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A neural set point for the long-term control of arterial pressure: beyond the arterial baroreceptor reflex

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Osborn, John W., Frédéric Jacob, and Pilar Guzman. A neural set point for the long-term control of arterial pressure: beyond the arterial baroreceptor reflex. Am J Physiol Regul Integr Comp Physiol 288: R846–R855, 2005. doi:10.1152/ajpregu.00474.2004.—Arterial baroreceptor reflex control of renal sympathetic nerve activity (RSNA) has been proposed to play a role in long-term control of arterial pressure. The hypothesis that the “set point” of the acute RSNA baroreflex curve determines the long-term level of arterial pressure is presented and challenged. Contrary to the hypothesis, studies on the long-term effects of sinoaortic denervation (SAD) on arterial pressure and RSNA, as well as more recent studies of chronic baroreceptor “unloading” on arterial pressure, suggest that the basal levels of sympathetic nerve activity and arterial pressure are regulated independent of arterial baroreceptor input to the brainstem. Studies of the effect of SAD on the long-term salt sensitivity of arterial pressure are consistent with a short-term role, rather than a long-term role for the arterial baroreceptor reflex in regulation of arterial pressure during changes in dietary salt intake. Renal denervation studies suggest that renal nerves contribute to maintenance of the basal levels of arterial pressure. However, evidence that baroreflex control of the kidney plays a role in the maintenance of arterial pressure during changes in dietary salt intake is lacking. It is proposed that a “baroreflex-independent” sympathetic control system must exist for the long-term regulation of sympathetic nerve activity and arterial pressure. The concept of a central nervous system “set point” for long-term control of mean arterial pressure (CNS-MAP set point), and its involvement in the pathogenesis of hypertension, is discussed.

sympathetic nervous system; hypertension; baroreflex

THE ROLE OF THE ARTERIAL BARORECEPTOR reflex in long-term control of arterial pressure has been a topic of considerable debate and controversy for decades. This debate was initiated in the 1970s by a series of studies from Cowley and coworkers demonstrating that sinoaortic denervation (SAD) had no long-term effect on the basal level of arterial pressure in the conscious dog (20). These findings have since been confirmed by several laboratories reporting a normal mean level of arterial pressure after SAD in several species (16, 61, 72). Cowley et al. (20) went on to show that in several models of renovascular hypertension in the dog the magnitude of hypertension was not affected by SAD, further supporting the concept that arterial baroreceptors are incapable of chronically buffering hypertensive stimuli (18, 19, 21). Consistent with this view, we reported that SAD does not alter the steady-state level of hypertension in a genetic model of human essential hypertension, that is, the spontaneously hypertensive rat (63). These observations, combined with the knowledge that arterial baroreceptors reset to sustained changes in arterial pressure (5, 57), led to the concept that the arterial baroreceptor reflex is incapable of long-term control of arterial pressure (17, 34).

However, three papers published over the past three years have sparked renewed interest in this topic and refueled the debate. In each of these studies, the responses of either arterial pressure or renal sympathetic nerve activity to a 7-day stimulus were examined in conscious animals, and the results were consistent with sustained baroreflex control of the cardiovascular system. In 2002, Thrasher (78) described an alternative surgical method for chronically decreasing baroreceptor afferent input to the brain and reported sustained hypertension in the dog (78). The following year, Barret and colleagues (7) demonstrated in conscious rabbits a marked reduction in renal sympathetic nerve activity in response to hypertension produced by 7 days of intravenous infusion of ANG II. Then, in 2004, Lohmeier et al. (55) reported that chronic electrical stimulation of the carotid sinus in dogs produces a sustained decrease in arterial pressure (55). These studies and their relevance to arterial baroreceptors and long-term control of arterial pressure are discussed in more detail in companion articles in this journal.

Further support for a long-term role of arterial baroreceptors is provided by the studies of Howe and colleagues (38, 39) and our laboratory (66, 67), demonstrating salt-dependent hypertension in SAD rats, which suggested that baroreceptors chronically buffer this hypertensive stimulus. These studies, in combination with the three cited above, suggest that the arterial baroreceptor reflex can impact on long-term control of arterial pressure under certain conditions.

