CALL FOR PAPERS | Baroreflex Control of Sodium Excretion and Arterial Pressure

Recent insights into the interactions between the baroreflex and the kidneys in hypertension

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Lohmeier, Thomas E., Drew A. Hildebrandt, Susan Warren, Paul J. May, and J. Thomas Cunningham. Recent insights into the interactions between the baroreflex and the kidneys in hypertension. Am J Physiol Regul Integr Comp Physiol 288: R828–R836, 2005; doi:10.1152/ajpregu.00591.2004.—Recent findings in chronically instrumented animals challenge the classic concept that baroreflexes do not play a role in the chronic regulation of arterial pressure. As alterations in renal excretory function are of paramount importance in the chronic regulation of arterial pressure, several of these recent studies have focused on the long-term interactions between the baroreflex and the kidneys during chronic perturbations in arterial pressure and body fluid volumes. An emerging body of evidence indicates that the baroreflex is chronically activated in several experimental models of hypertension, but in most cases, the duration of these studies has not exceeded 2 wk. Although these studies suggest that the baroreflex may play a compensatory role in attenuating the severity of the hypertension, possibly even in primary hypertension with uncertain causes of sympathetic activation, there has been only limited assessment of the quantitative importance of this interaction in the regulation of arterial pressure. In experimental models of secondary hypertension, baroreflex suppression of renal sympathetic nerve activity is sustained and chronically promotes sodium excretion. This raises the possibility that the renal nerves may be the critical efferent link for baroreceptor-induced suppression of central sympathetic output through which long-term compensatory reductions in arterial pressure are produced. This contention is supported by strong theoretical evidence but must be corroborated by experimental studies. Finally, although it is now clear that pressure-induced increases in baroreflex activity persist for longer periods of time than previously suggested, studies using new tools and novel approaches and extending beyond 2 wk of hypertension are needed to elucidate the true role of the baroreflex in the pathogenesis of clinical hypertension.

renal nerves; sympathetic nervous system; baroreceptors; sodium excretion; blood pressure; angiotensin

THERE IS A LONG-STANDING INTEREST in the mechanisms that influence sympathetic activity and the role of the sympathetic nervous system in the pathogenesis of cardiovascular disease. In regard to arterial pressure control, it is well established that the baroreflex is a powerful buffering mechanism that counteracts short-term fluctuations in arterial pressure. However, the role of the baroreflex in long-term control of arterial pressure is unclear and has been a topic of interest and debate for many years. Numerous experimental and clinical studies have reported altered baroreflex function in several forms of hypertension and in sodium-retaining states such as heart failure (9, 14, 16, 48). However, whether impaired baroreflex function results in a higher level of sympathetic activity that contributes to the abnormal regulation of sodium excretion and arterial pressure in these disease states is merely conjecture at the present time. This uncertainty is due to the paucity of techniques available to assess the long-term effects of the baroreflex on sympathetic activity and organ function. This article will focus on recent chronic studies in conscious animals that have provided new insight into the role of baroreflexes in long-term control of sympathetic activity and sodium excretion in hypertension.

RESETING OF THE BAROREFLEX AND SINOAORTIC DENERVATION

Two primary observations support the contention that baroreflexes do not play a role in long-term control of arterial pressure: 1) the baroreflex resets and 2) baroreceptor deafferentation (sinoaortic denervation; SAD) produces little or no sustained increase in arterial pressure. The basis for these observations, which discount the importance of the baroreflex in long-term control of arterial pressure, has been presented in detail previously (3, 7, 36) and need not be reiterated in this article. However, a few general comments are warranted. In response to a sustained increase in arterial pressure, the baroreflex resets in the direction of the new ambient pressure. In hypertensive states, this diminishes the initial inhibition of sympathetic activity induced by the baroreflex and, consequently, decreases the ability of the baroreflex to serve as a long-term compensatory mechanism for the control of arterial pressure. This resetting preserves the ability of the baroreflex to buffer acute fluctuations in arterial pressure around the new elevated pressure. Baroreflex resetting includes alterations in both baroreceptor activity and alterations in afferent processing within the central nervous system (6, 46). Unfortunately, because of technical limitations that preclude long-term recordings of nerve activity in conscious animals, virtually all information regarding baroreflex resetting has come from acute studies in anesthetized animals. Although considerable baroreflex resetting occurs acutely, it is incomplete, and the time course and extent of chronic baroreflex resetting have not been determined with any certainty. Nonetheless, it has been suggested from recordings of baroreceptor afferent activity in anesthetized rats that the process of baroreflex resetting is complete within 48 h of a step increase in arterial pressure (24). If baroreflex resetting is truly complete in chronic hypertension, then the baroreflex could not possibly suppress sympathetic activity and diminish the severity of hypertension. How-
ever, recent findings, discussed below, do not support this contention.

