What sets the long-term level of sympathetic nerve activity: is there a role for arterial baroreceptors?

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Malpas, Simon C. What sets the long-term level of sympathetic nerve activity: is there a role for arterial baroreceptors? Am J Physiol Regul Integr Comp Physiol 286: R1–R12, 2004; 10.1152/ajpregu.00496.2003.—Much of our knowledge of the influence of the sympathetic nervous system on the control of blood pressure is built on experimental approaches that focus very much on time scales <24 h. Although direct recordings of sympathetic nerve activity (SNA) over short time scales provide important information, it is difficult to place their relevance over the longer term where the development of chronic changes in blood pressure are likely to be a mixture of hormonal, renal, and neural influences. Recently new experimental approaches are now revealing a possible role for arterial baroreceptors in the chronic regulation of SNA. These studies reveal that chronic increases in blood pressure are associated with chronic changes in SNA that may be due to nonresetting of the blood pressure-SNA baroreflex relationship. This review discusses the implications of such information, highlighting new technologies for long-term recording of SNA that appear to hold much promise for revealing the role of SNA to the kidney for the long-term control of blood pressure.

THE CONTROL OF ARTERIAL PRESSURE is a complex mixture of the long- and short-term influences of hormones, local vascular factors, and neural mechanisms. With regard to neural influences, much progress has been made in recent years on the central nervous system pathways involved in regulating sympathetic nerve activity (SNA) and the effect of that activity on vascular resistance. However, our knowledge of this control is mostly confined to short time scales of seconds and minutes, with a paucity of studies extending their focus to the longer term aspects (>24 h). Yet such information is liable to be critical in understanding the pathogenesis of hypertension where the onset of the disease is most likely to be a combination of slowly developing factors. As new tools for assessing sympathetic activity over longer time scales emerge, there is a growing desire and ability to understand longer term aspects of the regulation of SNA. It is recognized that pathways involved in regulating blood volume, osmolarity, and oxygen levels, as well as chronic changes in central nervous system function, are all likely to be important factors in understanding how SNA is controlled. However, given the revival in the hypothesis that arterial baroreflexes play a role in regulating the long-term levels of blood pressure, this review concentrates on the recent research supporting this concept.

HISTORY

The first recordings of SNA by Bronk et al. (15) in the 1930s illustrated three dominant properties of SNA (Fig. 1). First, it is bursty. That is, that activity is composed of synchronized activation of many individual axons at approximately the same time, leading to the characteristic chugging sound heard when signals are amplified. Second, sympathetic bursts occur at a certain phase of the cardiac cycle. Finally, altering blood pressure leads to a rapid change in the pattern of SNA (15). Until the late 1970s, it was thought that bursts of SNA were predominantly due to reflex tonic input from baroreceptors; however, the seminal work of Barman and Gebber (9) identified that bursts of SNA still occurred in baroreceptor-denervated animals, but they had lost their phase relationship to the cardiac cycle, indicating that the central nervous system must be important in generating bursts of SNA. This observation subsequently stimulated an intensive investigation of what central nervous system cell groups may be involved in generating and regulating SNA. The last 20 years has seen what may be described as an avalanche of information on the role of various brain regions in the regulation of SNA. The cell groups and even relevant neurotransmitters have been mapped out for some regulatory pathways, most extensively those involved in the arterial baroreflexes and fluid balance regulation (38–40, 63, 67, 86). Although such neurophysiological information is very valuable it is also limited in that the time scales over which data are collected are generally restricted to minutes, rather than hours or days of recordings. Consequently, researchers naturally extrapolate over longer time scales to try and place the relevance of their work into a general schema for the long-term control of the cardiovascular system. Such extrapolation is perfectly acceptable given technological limitations in collecting such long-term data. But, if we are to truly understand the importance of SNA in long-term blood pressure control, then we must have technologies and experimental paradigms that allow us to directly test the hypothesis that long-term changes in SNA chronically control arterial pressure.

DOES THE LONG-TERM REGULATION OF SNA MATTER?