If the baroreceptor reflex does regulate arterial pressure chronically, it remains unresolved which peripheral targets of the sympathetic nervous system are involved in this control system. Clearly, alteration of sympathetic nerve activity (SNA) to most vascular beds (e.g., renal, splanchnic, skeletal muscle) result in acute arterial pressure responses, but the individual contributions of these targets in the chronic regulation of pressure still remain unclear. One reason is because over the past few decades, the primary focus of many studies has been on neural control of the kidney, as this vascular bed has been thought to play a major role in long-term control of arterial pressure. Increases in renal SNA results in several responses that potentially chronically elevate arterial pressure, including sodium and water retention, increased activity of the renin-angiotensin-aldosterone system, and increased renal vascular resistance (22). The focus on the kidney has also been driven by the elegant theoretical framework of Guyton and colleagues (34, 35). Guyton and colleagues propose that the only mech-
anism by which the sympathetic nervous system can chronically regulate arterial pressure is via alterations in the renal function curve (17, 33). This concept is supported by some studies demonstrating that renal denervation delays the development of the hypertensive process in some forms of experimental hypertension (40, 48, 49, 81).

The objective of this review is to critically evaluate the importance of arterial baroreceptor reflex control of the kidney in long-term control of arterial pressure. The emphasis will be on regulation of both the basal levels of arterial pressure, as well as the long-term salt-sensitivity of arterial pressure. Careful analysis of studies to date will suggest that, although the sympathetic nervous system is important in the chronic control of arterial pressure, arterial baroreceptors play little to no role in long-term regulation of the mean level of SNA or arterial pressure. In addition, although neural control of the kidney does contribute, in part, to long-term control of arterial pressure, other neural targets (e.g., heart, skeletal muscle, and splanchnic beds) are also required. This review will conclude with the hypothesis that a long-term set point for SNA and arterial pressure does indeed exist within the central nervous system (CNS), but that it operates independently of the arterial baroreceptor reflex.

**EXTRAPOLATION OF THE ACUTE RSNA BAROREFLEX CURVE SET POINT TO LONG-TERM CONTROL OF ARTERIAL PRESSURE: THE HYPOTHESIS**

Figure 1 illustrates the central hypothesis to be addressed in this review. Renal sympathetic nerve activity (RSNA) is under the tonic control of sympathetic premotor neurons in the rostral ventrolateral medulla (RVLM) of the brainstem. This level of RSNA modulates arterial pressure via the known actions of renal nerves on the kidney, including renin release, tubular sodium reabsorption, and renal vasomotor tone (22). The level of RSNA is dynamically controlled by input from the aortic and carotid baroreceptors which, via a series of projections to the nucleus tractus solitarius and caudal ventrolateral medulla, inhibit the activity of the RVLM and therefore RSNA (31). This negative feedback reflex results in the classic arterial baroreflex curve, in which the set-point determines the steady-state relationship between the basal level of RSNA and arterial pressure. Finally, this hypothesis assumes that there is a direct relationship between the basal levels of RSNA and arterial pressure.

The neuroanatomical and neurochemical substrates, as well as the underlying neurophysiological mechanisms of this pathway have been reviewed elsewhere (31, 69). Many of these details have been generated by acute studies in anesthetized animals using various “reductionist” approaches required to understand the cellular and molecular biology of this reflex pathway. However, this review will focus primarily on addressing whether this reflex is important in the long-term control of arterial pressure under physiological conditions. Therefore, the emphasis will be on studies in which arterial pressure has been measured over long periods of time in conscious animals in which the reflex pathway has been stimulated and/or manipulated experimentally. The outcome of these studies will be reviewed in the context of the following hypothesis: the long-term level of arterial pressure is determined by the set point of the MAP-RSNA baroreflex curve.

**ARTERIAL BAROREFLEX CONTROL OF RSNA IN LONG-TERM REGULATION OF ARTERIAL PRESSURE UNDER BASAL CONDITIONS**

Alterations in the afferent limb of the reflex: sinoaortic denervation studies. As soon as it was established that the baroreceptor reflex arc acts in a classical negative feedback fashion, it was proposed that denervation of the afferent projections of arterial baroreceptors should result in a sustained increase in SNA and hypertension secondary to loss of the loss of sympathoinhibitory input to the brainstem (for a historical review, see Ref. 68). Although early studies supported this concept, they were flawed in that arterial pressure was measured acutely under stressful conditions, and therefore the “hypertension” was an acute stress response rather than a chronic elevation in arterial pressure. It was not until the classic studies of Cowley and colleagues (20, 21), utilizing newly developed 24 h computerized monitoring of arterial pressure that it was evident that SAD dogs were not hypertensive. These studies were originally interpreted as evidence that the nervous system was not important in the long-term control of arterial pressure (33). Rather, it was suggested that the hypertension after SAD was temporary, and pressure returned to control levels as a result of pressure natriuresis and diuresis. Indeed, the normal levels of arterial pressure in SAD dogs have often been used as an argument for the dominant role of the kidneys in long-term control of arterial pressure (17, 35).