Other than the issue of baroreflex resetting, the argument often made to discount the importance of baroreflexes in chronic hypertension is that sympathetic activity and arterial pressure increases in response to SAD are only acute and are not sustained chronically. The presumption often made is that if complete abolition of baroreceptor afferent input into the central nervous system is unable to produce chronic hypertension, then it is unlikely that natural alterations in baroreceptor activity could have long-term effects on sympathetic activity that impact arterial pressure. It should be recognized, however, that because of technical limitations, temporal changes in sympathetic activity after SAD have not been established with certainty. Thus it is possible that SAD could result in long-term increments in sympathetic activity, but little or no hypertension, because of nonneural compensations that reduce arterial pressure. Additionally, because of the plasticity of the nervous system, the central reorganization of the baroreflex circuitry that occurs in response to transection of baroreceptor afferents may alter central neural control of the cardiovascular system (5, 20, 45). For example, in rats with long-standing SAD, there is a marked increase in GABA-mediated suppression of neurons in the nucleus tractus solitarius (NTS), the primary termination site of baroreceptor afferents (20). Consequently, this central inhibitory input may effectively eliminate the tonic role of the NTS in cardiovascular regulation and, in so doing, diminish the increase in sympathetic activity normally associated with decreased baroreceptor afferent input into the NTS. Furthermore, recent findings by Thrasher (47) challenge the relevance of SAD as a model for understanding the role of baroreflexes in the chronic regulation of the cardiovascular system. In this study, chronically instrumented dogs were subjected to occlusion of the common carotid artery proximal to the carotid sinus. Chronic unloading of carotid baroreceptors, which, like SAD, decreases baroreceptor input into the NTS, produced sustained (7 days) hypertension associated with sodium retention and increases in heart rate and plasma renin activity (PRA). Such responses indicated sustained increases in sympathetic activity to the heart and kidneys. This novel approach to studying baroreflex function clearly demonstrates that the long-term arterial pressure (and presumably the sympathetic) response to chronic unloading of baroreceptors differs markedly from the response to baroreceptor deafferentation. Thrasher’s study, along with several other recent studies discussed below, has provided new insight into the role of baroreflexes in long-term control of arterial pressure and sympathetic activity.

RENAL NERVES AS THE MEDIATOR OF THE LONG-TERM EFFECTS OF THE BAROREFLEX ON ARTERIAL PRESSURE

Long-term regulation of arterial pressure is closely linked to volume homeostasis through the renal body fluid feedback mechanism (18). A key feature of the renal body fluid feedback control system is pressure natriuresis or the intrinsic ability of the kidneys to respond to alterations in arterial pressure by altering the renal excretion of salt and water. In all forms of hypertension, pressure natriuresis is impaired, necessitating an increase in arterial pressure to achieve fluid balance (18). Importantly, neurally induced changes in peripheral resistance and cardiac output, which are essential for rapid regulation of arterial pressure, do not alter pressure natriuresis chronically, unless they are also associated with sustained changes in renal excretory function (as discussed in CHRONIC BILATERAL ELECTRICAL STIMULATION OF THE CAROTID BAROREFLEX and illustrated in Figures 7 and 8). Thus most studies of baroreflex function have provided limited insight into the role of baroreflexes in long-term regulation of arterial pressure because they have emphasized acute alterations in systemic hemodynamics that may have little to do with chronic changes in renal excretory function. It is unclear from such acute studies whether baroreflex-mediated changes in sympathetic activity have long-term effects on pressure natriuresis that are sufficient to chronically alter arterial pressure.

