Sympathetic Nervous System Overactivity and Its Role in the Development of Cardiovascular Disease

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Malpas SC. Sympathetic Nervous System Overactivity and Its Role in the Development of Cardiovascular Disease. *Physiol Rev* 90: 513–557, 2010; doi:10.1152/physrev.00007.2009.—This review examines how the sympathetic nervous system plays a major role in the regulation of cardiovascular function over multiple time scales. This is achieved through differential regulation of sympathetic outflow to a variety of organs. This differential control is a product of the topographical organization of the central nervous system and a myriad of afferent inputs. Together this organization produces sympathetic responses tailored to match stimuli. The long-term control of sympathetic nerve activity (SNA) is an area of considerable interest and involves a variety of mediators acting in a quite distinct fashion. These mediators include arterial baroreflexes, angiotensin II, blood volume and osmolarity, and a host of humoral factors. A key feature of many cardiovascular diseases is increased SNA. However, rather than there being a generalized increase in SNA, it is organ specific, in particular to the heart and kidneys. These increases in regional SNA are associated with increased mortality. Understanding the regulation of organ-specific SNA is likely to offer new targets for drug therapy. There is a need for the research community to develop better animal models and technologies that reflect the disease progression seen in humans. A particular focus is required on models in which SNA is chronically elevated.

I. INTRODUCTION

Historically, the sympathetic nervous system (SNS) has been taught to legions of medical and science students as one side of the autonomic nervous system, presented as opposing the parasympathetic nervous system. This review examines the evidence that over the past decade a new and more complex picture has emerged of the SNS as a key controller of the cardiovascular system under a variety of situations. Studies have revealed some of the central nervous system pathways underlying sympathetic control and where or how a variety of afferent inputs regulate sympathetic outflow. Our understanding of how sympathetic nerve activity regulates end organ function and blood pressure has increased along with the development of new technologies to directly record SNA in conscious animals and humans. Most importantly, increasing clinical evidence indicates a role for sympathoactivation in the development of cardiovascular diseases. Such information highlights the need to better understand how the SNS interfaces with the cardiovascular system and how this interaction may result in increased morbidity or mortality. Aspects of the SNS have been the subject of reviews in the past (79, 100, 185), and with between 1,300 and 2,000 publications published per year for the past 5 years involving various aspects of the SNS, it is not possible to cover in detail the wealth of recent information on this area. The accent of this review is on the nature of the activity present in sympathetic nerves, how it affects cardiovascular function, and how it is implicated in disease processes. It aims not to simply catalog the studies surrounding these areas, but rather attempts to distill down observations to provide future directions and pitfalls to be addressed.

II. RELEVANCE OF SYMPATHETIC NERVE ACTIVITY

SNS activity provides a critical aspect in the control of arterial pressure. By rapidly regulating the level of activity, the degree of vasoconstriction in the blood vessels of many key organs around the body is altered. This in turn increases or decreases blood flow through organs, affecting the function of the organ, peripheral resistance, and arterial pressure. In contrast to the activity present in motor nerves, sympathetic nerves are continuously active so all innervated blood vessels remain under some degree of continuous constriction. Since its first description in the 1930s (5, 46) sympathetic nerve activity (SNA) has engendered itself to researchers in two camps; neurophysiologists have seen its inherent properties as an opportunity to understand how areas of the central nervous system may be "wired" to generate and control such activity (152, 257, 337), while cardiovascular physiologists

saw its regulation of blood flow as a means to measure the response to different stimuli, drugs, and pathological conditions (101, 206, 327). However, the innervation to almost all arterioles and actions on specific organs such as the heart and kidney is not sufficient to justify its importance. What distinguishes the SNS is the emerging evidence that overactivity is strongly associated with a variety of cardiovascular diseases. A key question is, Does this increased SNA act as a driver of the disease progression or is it merely a follower? Furthermore, how does increased SNA accelerate the disease progression? Is it simply that it results in increased vascular resistance or are there subtle structural changes induced by elevated SNA or specific actions on organs such as the kidney through its regulation of the renin-angiotensin system and/or pressure natriuresis?