Subsequent studies over the past 20 years have clearly demonstrated that failure of SAD animals to remain hypertensive is because the sympathoexcitatory response to SAD is not sustained chronically. Although relatively few studies have characterized the time course of changes in arterial pressure after SAD, most are consistent in that arterial pressure rapidly increases but slowly returns to normal levels over time. The rate at which arterial pressure normalizes appears to be species dependent progressing from ~2–3 days in rats (64), to 5–7 days in rabbits (72), to 2–3 wk in dogs (77). A similar study in nonhuman primates revealed that arterial pressure had not returned to normal 3 wk after SAD at which time the protocol ended (73). This species dependence is critical to keep in mind in the interpretation of studies examining SAD and arterial baroreceptor “unloading” discussed below.
On the basis of measurements of arterial pressure, heart rate, and daily sodium excretion, we concluded that the return of arterial pressure 2–3 days after SAD in the rat was not due to pressure natriuresis/diuresis. This was based on the observation that cumulative sodium balance was actually positive, rather than negative, over the first 4 days following SAD. This occurred despite elevated renal perfusion pressure, and we concluded this was due to increased RSNA during this period. However, by the fifth day after SAD arterial pressure, sodium balance and heart rate had all returned to normal. On the basis of these results, we hypothesized that the normalization of arterial pressure following SAD was due to the return of cardiac, renal, and vasomotor SNA after SAD (64). It is important to note that a similar pattern was observed after denervation of aortic baroreceptors alone, suggesting that partial or complete arterial baroreceptor denervation results in the same steady-state responses of arterial pressure and sympathetic activity (64). Although this conclusion was based on functional responses to SNA, it is supported by indirect measures of SNA such as plasma norepinephrine (2, 11) and the depressor response to ganlionic blockade (3, 65) in SAD rats (See Table 1). More recently, direct recordings of RSNA in conscious rats, albeit only hours after electrode implantation, also suggest that RNNA returns to control levels after SAD (6, 41). Although each of these indices of SNA have their limitations, in combination, they provide compelling evidence that the long-term basal level of RSNA is regulated independent of arterial baroreceptor input. This conclusion remains to be confirmed by direct continuous recordings of SNA in animals fully recovered from surgical preparation in their home cage environment. It is important to acknowledge that in one report neither arterial pressure nor plasma norepinephrine were normalized 3 wk after SAD in baboons (73). However, as discussed above this may be the result of a slower time course of normalization of both SNA and arterial pressure following SAD in the nonhuman primate.

These studies suggest that arterial pressure eventually returns to normal after SAD as a result of SNA returning to baseline levels rather than secondary to pressure natriuresis/diuresis. It is important to note that the normalization of SNA after SAD cannot be explained by compensation of intact cardiopulmonary reflexes, as recently reviewed by Sved and colleagues (76). Taken together, these findings suggest that the long-term levels of SNA are regulated independent of the arterial baroreceptor reflex and that extrapolation of the acute RSNA-baroreflex curves to long-term control of arterial pressure is not valid. This conclusion then leads to the question: what is controlling the long-term level of RSNA and arterial pressure?

**Alterations in the afferent limb of the reflex: Chronic unloading of arterial baroreceptors.** The use of SAD animals to study the long-term role of arterial baroreceptors in the regulation of SNA and arterial pressure is complicated by the fact that chronic denervation may result in subsequent changes within the terminal synaptic fields of these primary afferents, leading to subsequent alterations in synaptic contacts within the reflex pathway (neural plasticity). Therefore, it may be incorrect to assume that SAD mimics a physiological reduction in arterial baroreceptor activity with no other changes in the reflex pathway. In other words, the SAD animal may be “rewired” and therefore not be comparable to an intact animal with a chronic decrease in baroreceptor nerve activity.

To circumvent this issue, Thrasher developed a novel surgical method for chronic unloading of arterial baroreceptors in the dog in which baroreceptors from one carotid sinus and the aortic arch are denervated and the perfusion pressure of the remaining innervated carotid sinus is decreased by ligation of the common carotid artery (78). This resulted in neurogenic hypertension that was sustained for 7 days and rapidly reversed when the carotid sinus pressure was returned to normal by removal of the ligation. These results suggested that decreasing arterial baroreceptor input to the brain did result in sustained neurogenic hypertension, and perhaps this model was a more physiological approach to study the long-term influence of baroreceptors on regulation arterial pressure than the SAD model.