One way in which the baroreflex could alter pressure natriuresis and contribute to long-term regulation of arterial pressure is by producing sustained changes in renal sympathetic activity (9, 26, 27, 48). Chronic increases in renal adrenergic activity shift the pressure natriuresis relationship to a higher level of arterial pressure (27, 42, 48), and increased renal sympathetic nerve activity is a common feature of primary hypertension (10, 11, 15, 19, 43). Conversely, renal denervation leads to long-term reductions in arterial pressure (21, 28). Furthermore, it is well established from acute studies that baroreflex-mediated changes in renal sympathetic nerve activity influence pressure natriuresis and play a role in the acute regulation of body fluid volume (7, 9, 48). However, the critical issue here is whether baroreflex-mediated changes in sympathetic activity in the kidneys are sustained chronically and whether the resultant changes in renal sympathetic nerve activity alter pressure natriuresis during long-term perturbations in body fluid volume and arterial pressure.

THE RENAL NERVES CHRONICALLY PROMOTE SODIUM EXCRETION IN SECONDARY HYPERTENSION

Primary hypertension is often associated with activation of the sympathetic nervous system, which includes increased sympathetic outflow to the kidneys (10, 11, 15, 19, 43). However, relatively little is known about the factors that chronically control the level of renal sympathetic nerve activity in hypertension. Furthermore, as secondary hypertension is usually not associated with increased sympathetic activity, less attention has been given to the determinants of sympathetic activity and to neural control of renal function and arterial pressure in this form of hypertension. One of our first clues that baroreflexes might have long-term effects on sodium excretion in hypertension came from studies in dogs with surgical division of the urinary bladder into hemi bladders and denervation of one kidney (34). The denervated kidney initially shows increased sodium excretion, but following compensation by unknown mechanisms, the sodium excretion rates in the two kidneys are approximately equal. In the chronic state, this is a powerful model for exposing a functional role of the renal nerves because both kidneys are exposed to the same perfusion pressure and hormonal influences. Consequently, any differences in sodium excretion between the kidneys can be attributed to the effects of the renal nerves on renal excretory function. In this case, the sympathomimetic norepinephrine (NE) was chronically infused (34). Figure 1 illustrates changes in the relative 24-h excretion rates of sodium from denervated
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Fig. 1. Chronic effects of norepinephrine (NE) infusion on plasma NE concentration (conc.), mean arterial pressure (MAP), and the relative 24-h excretion rates of sodium from denervated (DEN) and innervated (INN) kidneys (DEN/INN). *P < 0.05 vs. control values before NE infusion. [From Lohmeier et al. (34)].

(DEN) and innervated (INN) kidneys in dogs after 4–5 days of progressively higher rates of NE infusion. Chronic infusion of NE at rates up to 100 ng·kg⁻¹·min⁻¹ produced increments in plasma levels of NE as high as ~3,000 pg/ml or ~30 times normal. However, these pathophysiological levels of NE failed to produce significant chronic changes in either mean arterial pressure (MAP) or the relative excretion rates of sodium from denervated and innervated kidneys (DEN/INN). However, at the highest rate of NE infusion (200 ng·kg⁻¹·min⁻¹), which increased plasma NE concentration to ~70 times normal, the DEN/INN for sodium excretion decreased markedly in association with a chronic increase in MAP of 10–15 mmHg. One interpretation for the substantially greater rate of sodium excretion from innervated vs. denervated kidneys in response to supraphysiological plasma levels of NE is renal denervation supersensitivity (9). Another more interesting possibility to account for the decrease in the DEN/INN for sodium excretion under steady-state conditions is that chronic renal sympathoinhibition, as well as the attendant loss of sodium, is a long-term compensatory response to the hypertension.