One might begin by asking the question does SNA matter for the long-term control of blood pressure? Indeed, although it is clear from the different forms of autonomic neuropathy that a...
lack of sympathetic control in the short term (seconds-minutes) is certainly very debilitating, it does not necessarily follow that adjusting the level of SNA up or down from some baseline level over the long term is important in the long-term control of blood pressure. Our understanding of the long-term control of blood pressure is primarily built on knowledge of hormonal and renal systems, such as the renin-angiotensin-aldosterone axis or pressure natriuresis/diuresis. In this regard an extensive range of tools is available; for example, the levels of a particular hormone can be measured within the same individual over an extended period of time, or an antagonist for the receptor may be administered, and finally the use of genetically manipulated animals may illustrate their importance in the development and the maintenance of hypertension, etc. With regard to the sympathetic nervous system, we appear to have only a limited range of experimental approaches (see CURRENT APPROACHES FOR EXAMINING THE RELEVANCE OF THE SYMPATHETIC NERVOUS SYSTEM FOR LONG-TERM BLOOD PRESSURE CONTROL). Yet if one considers a list of treatments for hypertension since the 1940s, one notes a dominant theme of therapies that target the sympathetic nervous system in attempting to lower blood pressure (Table 1). This is perhaps surprising given it is relatively recently that strong clinical evidence of sympathetic overactivity occurring in hypertension has been found. The elegant work of Esler and colleagues (31, 32, 35, 36) using norepinephrine spillover techniques reveal directly several key features of neural control in the human. First, if one examines the relative contribution of various organs to total norepinephrine levels it is interesting to note the relative dominance of sympathetic outflow to the kidneys (Fig. 2). Total norepinephrine spillover is increased ∼40% in essential hypertension; however, half this increase is derived from increases to the heart and kidneys, suggesting selective overactivity in the sympathetic nerves to these organs. Importantly, this increase is most noticeable in younger or borderline hypertensive subjects rather than older established hypertensives. This observation is extremely pertinent for it clearly suggests that overactivity of the sympathetic nervous system is a feature in the development of hypertension. The question is how relevant is this increase and what mechanisms give rise to this increase? It is likely that the answers to such fundamental questions lie in studying animal models of the disease process.

CURRENT APPROACHES FOR EXAMINING THE RELEVANCE OF THE SYMPATHETIC NERVOUS SYSTEM FOR LONG-TERM BLOOD PRESSURE CONTROL

Currently the dominant range of experimental approaches for studying the long-term control of blood pressure via the sympathetic nervous system could be described as mostly removal-type scenarios; that is, either surgical sympathectomy, denervation of single organs (predominantly the kidney), or ganglionic blockade. Notwithstanding the conceptual limitation of an experimental approach that reduces SNA to zero in trying to study a disease process in which SNA is thought to be increased, these studies have been useful in several aspects. A number of studies now support that notion that rather than a generalized increase in sympathetic drive it may be a selective increase in activity to the kidney that is critical. The onset of hypertension appears to be delayed or the magnitude of the arterial pressure elevation reduced by chronic renal denervation (52, 53, 70, 91, 92). This interruption of arterial pressure elevation occurs in renin-dependent, renin-independent, volume-expanded, and genetic models of hypertension in rats, rabbits, and dogs. Other studies have used long-term infusions of norepinephrine directly into the renal artery to simulate increased renal SNA (RSNA) and caused the retention of sodium and water and produced sustained changes in arterial pressure (26, 77, 80). Recently Grisk and colleagues (41) studied the effect of neonatal sympathectomy on blood pressure after renal transplantation. Sympathectomy induced chronic changes in SHR kidney function, leading to an arterial pressure reduction even when extrarenal sympathetic tone was restored. They proposed that the chronic reduction in RSNA resets the kidney-fluid system to reduce arterial pressure. Recently Jacob and colleagues (49), using a simple experimental approach of bilateral renal denervation in rats and continuous monitoring of blood pressure via telemetry, revealed mean blood pressure to be lower in renal-denervated animals, suggesting that basal levels of RSNA are important in maintaining blood pressure. Our own work using low-frequency electrical stimulation of the renal nerves to a single kidney in the anesthetized rabbit produced an increase in blood pressure that was sustained over the 3 h of stimulation (56). Importantly the mechanism for this increase appeared to be the neurally mediated release of renin as blockade of angiotensin II formation with an ACE inhibitor abolished this increase in blood pressure (Fig. 3). Furthermore, in a strain of rabbits selectively bred with an impairment in baroreflex control of heart rate, placing such animals on a high-salt diet resulted in increased blood pressure (95). However, in renal-denervated rabbits this increase in blood pressure was abolished, suggesting that RSNA is important in the development of hypertension. These results may be interpreted to suggest that an integral relationship exists between functional sympathetic outflow to the kidneys and the development of hypertension.