III. HISTORY CAN BE MISINTERPRETED

It was Walter Cannon who portrayed the SNS as central to the regulation of homeostasis (60). Cannon showed that when an animal is strongly aroused, the sympathetic division of its autonomic nervous system "mobilizes the animal for an emergency response of flight or fight. The sympathico-adrenal system orchestrates changes in blood supply, sugar availability, and the blood's clotting capacity in a marshalling of resources keyed to the violent display of energy." In this setting, the SNS and parasympathetic nervous system were presented as two opposing forces with the parasympathetic endorsing "rest and digest" while the SNS "flight and fight." An unintended side effect advanced in some textbooks (446, 479) has been to portray the actions of sympathetic nerves as confined to extreme stimuli. As will be advanced in this review, the SNS plays a key role in the moment-to-moment regulation of cardiovascular function at all levels from quiet resting to extreme stimuli. While SNA can be quite low under quiet resting conditions, removal of all sympathetic tone via ganglionic blockade significantly lowers blood pressure (339). Furthermore, removal of SNA to only one organ such as the kidney can chronically lower blood pressure in some animals, indicating its importance in maintaining normal cardiovascular function (224).

IV. WHAT IS SYMPATHETIC NERVE ACTIVITY?

Evidence that sympathetic nerves are tonically active was established from the 1850s with the observation that section or electrical stimulation of the cervical sympathetic nerve led to changes in blood flow in the rabbit ear (31). However, it was not until the 1930s that Adrian, Bronk, and Phillips published the first description of actual sympathetic discharges (6). They observed two obvi-

ous features: *1)* that discharges occur in a synchronized fashion, with many of the nerves in the bundle being active at approximately the same time, and *2)* that discharges generally occur with each cardiac cycle in a highly rhythmical fashion. They also noted that by no means was the overall activity level constant as it was increased by asphyxia or a small fall in blood pressure. This was the first direct evidence supporting Hunt's assertion in 1899 (219) that "the heart is under the continual influence of sympathetic impulses." These early studies answered a number of questions on the nature of multifiber discharges, such as whether the activity present in the nerve bundle reflected that of single fibers firing very rapidly, or groups of fibers firing more or less synchronously. They also showed that the synchronized activation of postganglionic nerves was not a function of the ganglia as it could be observed in preganglionic nerves and that activity was bilaterally synchronous, that is, that activity in right and left cardiac nerves was the same.

The origin of the rhythmical discharges was considered in the 1930s to be a simple consequence of phasic input from arterial baroreceptors, which had been shown to display pulsatile activity (47). This proposal had the effect of diminishing the role of the central nervous system to that of a simple relay station and may go some way to explaining the lack of further interest in recording SNA until the late 1960s. Green and Heffron (169) then reexamined the question of the origin of SNA after noting a rapid sympathetic rhythm (at ~10 Hz) under certain conditions (mainly reduced baroreceptor afferent traffic) that was far faster than the cardiac rhythm. This indicated that the origin of bursts of SNA could not simply be a product of regular input from baroreceptors. Their suggestion that the fast rhythm did not have a cardiac or ganglionic origin, but was of brain stem origin, stimulated interest from neurophysiologists, who could use this phenomena for the study of the central nervous system.

Postganglionic sympathetic nerves are composed of hundreds to thousands of unmyelinated fibers (102), whose individual contributions to the recorded signal are exceedingly small. But fortunately, their ongoing activity can be measured from whole nerve recordings because large numbers of fibers fire action potentials at almost the same time (synchronization) to give discharges of summed spikes. Although it is possible to perform single unit recordings from postganglionic nerve fibers (39, 107, 258), the favored approach is a multiunit recording. This is obviously a much easier experimental preparation, which allows recordings in conscious animals. However, several important points can only be shown from single-unit recordings. First, while multifiber discharges can occur at quite fast rates (up to 10 Hz), the frequency of firing in the single unit is much lower. Average rates in anesthetized rabbits have been recorded between 2 and 2.5 spikes/s for renal nerves (107), ~1.2 spikes/s for

splenic nerves in the cat (346), and between 0.21 and 0.5 spikes/s in the human (268, 308). This slow firing rate means that the rhythmical properties of the single-unit discharges are not seen unless their activity is averaged over time against a reference such as the cardiac cycle or respiration (107). Single unit recordings also show the minimal firing interval for postganglionic neurons is between 90–100 ms (385). This indicates it is unlikely that multifiber discharges represent high frequency impulses from a single neuron, but rather the summation of impulses from multiple fibers that fire synchronously. These properties have subsequently been confirmed with single unit recordings in the human (268, 306–308). The low firing rate of individual nerves seems to preclude the same neuron being activated more than once in each multifiber discharge (107, 234, 258, 310). Rather, it would seem that the activated neurons are drawn from a neuronal pool. It is unlikely that the low firing rate is due to a long refractory period for the nerves, since the individual nerves can be induced to fire at quite fast rates by stimuli such as from chemoreceptors or nociceptors (107).