Compared with the denervated kidney, a higher rate of sodium excretion from the innervated kidney also occurs in response to reflex inhibition of renal sympathetic nerve activity during both acute and chronic expansion of extracellular fluid volume (9, 29, 44, 48). However, with regard to the split bladder preparation in combination with unilateral denervation, it is a conundrum why kidneys with intact innervation, albeit with suppressed renal sympathetic activity, excrete more sodium chronically than kidneys totally devoid of innervation. Thus there appears to be a permanent alteration in excretory function in denervated kidneys that limits sodium excretion. The impaired ability of denervated kidneys to modulate sodium excretion is exposed during either acute or chronic volume expansion and/or hypertension, although the factors that account for this abnormality are unknown.

Formally stated, the hypothesis proposed is that the baroreflex responds to hypertension by chronically suppressing renal sympathetic nerve activity, thus increasing sodium excretion in a compensatory fashion. Studies in patients with secondary hypertension are also consistent with this hypothesis. In a clinical study analogous to the NE infusion experiment, intramuscular postganglionic sympathetic nerve activity was assessed by microneurography in subjects with pheochromocytoma (17). In these patients with hypertension induced by high circulating levels of catecholamines, central sympathetic outflow was actually decreased. Additionally, intramuscular sympathetic nerve activity is suppressed in patients with primary aldosteronism (38), another form of secondary hypertension, providing further support for the above hypothesis. However, another possibility is that suppressed sympathetic activity may be secondary to low circulating levels of ANG II (as discussed in BAROREFLEX SUPPRESSION OF RENAL SYMPATHETIC NERVE ACTIVITY PROMOTES SODIUM EXCRETION IN ANG II HYPERTENSION). In contrast to pheochromocytoma and primary aldosteronism, results from studies using microneurography in patients with renovascular hypertension are inconsistent and have indicated either increased or normal sympathetic activity (14, 15, 22, 38). The basis for these inconsistent findings may lie in the interaction between circulating levels of ANG II and the duration of hypertension. High circulating levels of ANG II, when present, may directly increase sympathetic activity (3, 12, 49). On the other hand, if resetting is incomplete, sustained activation of the baroreflex would have the opposite effect on the sympathetic nervous system. The various sympathetic responses recorded in renovascular hypertension may thus reflect the net temporal effect of these two opposing forces.