However, as discussed above, the time course of the normalization of arterial pressure after SAD in the dog is 2–3 wk, and therefore it is important to follow the time course of arterial pressure longer than 1 wk after unloading. Thrasher has recently conducted such studies in which arterial pressure was measured in conscious dogs for 35 days following either SAD or baroreceptor unloading (77). Similar to the previous study (78), arterial pressure was increased ~25 mmHg 7 days after unloading. However, pressure subsequently returned toward control such that by the 4th wk after unloading, pressure was only slightly above normal levels. By comparison, arterial pressure was increased to a similar degree 1 wk after SAD but returned to control levels more rapidly than that observed after unloading and was normal within 3 wk after SAD.

In a study by Thrasher (78), we recently applied a similar strategy, with some modifications, to study baroreceptor unloading in the conscious rabbit. Rabbits were instrumented with telemetry transmitters for the measurement of arterial pressure and underwent aortic baroreceptor denervation and allowed to recover. Subsequently, carotid baroreceptors were chronically unloaded bilaterally by placing 0.35-mm silver clips on both common carotid arteries. Although preliminary at this stage, our results are consistent in that after carotid artery clipping, arterial pressure increased at the same rate and magnitude to that seen after SAD in the rabbit. More importantly, arterial pressure returned to control levels within 1–2 days after bilateral carotid artery stenosis (FD McBryde, JW Osborn and SC Malpas, unpublished observations).

Taken together, the results of the baroreceptor unloading studies in the dog and rabbit, along with the studies in SAD

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**Table 1. Summary of indirect and direct assessment of sympathetic nerve activity in sinoaortic denervated animals**

<table>
<thead>
<tr>
<th>Species</th>
<th>Indirect Assessment of SNA</th>
<th>Direct Assessment of SNA</th>
<th>Level of SNA</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>PNE</td>
<td>—</td>
<td>Normal</td>
<td>(2, 11)</td>
</tr>
<tr>
<td>Rat</td>
<td>GB</td>
<td>RSNA</td>
<td>Normal</td>
<td>(3, 65)</td>
</tr>
<tr>
<td>Rat</td>
<td>—</td>
<td>Normal</td>
<td>(6, 41)</td>
<td></td>
</tr>
<tr>
<td>Baboon</td>
<td>PNE</td>
<td>—</td>
<td>Elevated</td>
<td>(73)</td>
</tr>
</tbody>
</table>

Indirect measures include measurement of plasma norepinephrine concentration (PNE) and the depressor response to acute ganglionic blockade (GB). Direct measurements of renal sympathetic nerve activity (RSNA) are based on between animal comparisons. SNA, sympathetic nerve activity; dashes indicate data not available.
animals reviewed above, suggest that arterial pressure returns to normal after SAD and unloading, although the time course may be slightly different. These results suggest that long-term control of arterial pressure occurs independently of arterial baroreceptor input to cardiovascular sympathetic networks in the brain. If this proves to be true, it again raises the question: Is there a nonbaroreflex neural control system for long-term control of SNA and arterial pressure?

Alterations in the efferent limb of the reflex: Effect of renal denervation on basal levels of arterial pressure. If baroreceptor reflex control of RSNA is important in the long-term control of arterial pressure, then renal denervation (RDNX) should affect the basal level of pressure. Surprisingly, despite the numerous studies in which RDNX animals have been studied for a variety of experimental questions, it has been generally thought that RDNX has no effect on arterial pressure in normotensive salt-replete animals. However, in a recent study we investigated the effect of RDNX on the long-term salt-sensitivity of arterial pressure in conscious rats. Arterial pressure was measured 24 h/day by radio telemetry in sham-operated and RDNX rats. Surprisingly, we found that RDNX rats consistently had a lower arterial pressure than sham-operated rats (43). Although the magnitude of the decrease in arterial pressure was modest, ~10 mmHg, it was statistically significant and remained constant over a 100-fold range of dietary salt intake, suggesting it was not related to alterations in sodium and water balance. In addition, this effect was observed immediately (less than 1 h) following RDNX, further suggesting that this hypotensive effect was not related to denervation natriuresis and diuresis. In more recent studies, we have shown that denervation of one kidney lowers pressure half as much as bilateral denervation (44), and denervation of the sole remaining kidney in unilaterally nephrectomized rats decreases pressure to the same extent as bilateral denervation in rats with two kidneys (45). The mechanisms responsible for hypotension in renal denervation remain to be firmly established but likely involve loss of neurogenic control of renin release (44), loss of renal vasomotor activity, and/or impairment of renal afferent control of sympathetic activity (51, 74).

This observation supports the idea that the CNS is indeed important in the maintenance of arterial pressure in normal animals, as RDNX lowers pressure in the presence of other arterial pressure control systems, in particular the “renal-body fluid” arterial pressure control system, which is proposed to have “infinite gain” (34). However, since baroreceptor-independent pathways can control RNSA, this does not necessarily indicate that the arterial baroreceptor reflex regulates the basal level of RSNA.