One concept often overlooked by researchers investigating mechanisms of neurogenic hypertension is the primary reliance on pressure natriuresis as the key feature of the renal-body fluid-blood pressure control system. Although chronic changes in peripheral resistance and cardiac function may occur as a result of changes in SNA, the ability to chronically alter blood pressure is primarily built on knowledge of hormonal and renal systems, such as the renin-angiotensin-aldosterone axis or pressure natriuresis/diuresis.
pressure must also involve a change in renal excretory function. This change in renal function may occur secondary to other events or as a primary response to a stimulus. In the absence of a change in renal function, an increase in total peripheral resistance and/or cardiac pumping would increase pressure natriuresis. In turn, increased fluid excretion would decrease extracellular fluid volume until cardiac output and arterial pressure returned to normal and fluid balance is reestablished (59). Thus the key question in understanding the role of the sympathetic nervous system in the long-term control of blood pressure really lies in what is regulating RSNA and how does this influence renal function chronically?

**HOW MAY THE RENAL NERVES REGULATE BLOOD PRESSURE?**

The kidney receives a dense innervation of sympathetic nerves, which suggests that changes in the activity present in these nerves would affect renal hemodynamics, sodium excretion, and renin release. Early studies using electrical stimulation of renal nerves suggested that the renal vasculature was relatively insensitive to small changes in SNA, these being preferential for renin release and sodium excretion (45, 74). More recent experiments using direct recordings of SNA and renal blood flow suggest those early experiments were incorrect. Under acute conditions, the renal vasculature appears highly sensitive to changes in SNA in that increases in SNA associated with daily life in rats produce decreases in renal blood flow (37, 65). In our own laboratory, low-frequency stimulation of the renal nerves in anesthetized rabbits has always produced reductions in renal blood flow (57, 62). However, it is also now clear that this effect on renal blood flow is only temporary. Electrical stimulation of the renal nerves at 1 Hz for 180 min initially reduced renal blood flow; however, this reduction was not sustained and by 110 min was not significantly different from control conditions (56). Moreover, the reduction in sodium excretion and urine flow rate was sustained. This indicates an independence between the neural effects on the vasculature from those acting on the more long-term arterial pressure control mechanisms. Support for this concept is found in direct recordings of RSNA and renal blood flow in rabbits living in their home cages (11). Renal blood flow was recorded to both kidneys with the right side being denervated and the left side intact. Perhaps surprisingly, the overall mean level of renal blood flow was not significantly different between kidneys, indicating that the renal nerves were unimportant in setting the overall level of vascular tone. However, it was clear that there were periods when RSNA was increased and consequently renal resistance increased (Fig. 4). These elevations occurred throughout the day and night and appeared to be partly associated with movement and perhaps rapid eye movement sleep. Overall these observations indicate that acute increases in RSNA result in changes in vascular resistance and are important in regulating blood pressure in response to short-term stimuli. However, with longer term sympathetic activation the effect on the vasculature is transient with the effect on sodium excretion and renin release being dominant. This raises the question of whether it is the neurally

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**Fig. 2.** Top: percentage of norepinephrine (NE) spillover from a range of organs illustrating the dominance of renal SNA in the overall NE. Bottom left: increase in total norepinephrine spillover in hypertensive (HT) vs. normotensive (NT) individuals. Top of bar for the HT group indicates that the increase in total NE spillover is predominantly due to an increase in NE spillover to the heart and kidneys. Bottom right: increase in NE spillover from kidneys in hypertensive individuals. Figure redrawn from data presented by Esler et al. (31, 32, 35, 36).

**Fig. 3.** Mean arterial pressure (MAP) responses in anesthetized rabbits during low-frequency (1 Hz) electrical stimulation of left renal nerves. Dotted line reflect the changes in blood pressure in a separate group of rabbits pretreated with angiotensin converting enzyme inhibitor (enalaprilat). Data redrawn from Ref. 56.
mediated regulation of renin, or sodium excretion, that is important in long-term blood pressure control. However, testing this question experimentally is complicated as it is difficult to disassociate between the direct effect of SNA on the sodium reabsorption in the tubules and an indirect effect via neurally mediated increases in angiotensin II. Recently, using the approach of 180 min electrical stimulation of the renal nerves and comparing renal excretion between ACE-inhibited and control animals we observed that blockade of angiotensin II attenuated, but did not abolish, the changes in urine flow rate and sodium excretion, suggesting that the renal functional response to activation of the renal nerves is mediated by both the neurally mediated increases in angiotensin II and directly by the renal nerves (56).