BAROREFLEX SUPPRESSION OF RENAL SYMPATHETIC NERVE ACTIVITY PROMOTES SODIUM EXCRETION IN ANG II HYPERTENSION

In view of the inconsistent changes in intramuscular sympathetic nerve activity in renovascular hypertension and the well-established stimulatory effects of ANG II on the sympathetic nervous system, we reasoned that the ANG II infusion model of hypertension could provide an especially interesting test of the chronic baroreflex suppression hypothesis (31). Therefore, in dogs with the split bladder preparation in combination with unilateral renal denervation, ANG II was infused for 5 days at a rate (5 ng·kg⁻¹·min⁻¹) that produces an ~3–5 fold increase in plasma levels of ANG II (31). If the direct sympathoexcitatory effects of ANG II contribute substantially to ANG II hypertension (12) and the renal nerves are a critical mediator of neurally induced hypertension, then one would expect a lower rate of sodium excretion from the innervated, as opposed to the denervated, kidney during ANG II infusion. In fact, just the opposite response occurred. In dogs with intact baroreceptor afferents, MAP increased 30–35 mmHg during ANG II infusion (Fig. 2). Heart rate tended to decrease, but the changes were not statistically significant (Fig. 2). During ANG II infusion, total sodium excretion (from both kidneys) decreased for 1–2 days before sodium balance was subsequently achieved at an elevated MAP (Fig. 3). Moreover, as in NE hypertension (Fig. 1), the hypertension induced by ANG II infusion in dogs with intact baroreceptor afferents (Fig. 2) was associated with a relative increase in sodium excretion from the innervated vs. the
More germane to the focus of this article, following the absence of baroreflexes (Fig. 2). This suggests that there was prolonged activation of cardiac sympathetic nerves. In contrast to the baroreflex intact state, neither the degree of sodium retention (as reflected by total sodium excretion from both kidneys, Fig. 3) nor the severity of hypertension was greater following CPD+SAD because of the pronounced pressure natriuresis in denervated kidneys. A similar pattern of sympathetic activation was reported recently in response to acute infusion of ANG II in conscious rats (49). In the intact state, both heart rate and lumbar sympathetic nerve activity decreased in association with the acute rise in arterial pressure induced by ANG II infusion. In marked contrast, in chronic SAD rats, both lumbar sympathetic nerve activity and heart rate increased during ANG II infusion. Furthermore, direct recordings of renal sympathetic nerve activity in rabbits demonstrate that SAD greatly attenuates the chronic suppression of renal sympathetic nerve activity normally present in ANG II hypertension (2). Taken together, these studies illustrate the importance of baroreflex activation in opposing the direct sympathoexcitatory actions of ANG II. Moreover, the above chronic experimental studies are especially important in regard to long-term control of arterial pressure because they indicate that baroreflex suppression of renal sympathetic nerve activity, a determinant of renal excretory function (pressure natriuresis), is a sustained response for at least 10 days of ANG II hypertension. This contention is not supported by an earlier investigation in which the increase in MAP induced by ANG II was compared in separate groups of dogs with and without intact baroreflexes (8). In this study, the hypertensive response to chronic ANG II infusion was not significantly different in dogs with intact baroreflexes compared with dogs with SAD. However, the actual extent to which baroreflex-mediated suppression of renal sympathetic nerve activity attenuates ANG II and reninresponse exactly opposite to that observed when the baroreflexes were intact (Fig. 3). Thus, in the absence of baroreflexes, elevated plasma levels of ANG II chronically decreased renal excretory function more in innervated than denervated kidneys, presumably by increasing renal sympathetic nerve activity. However, compared with the baroreflex intact state, neither the degree of sodium retention (as reflected by total sodium excretion from both kidneys, Fig. 3) nor the severity of hypertension was greater following CPD+SAD because of the pronounced pressure natriuresis in denervated kidneys. 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Furthermore, in a subsequent investigation, the marked and sustained decrease in the DEN/INN for sodium excretion was found to persist for at least 10 days of ANG II infusion, the duration of the study (32). These findings suggest that renal sympathetic nerve activity is chronically suppressed in hypertension induced by ANG II, as well as by NE. This interpretation of the renal functional response to ANG II is entirely consistent with an earlier report in chronically instrumented dogs, indicating decreased renal NE spillover (an indirect index of renal sympathetic nerve activity) during long-term ANG II infusion (4). Moreover, very recently, the renal sympathetic response to ANG II hypertension has been confirmed by direct recordings of renal sympathetic nerve activity in rabbits (1). Using elegant technology to directly record renal sympathetic nerve activity 24 h/day, Barrett and colleagues (1) demonstrated distinct suppression of renal sympathetic nerve activity throughout the entire 7-day period of hypertension induced by ANG II infusion.

Subjecting split bladder/unilateral renal denervation dogs to deafferentation of their cardiopulmonary and arterial baroreceptors (CPD+SAD) has provided insight into the afferent mechanisms that lead to chronic suppression of renal sympathetic activity in ANG II hypertension (31). Baroreceptor denervation was achieved by stripping the vagus in the thorax and the adventitia in the area of the carotid bifurcation. After determination of the hemodynamic and renal excretory responses to ANG II infusion in the intact state, as discussed above, the ANG II infusion was repeated in the same dogs after CPD+SAD (Figs. 2 and 3). In contrast to the baroreflex intact state, in which there was little change in heart rate during ANG II hypertension, there was sustained tachycardia throughout ANG II infusion in the absence of baroreflexes (Fig. 2). This suggests that there was prolonged activation of cardiac sympathetic nerves. More germane to the focus of this article, following CPD+SAD, the DEN/INN for sodium excretion actually increased substantially during ANG II infusion (Fig. 3), a
other forms of hypertension remains to be determined and merits further investigation.