The other important feature observable in single unit recordings is the relationship of the individual action potentials to the cardiac cycle. Although the average discharge rate is low, when the nerves do fire, they do so at approximately the same time in the cardiac cycle. Originally it was thought that reflex tonic input from baroreceptors was critical in the production of bursts of SNA. However, the seminal work of Taylor and Gebber in 1975 (473) and Barman and Gebber in 1980 (24) identified that the SNA bursts still occurred in baroreceptor-denervated animals (vagotomy and arterial baroreceptor denervated), but there was no longer a phase relationship to the cardiac cycle. The continued occurrence of SNA bursts in baroreceptor-denervated animals indicates the presence of an input from baroreceptors is not critical in generating the bursts. However, the baroreceptors do provide important cues as to when bursts should occur (entrainment). This observation subsequently stimulated an intensive investigation of the central nervous system cell groups that may be involved in generating and regulating SNA (174, 175, 334, 352, 445).

Within the literature, the term baroreceptors has been loosely defined as receptors located within the periphery that sense stretch induced by changes in pressure, e.g., cardiopulmonary, renal, arterial, etc. (129, 144, 267). With regard to the bursting pattern of SNA, it has been implied that it is the signal from arterial baroreceptors, i.e., carotid and aortic receptors, that provides the timing cues for when the bursts should occur (152, 153). Timing in this context indicates the relation of an individual burst to the arterial pressure wave. Thus phasic input from the receptors in the carotid sinus and aortic arch provide information to the central nervous system that regulates two features of SNA: the timing of bursts and the mean

level of SNA in response to short-term changes in blood pressure (24). Therefore, the regulation of the average level of SNA and the timing of when individual bursts occur has been thought to be regulated by the same central nervous system cell groups and processes. However, a recent study has challenged this concept (322). In conscious rabbits, removal of aortic and carotid baroreceptor nerves resulted in loss of control over the average level of SNA in response to changes in blood pressure. However, the timing/entrainment of the bursts of SNA (relative to the arterial pulse wave) was maintained. It was proposed that the central nervous system appears to require only a very small input possibly from remaining baroreceptor fibers, which may run within the vagal nerve to entrain the timing of sympathetic discharges (in the fashion of a "hair trigger" or sensitive trigger mechanism). These results suggest distinct processes are involved in regulating mean SNA in response to changes in blood pressure as opposed to processes involved in generating and regulating when bursts of SNA occur.

Recording of single-unit activity gives information on the population properties of the multifiber preparation. In the case of the renal nerves, the active portion of the population seems to be relatively homogeneous with uniform firing properties, conduction velocities, and responses to baroreceptor and chemoreceptor activation (107). However, a subpopulation of nerves, normally silent, can be activated under thermal stimuli (102), although it is difficult to describe some functional relevance to these different properties, as it is currently impossible to identify the termination in the kidney of the nerves being recorded. Jänig (225) has reviewed the different types of neuronal discharge patterns based on functional properties of the vasoconstrictive neurons supplying skeletal muscle of the cat hindlimb as well as hairy and hairless skin. There are quite clear differences in the activity of the nerves depending on its terminus. Activity to the muscle is increased by inhibition of arterial baroreceptors, or stimulation of chemoreceptors or nociceptors. In contrast, the cutaneous vasoconstrictor neurons are only weakly affected by arterial baroreceptor activation but are activated by other stimuli such as vibration and nociception (38, 227). Such analysis has also been completed in the human for single neurons supplying the sweat glands (307) and muscle vasculature (310) and show results consistent with the above.

V. ASSESSING SYMPATHETIC NERVE ACTIVITY IN THE HUMAN

Early methods for assessing SNS activity in the human often quantified global SNA through measurement of plasma or urinary norepinephrine. However, these are now considered to be unreliable indexes of SNA (116, 483) because of their low sensitivity and they do not quantify regional SNA. Furthermore, there is the dependency of plasma norepinephrine concentrations on rates of removal of neurotransmitter from plasma and not just on the norepinephrine release (120).