**DIRECT MEASUREMENT OF SNA**

In studying the importance of the sympathetic nervous system for blood pressure control it is difficult to dismiss the advantages of direct recording techniques. For unlike the denervation studies described above, the direct measurement of SNA provides a temporal, quantitative index of SNA to a particular organ. Whereas some researchers may believe direct recordings of SNA are a nirvana, they are certainly not the magic bullet approach for several reasons. First, SNA is generally only measured in a single organ, most commonly the kidney. Because one of the strongest hallmarks of neural control is its ability to differentially regulate SNA to multiple organs (48, 71, 72), it is highly likely that the changes in SNA...
measured at one site are not reflective of global SNA levels. However, as already discussed in this review, it is suggested that this is not necessarily a serious limiting factor with regard to blood pressure control as it is likely that it is SNA in particular organs, such as the kidney, that dominate in the long-term control of blood pressure. Another issue with direct recordings is the limited ability to directly compare absolute voltages between animals. Although some researchers (66, 68) favor this approach, it is clear that differences in the physical contact between the nerve and the electrode will produce a large amount of variability in the data obtained and thus reduce the precision in determining the magnitude of changes in SNA. This means that experiments in which the design allows for within-animal comparisons, e.g., before, during, and after a treatment, provide data with considerably better precision than between-animal studies.

**NEW UNDERSTANDING COMES ABOUT THROUGH NEW METHODOLOGIES**

Recently, we developed a fully implantable amplifier dedicated to the recording of SNA (12). This system encompasses wireless digital transmission of sympathetic signals (1–10,000 Hz) from animals in their home cage environment (range up to 10 m). We successfully recorded RSNA in rabbits for up to 50 days after implantation and routinely record SNA for up to 4 wk. Such an approach opens up a host of possible experimental interventions that explore the nature of the long-term regulation of SNA, for now the same animal can be monitored before, during, and after a treatment/intervention. Furthermore, the home cage monitoring environment is more likely to provide results that are more reflective of the human condition than monitoring in a restrictive laboratory environment. We found the rabbit an excellent model for studying circulatory control in that its size is ideal for implanting a range of telemetry devices (such as blood pressure and SNA) and it does not require dedicated staff for maintenance as do larger animals. Often the criticism has been leveled that the rabbit is a docile animal, “a flower” in the animal kingdom. This impression possibly stems from their freezing reaction when placed in an unfamiliar environment such as the laboratory. However, we have noted that rabbits are more than capable of action against humans when humans enter the home cage environment. Most importantly the large diameter of the sympathetic nerves means that the nerves appear more robust and remain viable for recording for longer periods than the nerves found in the rat. Indeed it may be said that when neurophysiologists moved from the use of cats to rats in the early 1980s, it is sad that more did not explore the use of the rabbit as a model of cardiovascular control.

One relevant aspect that long-term direct recordings of SNA reveals is the recovery of SNA after surgery (Fig. 5). In the rabbit, and probably in most species, it is clear that SNA is high immediately after surgery, taking some 3–4 days to reach a stable baseline level (11). Circadian variations in heart rate and blood pressure also appear to take some time to be reestablished. It is of some concern then that many researchers record SNA in animals within 24 h after surgery to implant recording electrodes and define this as “conscious recordings” (28, 29).

**POSSIBLE MECHANISMS REGULATING THE LONG-TERM LEVEL OF SNA: A ROLE FOR BAROREFLEXES?**

In 1971, Arthur Guyton in writing in the 4th edition of his *Textbook of Medical Physiology* (42) wrote that the baroreceptor control system is of little or no importance in long-term

![Fig. 5. Data from a single rabbit for each measured parameter for the 5 days immediately after surgery (A) and between days 23 and 26 after surgery (B) illustrating the high level of SNA immediately after surgery. On average, the circadian rhythm in various parameters did not develop until 4 days after surgery. RSNA activity expressed as a percentage of the 24 h average from that animal between days 23 and 29. Adapted from (11).](http://ajpregu.physiology.org/)
regulation of mean arterial pressure. More than 30 years later it is perhaps surprising that our understanding of the mechanisms responsible for this phenomenon seem to have advanced little. The dominant rationale provided for excluding arterial baroreceptors from a role in long-term blood pressure control has been that the baroreceptors themselves reset in 1 to 2 days to whatever pressure level they are exposed. That is, if the pressure rises from the normal value of 100 to 160 mmHg, fast rates of baroreceptor afferent activity occur. However, during the next few seconds, the rate of firing diminishes considerably; then it diminishes more slowly during the next 1 to 2 days, at the end of which time the rate will have returned essentially to the normal level despite the fact that arterial pressure still remains at 160 mmHg (42). The concept that arterial baroreflexes play no role in the long-term regulation of arterial pressure is based on the following three experimental findings.