IMPAIRMENT OF ARTERIAL BAROREFLEX CONTROL OF RSNA AS A PRIMARY CAUSE OF SALT-DEPENDENT HYPERTENSION

The focus of the discussion above was on the contribution of baroreflex control of RSNA in determining the basal level of arterial pressure in normal animals in the absence of environmental stress or known hypertensive stimuli. Overall, the literature indicates that arterial baroreceptors have little to no influence on the long-term basal level of arterial pressure or RSNA under nonstressed conditions. In regard to whether the arterial baroreceptor reflex chronically buffers stimuli known to elevate arterial pressure, Cowley et al. have rejected this notion on the basis of the effect of SAD on the development of several models of experimental renovascular hypertension in the dog (21). However, other studies suggest that the long-term salt-sensitivity of arterial pressure is dependent on normal baroreceptor reflex function.

The RSNA-baroreceptor reflex in genetic models of salt-sensitive hypertension. The idea that a primary impairment of the baroreceptor reflex arc shown in Fig. 1 contributes to the development of hypertension in the Dahl salt-sensitive (DS) rat is supported by numerous studies demonstrating resetting both peripherally (4) and centrally (28, 29). However, it is virtually impossible to determine whether baroreflex impairment is the primary cause of salt-sensitive hypertension in this model since these rats also exhibit impaired vascular (8) and renal (70, 71) function at an early age. It has been reported that RDNX attenuates salt-sensitive hypertension in this model, suggesting that an increase in RSNA may be involved (62). But this may not necessarily be due to altered baroreceptor reflex per se, as there is evidence that salt-induced changes in sympathetic activity are driven by forebrain sites that project to the RVLM (75). If this is true, then the salt-dependent hypertension may not be the result of impairment of the baroreceptor reflex arc shown in Fig. 1 but rather a salt-induced activation of forebrain sympathoexcitatory sites.

Further evidence for a primary role of impaired baroreceptor reflex control in the development of salt-sensitive hypertension is provided from the studies of Weinstock and colleagues (80) using normotensive rabbits bred for differences in cardiac baroreflex sensitivity (79, 80). By selectively breeding rabbits in which the gain of the cardiac baroreflex is decreased, they have demonstrated that salt-dependent hypertension is correlated with reduced gain of the cardiac baroreflex. More importantly, this model of hypertension is prevented by renal denervation, suggesting that it is dependent on activation of RSNA. However, as with the DS rat, this model could also be due to a salt-induced activation of RSNA independent of the arterial baroreceptor reflex. Without a detailed understanding of how central sympathetic pathways are contributing to the decreased gain of the cardiac baroreflex, this possibility remains open.

Salt-sensitive hypertension in SAD animals. A more direct approach to determine whether a primary impairment of the arterial baroreceptor reflex results in salt-sensitive hypertension is to measure the effect of increasing dietary salt intake on arterial pressure in normal and SAD animals. Howe and coworkers were the first to demonstrate, using tail-cuff measurements of arterial pressure, that SAD rats became hypertensive when consuming a high-salt diet (38). This observation was later confirmed by direct measurements of arterial pressure in SAD rats in both Howe’s laboratory (39) and ours (67).

We recently investigated salt-sensitive hypertension in SAD rats in more detail using continuous telemetric measurements of arterial pressure (66). As shown in Fig. 2A and discussed above, the basal level of arterial pressure in intact (sham-operated) and SAD rats was similar when both groups were consuming a normal salt (0.4% NaCl) diet. However, increasing dietary salt to 4.0% NaCl resulted in a sustained increase in arterial pressure in SAD but not sham-operated rats during the 3-wk period of 4.0% NaCl intake. Note, however, that the difference between groups was not apparent until ~10 days after increasing salt intake. Similarly, increasing salt intake...
further (8.0% NaCl) resulted in a slightly greater increase in arterial pressure for an additional 3 wk. Finally, switching both groups back to a 0.4% NaCl diet resulted in an immediate normalization of arterial pressure in SAD rats.