Researchers have also attempted to use a measurement of heart rate variability as an index of sympathetic tone (156, 223, 401). However, there are serious limitations to this technique (313). Specifically, while the low-frequency ($\sim$0.1 Hz) variability in heart rate is influenced by the SNS, there were also many examples where known increases in SNA were not associated with changes in low frequency variability. Houle and Billman (217) observed in dogs with healed myocardial infarctions that a period of exercise or cardiac ischemia was associated with decreased strength of the oscillation in heart rate at 0.1 Hz despite evidence of increased mean levels of sympathetic activity. Similarly, Arai et al. (18) found that the strength of the slow oscillation is dramatically reduced during exercise, while sympathetic activity is increased. Saul et al. (432) observed that a reflex increase in SNA induced by nitroprusside infusion in humans was associated with an increase in heart rate variability at 0.1 Hz. However, no reduction in variability occurred when SNA was reflexly reduced by phenylephrine infusion. Furthermore, Adamopoulos et al. (4) showed that in patients with congestive heart failure, spectral indexes of autonomic activity correlate poorly with other measures of autonomic function.

Radiotracer technology has been used extensively for studying norepinephrine kinetics in humans (119) and has now become a gold standard for assessing SNA in humans (271–273). Norepinephrine in the plasma reflects the transmitter released by sympathetic nerves that has spilled over into the circulation. Rather than the rate of release of norepinephrine from sympathetic nerve varicosities, norepinephrine spillover rate gives the rate at which norepinephrine released enters plasma. The norepinephrine spillover approach is based on intravenous infusion of small amounts of tritiated norepinephrine combined with regional venous sampling. Specifically it is based on the arteriovenous norepinephrine difference across an organ, with correction for the extraction of arterial norepinephrine, multiplied by the organ plasma flow to provide an index of the neurotransmitter spillover from the neuroeffector junctions. Infusion of titrated norepinephrine followed by regional blood sampling, e.g., coronary sinus and renal veins allows neurotransmitters that "spillover" from the heart and kidneys, respectively, to be measured (118, 119, 126). While this technique offers good estimations of regional SNA, it does have limitations; the technique of regional blood sampling means few studies include repeated measurements within the same subject, and thus comparisons are made between subjects. In addition, the technique provides a single measure of regional SNA at a particular point in time, and thus it

does not allow for continuous recordings. There is some evidence that the relationship between actual SNA and the norepinephrine spillover is not a linear relationship as very high rates of nerve discharge produce a plateau in the neurotransmitter release (42). Additionally, some drugs modulate norepinephrine release through presynaptic actions (280, 443), and changes in local norepinephrine metabolism can affect measurements. Finally, it must be considered that only a fraction (estimated at <20%) of the norepinephrine released from the nerve terminals actually enters the plasma, with the majority returned to the nerve varicosity via the norepinephrine transporter (120, 212).

Direct recordings of muscle SNA provide another common approach for assessing SNA in humans. These recordings (normally from the peroneal nerve) reveal characteristic bursting patterns similar to those seen in animals (Fig. 1) (315). The resting level is generally lower than that seen in animal models when calculated as bursts per minute or bursts per 100 heart beats (485, 487), indicating that there are many heart beats in which there are no bursts of SNA (268). It has been observed that the absolute level of SNA varies as much as 5- to 10-fold between normotensive subjects (70, 486) (Fig. 2). Initially, this was thought to be due to differences in the placement of the recording electrode, where better contact with the nerve would give a larger signal. However, more recent analysis of larger groups of individuals indicates the level of SNA to be highly consistent between repeated measures within an individual, although it does tend to increase with age (Fig. 2) (130). The level of MSNA did not correlate to the resting heart rate or blood pressure (within normal range) but was found to relate to cardiac output and thus total peripheral resistance in males (Fig. 3) (69–71). In particular, while a wide range of resting cardiac output values were observed in normotensive subjects, those subjects with high baseline muscle SNA had low cardiac output, and vice versa. More recently, the positive relationship between MSNA and total peripheral resistance has been found to be confined to males and not females (197), with females additionally having lower resting MSNA compared with men. It was suggested among the factors that contribute to the overall level of total peripheral resistance, the magnitude of sympathetic nerve activity has a greater role in young men compared with young women. In addition, there is evidence that resting muscle SNA levels are higher in normotensive men than women (214) and that these differences appear to extend past menopause (213). Therefore, other factors may have a greater contribution to the control of total peripheral resistance in resting women and may explain why women have less autonomic support of blood pressure than men (145).