McCubbin and colleagues (64) first demonstrated arterial baroreflex resetting in chronically hypertensive dogs. Recordings from baroreceptor afferents in hypertensive dogs indicated a marked increase in the threshold pressure and normal phasic response. More recently, it has been shown that baroreceptor resetting begins in as little as 20 min (18, 21) and is essentially complete within 48 h based on electrophysiological criteria (54). Indeed, a number of acute studies have subsequently shown that arterial baroreceptors reset quite quickly, within minutes, after a step change in arterial pressure.

The classical studies of Cowley and colleagues (25) really cemented the concept that arterial baroreflexes did not regulate long-term levels of arterial pressure. They measured arterial pressure continuously for 3–5 days in dogs with chronic sinoaortic denervation and observed tremendous lability in arterial pressure, but average 24-h pressure measurements were not increased compared with intact animals. The lack of a hypertensive response to baroreceptor denervation has been confirmed in rats (73, 75, 76), rabbits (81), cats (78), and monkeys (23).

The third argument is that the reflex gain of the baroreceptor control system is not sufficiently strong to explain the long-term constancy of arterial pressure (24). Various studies in anesthetized dogs and rabbits have shown that arterial baroreceptors provide only 65–75% compensation for a given change in arterial pressure (50).

Although the above studies have provided a clear foundation for the proposal that baroreflexes play no role in the regulation of long-term levels of SNA it is also clear that there are several important limitations.

While resetting of the arterial baroreceptors is well established under experimental conditions, such conditions are not always representative of the conditions the receptors are exposed to everyday. Many of the studies examining resetting of the baroreceptors themselves have been carried out in isolated preparations, where the perfusion pressure is strictly controlled. Factors such as pulse pressure (8), heart rate (2), and prostaglandins (20) have all been suggested to influence baroreceptor activity, with evidence that the presence of a pulse may prevent or at least attenuate baroreceptor resetting during elevations in pressure (19).

The afferent baroreceptor nerves are mixed, comprised of both A and C fibers. The two types of fibers have very different properties, with differences in resting activity level, maximum firing frequency, threshold pressures, and operating ranges (22, 88, 89, 96). It has been proposed that the two types of fibers may act differentially, having different “purposes,” allowing arterial pressure to be buffered over a wide operating range and both rapid and slow changes in arterial pressure to be buffered (84). Importantly, there is evidence that the two fiber types may differ in their ability to reset (69, 85). It should also be noted that the typical methods for monitoring afferent baroreceptor activity, namely single or so-called whole nerve recordings, are biased toward A fibers with their larger spikes (1, 6), despite the fact that histological studies have shown that C fibers outnumber A fibers in baroreceptor nerves in both the rabbit (79) and rat (7). Thus, if, as Seagard et al. (85) suggest, only the myelinated A fibers reset, then afferent recordings of baroreceptor activity are likely to overestimate the importance of baroreceptor resetting.

There is evidence to suggest that the different subtypes of baroreceptor afferents may project to different regions of the nucleus of the solitary tract (NTS) (27) and ultimately have control over different reflex pathways (30). It is perhaps not surprising then that just because one branch of the efferent baroreflex pathway may reset this does not necessarily mean all reflex pathways will be reset, with evidence that reflex resetting of renal sympathetic activity may occur at a slower rate than resetting of the blood pressure (55) or heart rate (44).

Although resetting of the arterial baroreflex pathway is a consistent feature of many studies, it must be noted that although the baroreceptors themselves reset and the heart rate–arterial pressure relationship is shifted to the right with sustained increases in arterial pressure, it is also true that previous studies have not actually measured the arterial pressure to sympathetic activity relationship within the same animal over an extended period of time. As results from experiments described below indicate, the heart rate baroreflex cannot be used as an index of change in the sympathetic baroreflex.