These results, based on the 24-h averages of arterial pressure, were originally seen as evidence that arterial baroreceptors are important in the long-term control of arterial pressure during chronic increases in dietary salt. Indeed, this study has been cited by others as evidence for a long-term role of arterial baroreceptors in the regulation of arterial pressure (56, 78). However, further examination of the data on an hour-by-hour basis leads to a possible alternative explanation. Plotted in Fig. 2B are the hourly averages for the final 72 h of each level of dietary salt for sham-operated and SAD rats. The vertical gray bars indicate the night-cycle and the white bars represent the day-cycle. Note that the normal circadian rhythm of arterial pressure in sham-operated rats was unaffected by the level of dietary salt. In contrast, SAD rats exhibited marked increases in arterial pressure during the night, such that pressure increased ~20 mmHg over 12 h on the 4.0% salt diet and ~30 mmHg over 12 h on the 8.0% salt diet. It is also important to note that as soon as the light cycle began, arterial pressure fell steadily such that by mid-day, it was back to near-normal levels. This observation is important for two reasons. First, it demonstrates that single intermittent measurements of arterial pressure each day could potentially give erroneous results depending on the time of day that arterial pressure is measured. Second, the nighttime increases in pressure are likely due to the fact that rats ingest their food and water during the night resulting in 12-h oscillatory osmotic and volume stimuli. Since studies in the rat have shown it takes 48 h for arterial baroreceptors to reset (52), these 12-h volume and sodium loads could easily be buffered in the baroreceptor reflex. This is consistent with the more accepted role of the baroreceptor reflex in the short-term regulation of arterial pressure rather than long-term control.
The route and nature of salt and water loading is a subtle, but important distinction to make when comparing studies on the role of arterial baroreceptors in salt-dependent hypertension. For example, in the experiments by Cowley et al. (21) studying the effects of increases in salt intake in models of renovascular hypertension in the dog, salt intake was controlled by intravenous infusion and was increased in a “square wave” fashion by simply increasing the intravenous dose of saline (21). Under these “static” conditions, it is likely that the arterial baroreceptor reflex does indeed adapt, in contrast to the 12-h oscillatory salt and water load in the study above. Moreover, intravenous salt loading is unphysiological in that it bypasses the hepatoportal osmoreceptors, which have been shown to influence central autonomic pathways (1, 12, 13, 50), RSNA (42, 59, 60), and renal function (37, 60).

The above discussion raises an important question: what defines short-term vs. long-term control of arterial pressure? If baroreceptor dysfunction results in salt induced increases in arterial pressure over a period of hours, is this a disruption of short-term or long-term arterial pressure control system? Relative to studies on baroreceptor control of sympathetic nerve activity, it may be argued that this is indeed dysfunction of a long-term arterial pressure control system. However, from the perspective of the pathogenesis of hypertension, which occurs over a much longer timescale, this would appear to be disruption of a short-term control system. Although the authors take the latter perspective, the issue of what constitutes short-term and long-term control of arterial pressure remains to be defined.

Baroreflex control of RSNA during chronic increases in dietary salt. If the baroreceptor reflex controls RSNA during changes in dietary salt intake, then the increased salt-sensitivity of arterial pressure in SAD animals may be due to impaired baroreflex control of the kidney. There is indirect evidence that RSNA is chronically suppressed in dogs on a high-salt intake (54), but unfortunately, this has yet to be confirmed by continuous direct recordings of RSNA before and after chronic salt loading. We did not observe an impaired ability of SAD rats to excrete a dietary salt load, suggesting that impairment of the baroreceptor reflex control of the kidney is not the cause of salt-dependent hypertension in SAD rats (67). This is contradicted by a recent report demonstrating that SAD rats had an impaired ability to excrete a salt load (23). Comparison of these studies is not straightforward since, in that latter report (23), salt and water were administered as a saline drinking solution, rather than the more physiological route of in the diet, and arterial pressure was not measured in the conscious state.

If neural control of the kidney is important in the long-term regulation of arterial pressure during changes in dietary salt intake, then RDNX should increase the long-term salt sensitivity of arterial pressure. Consistent with this hypothesis, unilateral RDNX impairs urinary sodium excretion from the denervated kidney, compared with the innervated kidney, of the dog (54). On the basis of these findings and the theoretical relationship between sodium balance and arterial pressure (34), we predicted that bilateral RDNX should increase the long-term salt-sensitivity of arterial pressure. However, we found no differences between RDNX and sham-operated rats in the salt-sensitivity of arterial pressure over a 100-fold range (0.04% to 4.0% NaCl diet) of dietary salt intake (43). We also did not observe any differences in daily sodium or water balances between groups when dietary salt intake was either increased or decreased 10-fold from normal. Although it is possible, since balance measurements were conducted over a 24-h period using standard metabolic cages, that small immeasurable changes in balance did occur in this study, it is clear that such differences had absolutely no impact on the regulation of arterial pressure as determined by continuous telemetric monitoring.