Studies in identical twins have found the level of muscle SNA to be almost identical (490), suggesting the
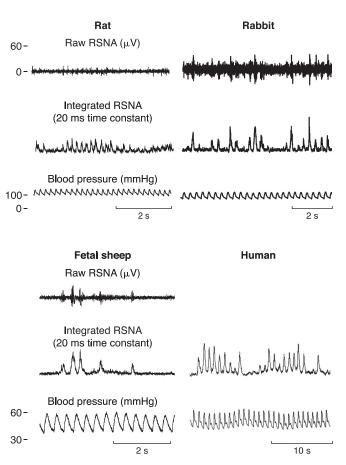

FIG. 1. Sympathetic nerve activity (SNA) recorded in four species: rat, rabbit, fetal sheep, and human. All data were collected under conscious unrestrained conditions (fetal sheep in utero) and are from the renal nerve except for the human for which muscle SNA is presented. Raw SNA for the rat, rabbit, and sheep was recorded with band-pass filter set at 50–2,000 Hz. This signal was rectified and integrated with a 20-ms time constant to produce the integrated SNA for the sheep, rat, and rabbit. Muscle SNA in the human was recorded with an integrator time constant of 100 ms. Note the variation in the amplitude of discharges even between neighboring bursts of SNA. Although average burst frequency is different between species, the timing of when the burst occurs is consistent between species. Human data were kindly provided by David Jardine. Other data are from the author's laboratory.

tone of SNA to be at least partly inheritable. Between subjects the level of muscle SNA has been correlated to blood pressure in subjects over 40 yr (but not under 40 yr) (372) and to body mass index (269). By the age of 60–70 yr, healthy subjects have muscle SNA values that are on average twice that of younger subjects (442, 468). Overall, while there appears to be a profound variation in the MSNA levels between individuals, rather than this being due to variations in recording techniques, the variation appears to have a physiological basis. Understanding more about the mechanisms underlying these relationships will be important if we wish to understand how SNA is increased in some cardiovascular diseases.

While there is only a weak relationship between baseline muscle SNA and blood pressure (70, 468), a
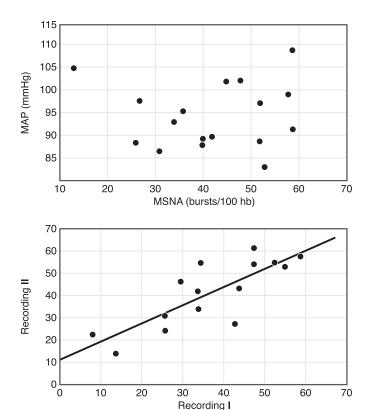
FIG. 2. The large variation in resting muscle SNA (MSNA) levels observed between normal subjects (*top panel*) (calculated as bursts per 100 heartbeats; hb). This figure also illustrates the lack of relationship between MSNA and resting blood pressure levels in normotensive subjects. [From Charkoudian et al. (70).] The *bottom panel* is measurements of MSNA obtained from the same subjects with an average of 12 years between recordings. The data indicate a strong degree of correlation between the recordings, indicating that the variation seen between subjects is not due to differences in the contact between the nerve and the recording electrode but inherent to the subject [From Fagius and Wallin (130).]

reciprocal relationship between SNA and counterbalancing vasodilator pathways has been postulated (237). Skarphendinsson et al. (451) demonstrated a linear relationship between plasma nitrates (a marker of whole body nitric oxide) and muscle SNA in normotensive humans, suggesting the high vasodilator tone might limit the blood pressure-raising effects of high SNA. Additionally, infusions of a nitric oxide synthase inhibitor produce a greater rise in blood pressure in individuals who had higher baseline muscle SNA, although this was confounded by differences in cardiac output. Finally, sympathetic vascular tone in the forearm circulation was not increased in obese normotensive subjects despite increased sympathetic outflow (7). Thus vasodilator factors or mechanisms occurring in some subjects could oppose the vasoconstrictor actions of increased sympathoactivation. Overall, there are a number of examples where there is an "uncoupling" of SNA from target organ responses. One classic example is during exercise where there is a

substantial increase in skeletal muscle blood flow while SNA is also increased (194, 430).

Results from single-unit recordings of SNA are broadly supportive of recordings from the whole nerve (268, 309, 310, 331). As noted above, the baseline firing rate is quite low in humans, yet rapid discharges from single units can occur in response to acute sympathoexcitation stimuli such as apnea, premature heartbeats, and the valsalva maneuver (364). Although a range of cardiovascular diseases are associated with increased firing rates from single nerves (113, 306), it remains to be established whether this is evidence of a disturbed firing pattern in those fibers, as has been proposed by some (268, 270). If this was the case, it would support the concept that an alteration in the central nervous system generation and control of sympathetic discharges occurs in cardiovascular disease.