The classical studies above (25) clearly show that baroreceptor denervation does not lead to sustained increased in arterial pressure. There is no doubt that these studies were carefully conducted with arterial pressure measured in dogs under quiet resting conditions (25). However, simply measuring arterial pressure alone after the removal of a major cardiovascular control pathway such as the baroreflex may not reveal all ways in which the baroreflex is involved in the control of arterial pressure (particularly long-term arterial pressure control). Other pathways may partially compensate for the loss of baroreceptors. For example, RSNA and arterial pressure are acutely increased after baroreceptor denervation, but chronically, both return to control levels (10, 47, 75). This normalization of RSNA suggests that adaptation to loss of inhibitory inputs from baroreceptors may have occurred.

**RECENT KEY STUDIES SUGGEST A ROLE FOR BAROREFLEXES IN THE LONG-TERM REGULATION OF BLOOD PRESSURE**

Recently, novel experimental approaches have revealed new data that suggest revision of our understanding of the role arterial baroreflexes play in regulating arterial pressure and whether SNA is required. Lohmeier and colleagues (60) studied responses to 5 days of angiotensin II infusion in dogs using a split-bladder preparation combined with denervation of one kidney. During angiotensin II infusion, sodium excretion from the innervated kidney significantly increased compared with the denervated kidney, indicating a chronic decrease in RSNA.
It was proposed that this decrease in RSNA was being mediated by baroreflexes, because after cardiopulmonary and sinoaortic denervation the sodium excretion from the innervated kidney actually decreased compared with the excretion from the denervated kidney during angiotensin II infusion.

The above study is further supported by evidence of sustained activation of central pathways involved in the arterial baroreflex pathway (61). Using Fos-like (Fos-Li) protein immunohistochemical methods to determine long-term activation of neurons in the NTS, caudal ventrolateral medulla (CVLM), and rostral ventrolateral medulla (RVLM) after acute (21 h) and chronic (5 days) angiotensin II infusion, there was a two- to threefold increase in Fos-Li staining in the NTS and CVLM, but no increase in staining in RVLM neurons. As baroreceptor suppression of sympathoexcitatory cells in the RVLM is mediated by activation of neurons in the NTS and CVLM, these results were expected. More importantly, this same pattern of central neuronal activation was observed during chronic angiotensin II hypertension.

Other studies suggest that arterial baroreceptors may be important in long-term regulation of arterial pressure under conditions of increased salt intake. Howe and colleagues (46) reported that increasing dietary salt intake resulted in hypertension in sinoaortic-denervated but not baroreceptor-intact rats. This study is supported by a more recent study by Osborn and Hornfeldt (76), who recorded arterial pressure via telemetry in Sprague-Dawley rats fed three levels of dietary salt, 0.4, 4.0, and 8.0%. By the third week of a 4.0% salt diet, arterial pressure was elevated significantly in sinoaortic-denervated but not sham-denervated rats. By the end of the third week of an 8.0% salt diet, 24-h arterial pressure was elevated 15 ± 2 mmHg above control in sinoaortic-denervated rats compared with a 4 ± 1 mmHg increase in sham-denervated rats. Hourly analysis of the final 72 h of each level of dietary salt revealed a marked effect of dietary salt on arterial pressure in sinoaortic-denervated rats, particularly during the dark cycle. Arterial pressure increased ~20 and 30 mmHg in sinoaortic-denervated rats over the 12-h dark cycle for 4.0 and 8.0% NaCl diets, respectively. In contrast, increased dietary salt had no effect on arterial pressure during any phase of the light or dark period in sham-denervated rats. These data support the hypothesis that arterial baroreceptors play a critical role in long-term regulation of arterial pressure under conditions of altered dietary salt intake.

Perhaps the most exciting new approach to examining the role of arterial baroreflexes comes from Thrasher (90), who recently developed a new surgical method to produce chronic unloading of arterial baroreceptors in dogs where the aortic baroreceptor nerves were cut and the carotid sinus isolated from the systemic arterial pressure. Baroreceptor unloading was induced by ligation of the common carotid artery proximal to the innervated sinus. Arterial pressure was consequently increased an average of 22 mmHg above control (Fig. 6). Removal of the ligature to restore normal flow through the carotid resulted in normalization of arterial pressure. Although SNA was not directly recorded, indirect evidence was provided that sympathetic drive was increased during the period of baroreceptor unloading. First, a significant increase in heart rate was evident throughout the period of baroreceptor unloading. Second, plasma renin activity was significantly increased, despite an increase in arterial pressure. Finally, and perhaps most significantly, the increase in renal perfusion pressure should have resulted in a pressure natriuresis; however, with baroreceptor unloading sodium excretion actually initially went down before returning to normal. The observation that sodium excretion was normal in the presence of a sustained increase in renal perfusion pressure must mean that the excretory ability of the kidneys was impaired. The exciting aspect of the Thrasher model is that the chronic unloading of baroreceptors may increase SNA. Many of our current interventions produce decreases in SNA either using interventions such as high-salt diets or removal of SNA completely via denervation; thus a stimulus that produces increases in SNA may be more reflective of the human condition of neurogenic hypertension with its associated increases in SNA.