These findings can be interpreted in several ways. First, it is possible that under the conditions of this study, dietary salt loading has no effect on RSNA. Although changes in dietary salt theoretically influence RSNA chronically, this has not been established by direct nerve recordings in conscious animals before and after changes in dietary salt intake. Second, the contribution of renal nerves to the maintenance of sodium balance has been demonstrated under conditions of extreme changes in sodium intake (30), but they may play a minor role in the regulation of sodium balance over a more physiological range of dietary salt intake in the rat. Third, although there is a proposed theoretical link between sodium and water balance and arterial pressure (34), this link may not be as strong as proposed and it may be incorrect to assume that changes in sodium balance are always translated to changes in arterial pressure. Finally, since RDNX results in essentially “zero” functional RSNA, in contrast to what is likely to be a normal level of RSNA in SAD animals (see discussion above), this may lead to different responses of SAD and RDNX rats to salt loading.

In summary, despite a well-known theoretical role for baroreceptor reflex control of RSNA regulating the long-term salt-sensitivity of arterial pressure under physiological conditions, the evidence supporting this hypothesis is not particularly convincing. Indeed, the physiological links between dietary salt and RSNA, changes in RSNA and sodium balance, and finally, sodium balance and arterial pressure, have yet to be fully defined.

A NEURAL SET POINT FOR THE LONG-TERM CONTROL OF ARTERIAL PRESSURE: BEYOND THE ARTERIAL BARORECEPTOR REFLEX

This review addressed the hypothesis that arterial baroreceptor reflex control of the kidney is important in the long-term control of arterial pressure. However, several observations are inconsistent with this hypothesis. First and foremost, a large number of studies conducted over the past two decades, utilizing indirect and direct measures of RSNA, lead to the conclusion that RSNA and arterial pressure return to normal levels after surgical denervation of arterial baroreceptors. Although similar measurements of RSNA have not been carried out in the newer model of baroreceptor unloading, early indications are consistent with the view that arterial pressure also returns toward normal in this model. Second, although the long-term salt sensitivity of arterial pressure is increased in SAD animals, continuous monitoring of arterial pressure indicate this is due to impairment of the short-term buffering of acute salt and water loads. Finally, although renal denervation chronically lowers arterial pressure it does not alter the long-term salt sensitivity of arterial pressure. Taken together, these studies utilizing different experimental approaches in different species, are consistent with the “classic” view that the arterial barore-
ceceptor reflex is important in the short-term control of SNA and arterial pressure but has little importance in long-term regulation of these variables.

The failure of SAD to alter long-term levels of arterial pressure was originally used as an argument against a role for the entire nervous system in arterial pressure regulation (32). This is understandable because these interpretations were made at a time when the arterial baroreceptor reflex was seen as the primary neural control system for arterial pressure. Since that time, our understanding of autonomic control of the circulation, in particular, forebrain sites that influence SNA, have grown tremendously, and we now need to incorporate this new knowledge into an updated neural model for long-term control of arterial pressure.

If we accept that RSNA is normal in the absence of arterial baroreceptor input, we are then led to question of whether a baroreceptor-independent, central nervous system set point exists for the long-term control of SNA and mean arterial pressure (CNS-MAP set point). The term “set point” is used to designate a true control system for SNA and arterial pressure rather than a system that simply modulates SNA and arterial pressure without regard to the maintenance of a long-term level of these variables. There are several neural pathways within the central nervous system that modulate the basal level of SNA chronically, but are these pathways part of a control system that has a true set point for arterial pressure? If so, what type of “error signals” (inputs) cause primary shifts in this set point? Finally, what efferent pathways (outputs) mediate the long-term changes in arterial pressure? These are questions that must be addressed by future research.

A simplified conceptual scheme of this system is illustrated in Fig. 3. The neuroanatomical details of this theoretical system remain to be fully elucidated, but it is logical to suggest that it incorporates pathways involved in the maintenance of body fluid homeostasis (46, 58). These pathways are responsive to a number of signals linked to arterial pressure and regulate key autonomic nuclei which ultimately influence the activity of sympathetic premotor neurons in the RVLM. In addition, hormones linked to sodium and water homeostasis such as ANG II, vasopressin, and aldosterone modulate sympathetic activity via binding in circumventricular organs and subsequent modulation of autonomic activity (47). Finally, these same pathways are responsive to changes in the osmolality of body fluids (47, 58). A shown in Fig. 3, the arterial baroreceptor reflex controls the short-term variability of arterial pressure in the classic sense as reviewed above. However, the basal level of both SNA and arterial pressure, over long periods of time, are controlled by this nonbaroreflex system in which the set point is established by the integration of multiple inputs linked to arterial pressure. Because both of these systems converge on sympathetic premotor neurons in the RVLM, changes in activity of the CNS-MAP set point system will clearly alter the characteristics of the arterial baroreceptor reflex (central resetting). However, the converse is not true in that changes in the arterial baroreceptor reflex will not alter the operation of the CNS-MAP set point control system. This explains why SAD does not alter the basal level of SNA.