**SUSTAINED ACTIVATION OF NEURONS IN THE CENTRAL BAROREFLEX PATHWAY IN BOTH PRIMARY AND SECONDARY HYPERTENSION**

Further evidence that activation of the baroreflex is a general response in hypertension comes from studies employing Fos-like (Fos-Li) immunohistochemistry to determine sites of neuronal activation in the central baroreflex pathway. Studies using Fos-Li immunohistochemistry have clearly identified medullary neurons of the baroreflex that are activated in response to acute increases in arterial pressure induced by pressor agents, including ANG II (25, 33, 40, 41). However, few studies have used this methodology to identify sites of neural activation in chronic hypertension. To further test the concept that the baroreflex is chronically activated in ANG II hypertension, ANG II was infused (5 ng·kg⁻¹·min⁻¹) both acutely and chronically in dogs, and Fos-Li immunohistochemistry was used to determine activation of neurons in the central baroreflex pathway (33). During acute ANG II infusion, there were significant increases in Fos-Li staining in the NTS and caudal ventrolateral medulla (CVLM) but no increase in neuronal staining in the rostral ventrolateral medulla (RVLM). As baroreflex suppression of sympathoexcitatory neurons is mediated by activation of neurons in the NTS and CVLM, these acute responses were expected and confirmed the findings of others in both the rat and rabbit (25, 40). More importantly, this same pattern of central activation was observed during chronic (5 days) ANG II infusion in dogs (Fig. 4). Therefore, these findings provide further support for the hypothesis that baroreflex suppression of renal sympathetic activity is a long-term compensatory response in ANG II hypertension. It should be noted that in contrast to our observations, increased Fos-Li staining in the RVLM was reported after 18 h of a 10-fold higher infusion rate of ANG II (50 ng·kg⁻¹·min⁻¹) in the rat (25). This was interpreted to indicate a centrally mediated increase in sympathetic outflow with chronic ANG II infusion.

Although the above studies in dogs clearly indicate sustained activation of the baroreflex for up to 10 days of ANG II hypertension, they did not reveal the influence of the baroreflex on sympathetic activity in more long-standing hypertension. Thus we hypothesized that if sustained activation of the baroreflex is a common long-term compensatory response in hypertension, then the canine model of obesity hypertension should also produce increased activation of neurons that are part of the central baroreflex pathway (35). This clinically relevant model of hypertension presents an interesting challenge to this hypothesis because, unlike ANG II hypertension, obesity hypertension is not associated with decreased renal sympathetic nerve activity. Rather, there is strong evidence, both in experimental animals and human subjects, that renal sympathetic nerve activity is increased in obesity hypertension (10, 11, 19, 43). As illustrated in Fig. 4, the number of Fos-Li positive cells in the NTS and CVLM was 3–5 times greater in obese dogs fed a high-fat diet for ~6 wk than in controls. This response was qualitatively similar to that observed during chronic ANG II hypertension and suggests the neurons subserving the baroreflex were chronically activated in obesity, as well as ANG II hypertension. However, there was one notable difference between ANG II and obesity hypertension. The obese dogs also demonstrated increased staining of RVLM neurons. As spinoally projecting neurons in the RVLM provide tonic excitatory drive to sympathetic preganglionic neurons that control sympathetic output to the peripheral circulation, the increased Fos-Li staining in RVLM neurons is consistent with reports of increased sympathetic activation in obesity hypertension. Similarly, increased Fos immunoreactivity has also been reported in RVLM neurons of spontaneously hypertensive rats, another animal model of hypertension characterized by increased sympathetic activity (37). Taken together, these results suggest that sympathoexcitatory inputs into the RVLM predominate over the inhibitory effects of the baroreflex in obesity hypertension. Nonetheless, these results support the hypothesis that the baroreflex tends to suppress renal sympathetic activity in primary, as well as secondary hypertension. Furthermore, as baroreflex suppression of sympathetic activity is progressively impaired during the evolution of obesity hypertension (16), baroreflex dysfunction may play an increasingly significant role in contributing to further increments in sympathetic activity and arterial pressure in the more advanced stages of this prevalent form of hypertension.