Although Cowley (24) argued that the reflex gain of the baroreceptor control system is not sufficiently strong to regulate long-term arterial pressure, it is now clear that this concept fails to recognize the potential impact of the renal nerves in renal excretion, which is of paramount importance in long-term control of arterial pressure. Overall these results indicate that chronic unloading of carotid baroreceptors can produce neurogenic hypertension and provide strong evidence that arterial baroreceptors are involved in the long-term control of arterial pressure.

One serious limitation of the above studies is that the length of the experiments (5–10 days) is certainly not long enough to...
definitively conclude that baroreceptors will not adapt to a sustained stimulus. Previous studies have suggested that arterial baroreflexes are completely reset by 5 wk of hypertension induced by renal encapsulation (14). Furthermore, in renal clip hypertension the RSNA baroreflex gain was impaired at 3 wk but returned to normal at 6 wk (44). Although SNA was not measured in the same animal over this period, it does strongly indicate that resetting can occur under some conditions. Clearly a range of further experiments needs to be conducted to elucidate not only the ability of arterial baroreceptors to reset but most importantly to determine whether the baroreflex pathway really contributes to the development of hypertension.

THE ROLE OF ANGIOTENSIN IN REGULATING LONG-TERM LEVELS OF SNA

The possible role of angiotensin II in regulating long-term blood pressure via SNA has been receiving increasing attention. Acutely angiotensin II increases arterial pressure primarily through actions on the vasculature. However, there is substantial evidence that angiotensin II contributes to regulation of arterial pressure via actions on several brain sites. Angiotensin II receptor-binding sites are found in discrete areas of the forebrain and brain stem that are involved in the control of RSNA (3–5). In particular, dense angiotensin receptor binding is found in the NTS and the rostral and caudal regions of the ventrolateral medulla (3–5), and microinjection of angiotensin II or antagonists into these regions alters SNA. All these sites are critical nuclei involved in baroreflex pathway and suggest that angiotensin could exert its action on SNA via modulation of the baroreflex pathway.

Studies using ganglionic blockade as an indirect index of SNA have shown that the blood pressure decrease, in response to ganglionic blockade, is greater during angiotensin II-induced hypertension than before, suggesting sympathetic activ-

Fig. 7. Mean responses from 6 rabbits to a continuous infusion of angiotensin II for 7 days. Data are presented from the mean value for each 20-min period of record. Error bars represent SE for each day of recording. Angiotensin II infusion began at time 0 and ceased after 7 days as indicated by the vertical dotted lines. nu, Normalized units (the unit is %). [Reprinted with permission from Barrett et al. (12)].
ity is elevated during angiotensin II-induced hypertension (58). However, this is not without debate, as measurements of peripheral plasma catecholamine levels during angiotensin II suggest sympathetic activity does not change (17, 51), whereas renal norepinephrine spillover levels suggest sympathetic activity is decreased during angiotensin II hypertension (17). In part, this may reflect a differential nature of sympathetic activation with activation of RSNA and no change to other organs.