Muscle SNA recordings are often used as surrogate estimates of global changes in SNA. While it has been observed that baseline muscle SNA is correlated with whole body norepinephrine spillover, and both renal and cardiac norepinephrine spillover under resting conditions (488, 492), it does not follow that this correlation occurs for all conditions. As discussed elsewhere in this review, SNA is differentially regulated to different target organs
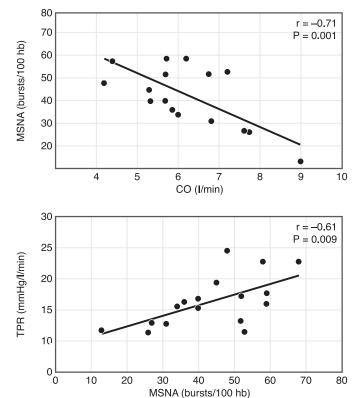

FIG. 3. The relation between MSNA and cardiac output (CO) (*top*) and the consequent positive relationship to the derived parameter total peripheral resistance (TPR) (*bottom*). MSNA was measured as bursts per 100 heartbeats (hb). [From Charkoudian et al. (70).]

and thus muscle SNA should ideally only be used as an index of muscle SNA. Overall, despite this limitation, regional norepinephrine and muscle SNA provide different but complementary information on the human SNS.

VI. ASSESSING SYMPATHETIC NERVE ACTIVITY IN ANIMALS

With regard to the measurement of SNA in animals, the most common approach is placement of a bipolar electrode directly around the intact nerve. The nerve and electrode is then insulated from the surrounding tissues, and the signal is amplified and recorded. The major recent advance is the ability to record SNA for an extended period in a range of conscious animals. In the rat, there have been a number of groups recording SNA for over a month (58, 349, 350, 481, 506, 507) and in the rabbit for 2–3 mo (182). It had been generally thought that the reason the nerve recording ceased was that either the nerve died or it became encased in connective tissue which insulated the nerve from the electrode. It is likely that nerve death does occur in some cases, but this is most likely within the first few days of implantation and may be associated with reduced blood supply to the nerve. The normal level of SNA is generally high after surgery and takes between 3 and 7 days to reach a steady baseline (26). While placement of electrodes on a sympathetic nerve is likely to always be a challenge due to the small size and frailty of the nerves, there are several key aspects that researchers can employ to improve the likelihood of obtaining viable signals: *1*) take extreme care to avoid stretching or crushing the nerve when freeing it from the surrounding tissue; *2*) tie the electrode firmly in place with two to four sutures to the underlying tissue, e.g., the artery; and *3*) use only the smallest amount of silicone elastomer to cover the nerve/electrode assembly. This is to ensure that movement of the assembly is unlikely to result in the nerve being stretched as it enters the silicone.

Until recently, researchers wishing to record SNA in conscious animals were forced to exteriorize the nerve leads and utilize a tether. However, implantable telemetry units now offer the opportunity to record SNA and blood pressure in freely moving animals living in their home cage (40, 322). This technology reveals that after the postsurgical recovery is complete, the nerve recording is relatively stable day to day. If nerve death and the growth of an insulating layer between nerve and electrode are not factors in these recordings, then it may be possible to maintain the nerve recording indefinitely. Clearly, such a possibility offers an exciting avenue for future research as it may be possible to follow the level of SNA throughout disease development within the same animal.

VII. QUANTIFYING SYMPATHETIC NERVE ACTIVITY

One major analytical problem in the assessment of SNA arises from the fact that the signal is measured in microvolts, and a number of factors, including differences in contact between the nerve and electrode, could lead to differences in the amplitude of the recorded signal. The most common approach to quantify SNA has been to report changes after some intervention as a percentage of the baseline level in the same animal. Although this approach is well suited to within-animal comparisons using short-term recordings lasting several hours, more recently a variety of groups have begun to record SNA over much longer time periods (27, 143, 349, 481, 507). The development of new technologies for remotely recording SNA and blood pressure in freely moving animals opens the door to measuring SNA within the same animal throughout the disease progression or between animals in different disease states.