Evidence that such a CNS-MAP set point exists and is altered in hypertension is suggested by studies of angiotensin-induced hypertension. There is now abundant evidence that circulating ANG II chronically increases SNA via an action on central sympathetic neural pathways (26). Although the details have not been entirely elucidated, these long-term sympathoexcitatory actions of ANG II are generally thought to occur as a result of binding to AT1 receptors in circumventricular organs such as the area postrema of the hindbrain and the subfornical organ of the hypothalamus. Lesions from both of these sites prevent the hypertensive response to exogenous ANG II (27, 36) and the chronic hypotensive response to AT1 receptor blockade with losartan (14, 15). The sympathoexcitatory actions of ANG II are independent of the baroreceptor reflex since the steady-state level of angiotensin-induced hypertension is not affected by sinoaortic denervation (18). These observations support the hypothesis, originally proposed in the 1970s (10, 25), that ANG II causes hypertension via actions on the central neural pathways, which ultimately act on the RVLM to increase sympathetic activity (26).

But what is the evidence that ANG II acts on a CNS-MAP set point to cause hypertension? Neurogenic hypertension caused by hormones that regulate sodium and water homeostasis, such as ANG II, could simply result from pathological activation of the sympathetic nervous system. At the present time, there is not enough data to accept or reject the CNS-MAP set point hypothesis, but it does provide a logical explanation for long-term regulation of SNA and arterial pressure. It is important to note that this concept has been suggested in the past. More than 20 years ago, Bohr hypothesized that DOCA-salt hypertension is due mineralocorticoid actions on hypothalamic circumventricular organs and “resetting of a pressure-regulating center in the hypothalamus” (9). However, this hypothesis has yet to be firmly established within the hypertension field and remains to be challenged.

Testing the CNS-MAP set point hypothesis will be difficult since it is likely to be an extremely complex system involving the integration of multiple inputs, including hormone plasma concentrations (circumventricular organs), body fluid osmolality (central and peripheral osmoreceptors), and cardiovascular pressures (arterial and cardiopulmonary baroreceptors). Additional inputs related to energy metabolism, immune system activity, stress etc. are also likely to influence the CNS-MAP set point. Similarly, it is likely that this system controls arterial pressure by regula-
tion of efferent sympathetic activity to multiple target organs, including, but not limited to, the kidney. Despite the difficulty of testing this hypothesis, it is clearly a high priority since sympathetic dysfunction contributes to not only hypertension but many other cardiovascular diseases.

If the arterial baroreceptor reflex is not important in the long-term control of arterial pressure, then how do we reconcile the recent studies by Barrett et al. (7) and Lohmeier and colleagues (55) suggesting that it is? In the study of Barrett et al., RSNA was suppressed during 7 days of ANG II infusion. This study used a pressor dose of ANG II, and the suppression of RSNA seems to contradict the sympathoexcitatory actions reported for subpressor doses of ANG II (24, 26, 53). One possibility is that the 7-day ANG II infusion period was simply not long enough for resetting of the baroreceptor reflex to occur. This is suggested by the baroreceptor unloading studies of Thrasher discussed earlier in which entirely different conclusions were reached when comparing the arterial pressure responses of 7 days of unloading to 28 days of unloading. Additional studies are needed in which both the dose of ANG II and the duration of infusion are compared. The study of Lohmeier et al. (55) showing that chronic stimulation of the carotid sinus lowers arterial pressure illustrates that chronic suppression of SNA in the dog has marked effects on arterial pressure and supports an important role for the nervous system in long-term control of arterial pressure. However, this technique bypasses the baroreceptors themselves, which are a critical component of the system and a site where much of the resetting of the reflex occurs. As such, it is questionable whether electrical stimulation of baroreceptor afferents mimics the physiological response to an increase in arterial pressure. Nonetheless, this approach may lead to a novel therapeutic approach to the treatment of hypertension.

Perspectives

Despite recent evidence suggesting the arterial baroreceptor reflex plays an important role in the long-term control of SNA and arterial pressure, a critical evaluation of the literature to date is most consistent with a short-term role of this reflex in cardiovascular regulation. A more important and complicated picture is emerging in which the long-term level of SNA is regulated in the absence of arterial baroreceptor input to the brain. Indeed, numerous studies suggest the existence of a long-term central nervous system control system that operates independently of the arterial baroreceptor reflex. Despite the complexity of this theoretical system, our future success in understanding the pathogenesis of neurogenic hypertension could be aided by studies designed to test the CNS-MAP set point hypothesis.

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