**CHRONIC BILATERAL ELECTRICAL STIMULATION OF THE CAROTID BAROREFLEX**

The studies discussed above are especially important because they suggest that baroreflexes do not completely reset and are instead chronically activated in hypertension. Furthermore, suppression of renal sympathetic nerve activity and attendant increments in renal excretory function are sustained responses to baroreflex activation that may play a key role in mediating the antihypertensive effects of prolonged baroreflex activation. Although increased renal sympathetic nerve activity is prevalent in primary hypertension (10, 11, 15, 43), sustained baroreflex activation may still act to attenuate the sympathetic hyperactivity to the kidneys. However, additional studies are needed to provide direct support for this hypothesis and to assess the quantitative importance of sustained baroreflex activation in attenuating the severity of different forms of hypertension.
We have recently established a novel approach to quantitatively investigate both the time dependency and underlying mechanisms of the blood pressure-lowering response to prolonged baroreflex activation (30). As these goals would be virtually impossible to achieve by controlling pressure in an isolated carotid sinus preparation, we elected to electrically activate the carotid sinus. This was achieved by chronically implanting electrodes around both carotid sinuses of dogs to electrically activate them. In studies to date, a pulse generator has been programmed at stimulation parameters that likely activate both A- and C-type fibers at frequencies near maximal recorded discharge rates and at intensities that approximate a maximal hypotensive response. As direct activation of sensory neurons bypasses the baroreceptor pressure-encoding step, an additional advantage of this technique is that it permits investigation into the central processing of baroreceptor input. It was reasoned that if the carotid baroreflex does have significant long-term antihypertensive effects, prolonged electrical activation of the afferent limb of this reflex should produce appreciable long-term reductions in arterial pressure.

As illustrated in Fig. 5, the MAP response to prolonged activation of the carotid baroreflex was impressive in both magnitude and duration. Immediately following baroreflex activation, MAP decreased ~25 mmHg (Fig. 6) in association with modest reductions in heart rate (30). These responses reflect the reciprocal effects of baroreflex activation on the sympathetic and parasympathetic nervous systems. More importantly, the marked hypotensive response to carotid sinus stimulation was sustained throughout the entire 7 days of baroreflex activation. Reductions in MAP and plasma NE concentration occurred in parallel during chronic activation of the carotid baroreflex, indicating sustained suppression of the sympathetic nervous system. Additionally, the chronic increase in baroreceptor afferent input during electrical stimulation of the carotid sinus produced sustained activation of neurons in nuclei contributing to the baroreflex pathway (Fig. 4). These results support the studies discussed above in suggesting that the baroreflex has sustained suppressive effects on sympathetic activity and so may serve as a compensatory mechanism that attenuates the severity of hypertension.

But how does prolonged baroreflex activation lead to chronic reductions in arterial pressure? As the kidneys play a central role in long-term regulation in arterial pressure, the chronic maintenance of sodium balance at a reduced arterial pressure (Fig. 5) indicates that prolonged activation of the carotid baroreflex produced a sustained enhancement of renal excretory function, shifting pressure natriuresis to a lower pressure level (18, 27). While baroreflex-mediated reductions in the peripheral resistance and cardiac pumping account for the acute fall in arterial pressure (Fig. 6), computer analyses of the circulation (Figs. 7 and 8; Ref. 18) indicate that these responses, even if sustained, would have little long-term effect on arterial pressure in the absence of an increase in renal excretory function. In the computer simulations illustrated in Figs. 7 and 8, a chronic α- and β-adrenergic blockade served to mimic the effects of prolonged baroreflex activation. The chronic changes in MAP and sodium excretion in response to global adrenergic blockade (Fig. 7) were similar to those achieved experimentally during prolonged baroreflex activation (Fig. 5). The transient fall in sodium excretion on day 1 of baroreflex activation can be attributed to the acute fall in arterial pressure. However, because of the sustained influence of adrenergic blockade to increase renal excretory function, sodium balance was eventually achieved at a substantially

**Fig. 5.** Effects of prolonged bilateral electrical activation of the carotid baroreflex on MAP and the daily excretion rate of sodium. *P < 0.05 vs. control. [Adapted from Ref. 30].

**Fig. 6.** A representative tracing illustrating the acute MAP response to bilateral electrical activation of the carotid baroreflex.