The optimum method initially for assessing SNA is simply to listen to the audible nature of the discharges. In addition, when using the systolic pressure waveform as a trigger and multiple sweeps of SNA are obtained to give an average signal, it is possible to see the rhythmic nature of the sympathetic discharges (Fig. 4). In a "good" sympathetic recording, where bursts can be seen in the filtered SNA (sometimes termed original SNA) signal and in the integrated SNA data, the systolic wave-triggered averages show a distinct phasic relationship between arterial pressure and the renal SNA (322). This can be compared with the signal (Fig. 4*B*), where no distinct bursts can be seen and there is no phasic relationship between the SNA signal and the arterial pressure pulse. Such a poor SNA signal would likely exclude the animal from further protocols. However, it should be noted that in animals that are well recovered from surgery and are undisturbed in their home cage may well have an SNA signal with very few distinct bursts but will respond to stimuli such as a decrease in arterial pressure (e.g., infusion of sodium nitroprusside) or nasopharyngeal activation (see below).

The most common approach to recording SNA is to apply bandpass filters with a high pass around 50 Hz and a low pass between 1 and 5 kHz. By calibrating the amplifier, one can calculate the actual microvolt level of each discharge. However, because the signal displays positive and negative voltage changes centered about zero, the average level over time will be zero. To allow calculation of the overall level of SNA, either the individual spikes must be identified and counted, or more commonly the signal is rectified and integrated. A common method is to use a "leaky integrator" with a 20-ms time constant (321). The integrator serves as a low-pass filter, providing an indication of the average discharge intensity during sustained bursts of activity (>20 ms). As a result of the
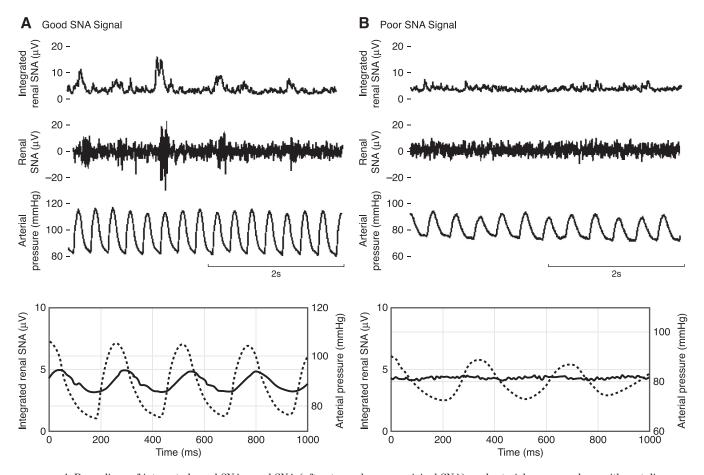
FIG. 4. Recordings of integrated renal SNA, renal SNA (often termed raw or original SNA), and arterial pressure along with systolic pressure triggered averaged records of arterial pressure (dashed lines) and renal SNA (solid lines) (*bottom plots*). Examples are shown from two individual conscious rabbits with "good" SNA signal (*A*) and poor SNA signal (*B*). Note that each recording was obtained from a separate animal, hence the different scales.

integration, bursts of SNA are converted into a series of peaks (Fig. 1). The amplitude and frequency variations between bursts are clearly visible. Bursts can be detected in the integrated signal using either a threshold voltage or a rate of rise of the voltage or often a mixture of the two (321, 336). While the amplitude of a single synchronized discharge can be measured in the filtered signal, it is apparent that there have been few attempts previously to provide units for the integrated signal. Terms such as normalized units, arbitrary units, and percentage are in common use. However, as can be seen from Figure 5, if the gains of the recording amplifier and integrator circuits are known and used to calibrate the output signals, the integrated SNA signal describes the amplitude of the original SNA signal faithfully. It is therefore proposed that the units of microvolts are appropriate when describing the integrated SNA signal.

Recently, Guild et al. (41) have proposed that with the use of units of microvolts it is possible to report the absolute level of SNA for a group of animals. Some researchers have measured the absolute microvolt level of SNA and compared between groups (304, 357). As noted

above, it has been considered that differences in the contact between the nerve and electrode result in differences in the microvolt signal amplitude and in particular the level of noise on the signal. By measuring the variation in the baseline level of renal SNA in a group of 20 rabbits, Guild et al. (41) estimated the magnitude of a change in SNA that would be required for an intervention to be considered to have had a significant effect. They predicted that given a group size of eight, one could detect (with 80% power) a ≥50% change in SNA when comparing between two groups. While this number appears large, it should be noted that the baseline SNA levels in their animals were very low so only a small absolute change is required to see a large relative change. Also, a within-animal design would be expected to increase the sensitivity to detect a smaller change.

