in mediating this form of hypertension. Why the uncertainty? This is largely because of the varied and often times ambiguous experimental approaches to address this issue. More specifically, the uncertainty arises from studies using different animals, different sites of Ang II administration (central, intravenous, and subcutaneous), different rates of Ang II infusion, and different time courses of study. In addition, in most studies, measures of Ang II levels have not been made, making it difficult to determine whether reported effects are physiological, pathophysiological, or pharmacological. In addition, precise measures of sympathetic activity must be made before specific inferences regarding its role in Ang II hypertension can be made. Beyond these considerations, there are additional limitations that impede a clear resolution of this topic.

The kidneys play a primary role in mediating long-term changes in arterial pressure, and, therefore, neurogenic mechanisms of hypertension must in some way impair renal excretory function. Because the renal nerves provide an obvious link between alterations in central sympathetic outflow and renal excretory function (Figure), an understanding of the role of neurogenic mechanisms in the maintenance of hypertension depends on measurement of renal sympathetic nerve activity (RSNA) and assessment of the influence of this sympathetic outflow on steady-state levels of arterial pressure. Unfortunately, technical limitations often preclude these chronic determinations. In this regard, the Circulatory Control Laboratory at the University of Auckland (Auckland, New Zealand) has provided unique insight into neurogenic mechanisms of hypertension by developing technology to directly measure RSNA continuously in conscious animals over long time periods (several weeks). To provide greater insight into a possible role of the sympathetic nervous system in mediating Ang II hypertension, they report in the current issue of Hypertension continuous radiotelemetric recordings of RSNA in rabbits chronically infused with Ang II while maintained on a high-salt intake.

An alternate approach that has been used successfully in experimental and clinical studies to determine regional specific sympathetic activity, including RSNA, has been to measure the spillover of norepinephrine (NE) to plasma. In regard to the kidneys, renal NE spillover captures a “snapshot” of RSNA at any given point in time. In clinical studies, measurements of organ-specific NE spillover have shown that the control of sympathetic activity to organs is differentially regulated, and the progression of primary hypertension is associated with early and sustained activation of RSNA. The importance of this latter observation has been highlighted recently by studies showing that bilateral renal denervation and chronic suppression of RSNA by baroreflex activation have appreciable blood pressure–lowering effects in human subjects with resistant hypertension and in animals with clinically relevant hypertension.

The ability to directly measure RSNA continuously by telemetry from chronically implanted electrodes placed around the renal nerves has been a tour de force of the Circulatory Control Laboratory at the University of Auckland. Using this technology, they identified previously the confounding effect of sustained baroreflex activation in studies designed to investigate the role of sympathetic activation in mediating Ang II hypertension. In rabbits subjected to a rate of Ang II infusion that had immediate pressor effects, these investigators clearly showed marked suppression of RSNA throughout a 7-day period of Ang II hypertension. Furthermore, when this study was repeated in another group of rabbits after sinoaortic denervation, suppression of RSNA did not occur, indicating that this renal sympathoinhibition was mediated by baroreflex activation attributed to the increase in arterial pressure. However, because RSNA did not increase after sinoaortic denervation, this study did not support the hypothesis that Ang II can act centrally to increase RSNA even in the absence of sympathetic inhibition by baroreflex activation. These elegant studies are consistent with earlier findings in dogs made hypertensive by chronic infusion of Ang II hypertension. In one of these studies, the snapshot technology provided by measurement of renal NE spillover demonstrated sustained suppression of renal NE spillover in chronic Ang II hypertension. Subsequent studies by this same group further supported the hypothesis that the sustained suppression of RSNA was mediated by chronic...
activation of the baroreflex and that inhibition of RSNA has sustained effects to increase renal excretory function during Ang II hypertension.8,9 Taken together, these complementary techniques for determination of RSNA suggested that chronic baroreflex suppression of RSNA increases renal excretory function and, therefore, may serve as a compensatory mechanism to attenuate the severity of hypertension.

Although a few observations suggest that high salt intake may potentiate the central sympathoexcitatory actions of Ang II, there are no data that indicate that the combination of high salt and Ang II leads to long-term increases in RSNA. In fact, in a study in rats maintained on a high-salt diet and chronically infused with Ang II, Yoshimoto et al10 reported just the opposite. Confirming the observations indicated above in rabbits and dogs, these investigators reported that a pressor infusion of Ang II in combination with high salt intake decreased RSNA.

Based on their past studies that RSNA did not increase during chronic infusion of Ang II in rabbits maintained on a normal salt intake even after sinoaortic denervation,7,8 Guild et al1 further investigated the influence of high salt intake on sympathetic outflow to the kidneys during a relatively low rate of Ang II infusion. By using a relatively low infusion rate of Ang II that slowly increased arterial pressure over a 21-day period, the strategy was to minimize any potential effects of baroreflex activation that might counteract the central sympathoexcitatory actions of Ang II. The results, published in the present issue of Hypertension, showed that there were no changes in RSNA as arterial pressure gradually increased during the first half of the 21-day Ang II infusion period. However, after stabilization of hypertension around day 11, RSNA increased several days later. Thus, by presumably allowing sufficient time for appreciable baroreceptor resetting and minimizing the confounding effects of baroreflex activation, this study provides the best evidence to date that, in this model of hypertension, the combination of high salt intake and Ang II in some way leads to increased sympathetic drive to the kidneys. Guild et al1 concluded that the increase in RSNA could possibly contribute to the hypertension.

However, closer inspection of the data from this and previous studies provides a different perspective. Beginning on day 11 when the hypertension was stable, there was a further increase in salt consumption, and, yet, the severity of hypertension did not intensify. Because Ang II hypertension is salt sensitive, arterial pressure should have increased further, particularly during the subsequent increase in RSNA. Possible explanations to account for the unchanged arterial pressure are the activation of counteracting natriuretic mechanisms and that increased RSNA does not play a role in the maintenance of the hypertension. This latter possibility is consistent with an earlier study from this laboratory demonstrating that bilateral renal denervation failed to attenuate the severity of hypertension produced by this same infusion rate of Ang II in rabbits maintained on the same high-salt intake.11 An additional relevant point is the following. As indicated above, although pressor rates of Ang II infusion are associated with baroreflex suppression of RSNA, suggesting a compensatory response that may diminish the severity of the hypertension, sinoaortic denervation does not exacerbate the severity of Ang II hypertension.8,12 Furthermore, even chronic suppression of central sympathetic outflow by continuous electric stimulation of the carotid baroreflex has minimal long-term blood pressure–lowering effects in dogs made hypertensive by chronic infusion of Ang II.13 Thus, taken in the context of the importance of the kidneys in long-term control of arterial pressure, the overall message from the studies summarized above is that neither increases nor decreases in RSNA, to the extent that they may occur, significantly influence the final level of arterial pressure in this model of Ang II hypertension. Rather, they suggest that the direct and indirect (through stimulation of aldosterone secretion) antinatriuretic effects of Ang II are dominant in determining the severity of hypertension (Figure).

The value of this study extends beyond unraveling the complex interactions among salt, the sympathetic nervous system, and Ang II in the progression of this simple form of Ang II hypertension. Of broader significance, this study suggests that continuous time-dependent determinations of renal specific sympathetic outflow will continue to offer novel insights into the role of the nervous system and its interactions with the kidneys in long-term control of arterial pressure.

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