**Fig. 7.** Computer simulations of the changes in MAP and urinary sodium excretion in response to blockade of α- and β-adrenergic receptors throughout the entire systemic circulation.
activity induced by electrical stimulation of the carotid sinus inhibited during reflex suppression of renal sympathetic nerve chronically instrumented dogs. Specifically, renin secretion is the baroreflex. This view is supported by acute observations in inhibitory effect on renin secretion during chronic activation of activity may be the primary mechanism to account for the sustained influence renin release, decreased renal sympathetic nerve activ-

In marked contrast, sustained reductions in adrenergic activity throughout the circulation except the kidneys (global except kidneys) resulted in only acute reductions in arterial pressure (Fig. 8). This is because in the absence of decreased renal adrenergic activity, reductions in arterial pressure caused the kidneys to retain sufficient amounts of salt and water until arterial pressure returned to control. Thus extrarenal decreases in peripheral resistance may be associated with prolonged baroreflex-mediated hypotension, but such responses do not appear to be the cause of the sustained fall in arterial pressure. These simulations support the view that the renal nerves play a critical role in increasing renal excretory function and mediating long-term reductions in arterial pressure during prolonged activation of the baroreflex. Importantly, the procedure for prolonged electrical activation of the carotid baroreflex will permit direct experimental evaluation of these important theoretical analyses. Specifically, if prolonged activation of the baroreflex is able to produce a sustained fall in arterial pressure in dogs with chronic bilateral renal denervation, this would indicate that mechanisms other than suppression of renal sympathetic nerve activity contribute to the long-term blood pressure lowering effects of the baroreflex.

With further regard to the mechanisms that mediate the hypotensive response to baroreflex activation, a potentially important finding in our initial study was that PRA and plasma aldosterone concentration did not increase concomitantly with the fall in MAP (30). Because reductions in MAP of the magnitude of 20–25 mmHg normally stimulate renin secretion (23, 39, 50), the absence of an increase in PRA suggests an inhibitory influence on renin release during prolonged baroreflex activation. As alterations in renal adrenergic activity influence renin release, decreased renal sympathetic nerve activity may be the primary mechanism to account for the sustained inhibitory effect on renin secretion during chronic activation of the baroreflex. This view is supported by acute observations in chronically instrumented dogs. Specifically, renin secretion is inhibited during reflex suppression of renal sympathetic nerve activity induced by electrical stimulation of the carotid sinus nerve (39). Furthermore, as the renin-angiotensin-aldosterone system has powerful long-term effects on sodium excretion and arterial pressure, neurally mediated suppression of renin secretion may be a critical determinant of the long-term hypotensive response to baroreflex activation. That is, in the absence of the renal sympathoinhibitory effect on renin secretion, the hypotensive response to baroreflex activation would be greatly diminished. Additional experiments are needed to test this hypothesis.

SUMMARY AND CONCLUSIONS

In recent years, results from a number of experimental studies in chronically instrumented animals, as well as hints from clinical observations in patients with secondary hypertension, have challenged the older contention that baroreflexes are not chronically activated and have no functional role in the chronic regulation of arterial pressure. Although experimental studies indicate that the resetting of the baroreflex is incomplete and functional effects of the baroreflex persist for no less than 2 wk of hypertension, studies of longer duration are needed to clearly demonstrate a chronic role of the baroreflex in the pathogenesis of clinical hypertension. An emerging body of experimental and theoretical evidence suggests that the renal nerves are the critical efferent mechanism linking baroreceptor-induced changes in central sympathetic output to alterations in renal excretory function, which are of paramount importance in mediating long-term changes in arterial pressure. However, additional experimental studies are needed to clearly define the efferent mechanisms that mediate the long-term effects of the baroreflex on arterial pressure and to critically test the hypothesis that changes in renal sympathetic nerve activity are, in fact, the primary determinant of this response.

There is considerable evidence that the sympathetic nervous system is activated in primary, but not in secondary hypertension. Although the experimental studies described above are provocative in that they suggest that baroreflex inhibition of renal sympathetic nerve activity may be a sustained response in hypertension, further studies are needed to evaluate whether baroreflex activation accounts for the sympathoinhibition in secondary hypertension such as reported in primary aldoste-

The pathogenesis of hypertension will provide a challenge for future investigations and will necessitate development of new tools and novel approaches, in addition to those discussed in this article.

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