Recently, using direct long-term recordings of SNA and blood pressure in rabbits we explored the relationship between increased angiotensin II levels, SNA, and baroreflexes (12). A 1-wk period of angiotensin II infusion (50 ng·kg⁻¹·min⁻¹) caused a sustained increase in arterial pressure (~18 mmHg). Surprisingly, there was a sustained decrease in RSNA throughout the whole angiotensin II infusion, not an increase as previous literature would suggest (Fig. 7). Cessation of the angiotensin II caused blood pressure and SNA to return to control levels. The observation of sympathoinhibition during angiotensin II infusions is supported by Carroll et al. (17), who measured renal norepinephrine overflow as an indirect index of RSNA. Six days of angiotensin II hypertension was associated with marked reductions (not increases) in renal norepinephrine spillover. One explanation for the decrease in SNA is that the increase in blood pressure associated with the angiotensin II resulted in a sustained baroreflex-mediated reduction in SNA. The heart rate-to-blood pressure baroreflex response displayed evidence of the classical resetting with a rightward shift in the curve (Fig. 8). However, in the blood pressure-to-SNA relationship, there was no evidence of resetting (Fig. 8). In particular, there was an obvious decrease in the range of the reflex at days 2 and 7 of angiotensin II infusion. Significantly, before the angiotensin II infusion the resting point of the baroreflex curve lay near the steepest point of the arterial pressure-RSNA curve; however, during the angiotensin II infusion the resting point lay close to the lower plateau. Thus producing an increase in arterial pressure from this point using a rapid phenylephrine infusion did not result in any further decrease nerve activity. The arterial pressure at half the reflex range was not altered during the angiotensin II infusion; in other words, the overall curve was not shifted to the left or right. The gain of the curve was also unaffected, despite the decrease in range. On angiotensin II cessation, all baroreflex parameters had returned to control values when measured 3 days after stopping angiotensin II (Fig. 8). It was proposed that the lack of resetting of the blood pressure-SNA curve, with the resting point lying near the lower plateau, suggests the sustained decrease in RSNA during angiotensin II is baroreflex mediated. These results provide further support to the concept that arterial baroreflexes may play a significant role in the control of SNA and arterial pressure in the long term. The observation of a profound decrease in the range of the blood pressure-SNA relationship throughout all the period of angiotensin II infusion is similar with that described by Sanderford and Bishop (82, 83) after only 5 min of intravenous infusions of angiotensin II in conscious rabbits. They suggested this effect of angiotensin on the baroreflex relationship was due to a central action of angiotensin II, as opposed to a direct pressure effect because when the pressor effects of angiotensin were prevented using sodium nitroprusside, angiotensin II still caused a similar decrease in the range of the blood pressure-SNA curve (82, 83). The attenuation of the maximum RSNA during infusions of angiotensin II has been proposed to involve the area postrema, because in area postrema-lesioned rabbits, angiotensin II has no effect on the MAP-RSNA relationship (82). The lack of a blood-brain barrier in the region of the circumventricular organs, such as the area postrema, makes these organs prime targets for circulating angiotensin II. On first assessment, the above studies do not support the hypothesis that RSNA is involved in the development of hypertension as a result of increases in circulating angiotensin II. However, it is also clear that the changes in SNA observed during angiotensin II hypertension may be dependent on the pressure-induced changes in baroreflex function. Thus circulating angiotensin II may still influence SNA via some central control targets for circulating angiotensin II.
administration to baroreceptor-denervated rabbits appear to show RSNA being unchanged from baseline (13). It must also be noted that the action of angiotensin II itself may be complicated by an action on central nervous system pathways responsible for regulating SNA, in particular the central baroreflex pathway. Thus experiments using alternative pressor agents or surgical approaches [e.g., the Thrasher model (90)] will be critical in determining the ability of baroreflexes and angiotensin II to influence the long-term levels of SNA. It must be acknowledged that cardiopulmonary receptors are also likely to play an important role in regulating the response to angiotensin II. Administration of angiotensin II and changing blood pressure will also alter the stimuli to cardiopulmonary receptors, and the removal of arterial baroreceptors via sino-aortic denervation is unlikely to assist in delineating the role of the nonarterial baroreflexes. Such reflex pathways are likely to be very important in regulating the sympathetic response in heart failure.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

This review concentrated on the importance of understanding the long-term regulation of RSNA and the possibility that arterial baroreflexes, although initially dismissed, may play an important role in setting the long-term level of SNA and thereby blood pressure. It must be acknowledged that such pathways will certainly not be the only mechanism by which SNA is chronically regulated. Other pathways include the cardiopulmonary reflex and blood volume regulation, which also display evidence of a chronic effect on SNA (87, 93). In addition, chronic alterations within the central pathways themselves may also regulate the long-term levels of SNA (43, 59, 94).

In 1995, Brooks and Osborn (16) in an invited opinion article for this journal explored the concept that circulating hormones such as vasopressin and angiotensin II provide a long-term afferent signal to the central nervous system via binding to specific receptors in central sites. They suggested that the release of the hormones and the sympathetic response may be nonadaptive and thus a hormonal-sympathetic reflex was proposed. One of the primary bases for formulating this hypothesis was that the arterial baroreflex pathway was not involved as it supposedly reset to sustained increases in blood pressure. Now, as we approach a decade since that hypothesis was proposed and 30 years since arterial baroreflexes were dismissed (25), it appears that the wheel has turned and we must begin to revisit these questions again with new technologies and approaches.

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