A variety of approaches have been utilized to attempt to scale the signal; for example, the baseline level has been given an arbitrary value of 100% and then changes are referenced to this. Alternatively, baroreceptor unloading or nasopharyngeal stimuli (via a small puff of smoke to the face of the animal) have been used to increase SNA
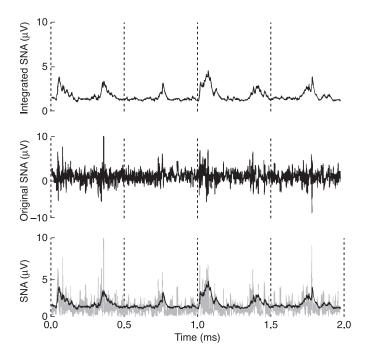
FIG. 5. Recording of renal SNA from a conscious rabbit showing the integrated SNA (*top panel*) and original SNA (*middle panel*, filtered between 50 and 2,000 Hz). The integrated SNA (black line) overlays the rectified original SNA signal (gray line) (*bottom panel*) and indicates that the same units (μV) can be used for both signals.

and the resulting level classified as 100% (56). Nasopharyngeal stimuli evokes the largest known recruitment of renal nerves (108) and has been found to be highly reproducible within an animal (56). With the use of this stimulus, where mean renal SNA can increase up to fivefold, it has been estimated that resting nerve activity may only comprise the activation of 10–20% of the nerves in the bundle (323). Burke and Head (56) showed that normalization using the SNA response to the nasopharyngeal stimulation could remove differences in the blood pressure to renal SNA baroreflex curves between two groups of rabbits separated on the basis of having either low or high baseline SNA. Furthermore, this form of normalization could also remove the 50% decay that they observed in baseline SNA over 5-wk recordings. They also showed that calibration of renal SNA against the response to nasopharyngeal stimulation, when comparing a group of hypertensive rabbits to a control group, revealed the blunting of the baroreflex in the hypertensive animals (56). This blunted response was not detectable when the SNA was calibrated using other methods such as airjet stress, the upper plateau of the baroreflex curve, or the baseline level of SNA. This suggests that nasopharyngeal stimulation of SNA provides a means to calibrate SNA both between groups of animals and during within-animal chronic experiments. While this technique has been used extensively in rabbits, caution is required as it appears

that the technique has yet to be examined and validated in other species, including the rat.

Ganglionic blockade has also been used to provide a zero baseline level, the nasopharyngeal stimulation of 100%, and the resting SNA level set against this. Thus one normalized unit reflects 1% of the difference between minimum and maximum SNA. However, the use of ganglionic blockade may not always be practical or even possible. In some research models, such as heart failure, the risk of death or prolonged residual actions following ganglionic blockade may deter researchers from its use. Guild et al. (180) have noted that the quiet period between SNA bursts is comparable to the zero level measured during ganglionic blockade.

In multifiber recordings, if there are single nerve fibers which are tonically active, but which discharge in a nonsynchronized fashion, for example, not related to the cardiac cycle, these will not be observable in the recorded signal and thus may be counted within the noise of the signal. Such possibilities exist for nerves that may perform nonvasoconstrictive functions or have a thermoregulatory function as, in the case of the skin SNA (307). One concern, raised by some researchers regarding the interpretation of measurements of efferent renal SNA, is the potential confounding effect of changes in renal afferent nerve activity. The firing properties of renal afferent nerves are, however, quite different from efferent activity in that discharges are from single units that do not display coordination/entrainment into groups or bursts. This means that in the recording of nerve activity from an intact nerve, it will not be possible to observe the afferent units as their activity will be considerably smaller than the efferent signals, often within the noise level. The afferent activity is increased by a range of stimuli including increased renal pelvic pressure and altered chemical composition of the urine (261, 360, 361). Given the low firing rate of the afferent nerves, their firing properties, and sensitivities, it would appear unlikely that measured changes in renal efferent activity are confounded by increases in renal afferent activity. Finally, the renal afferent nerves only account for ~5–10% of the total nerve bundle.

Overall, it is recommended that actual microvolt levels of integrated SNA be presented (with the zero/noise level subtracted) along with burst amplitude and frequency information whenever possible. It is hoped that standardization of the quantifying/reporting of SNA will allow better comparison between disease models between research groups and ultimately allow data to be more reflective of the human situation.

VIII. AMPLITUDE AND FREQUENCY OF SYMPATHETIC DISCHARGES

Green and Heffron (169) were the first to comment on variation in the amplitude of discharges. Their obser-

vations raised the possibility that this aspect of SNA may be under separate control from discharge frequency. They observed that activation of right atrial receptors led to a reduction in overall SNA by reducing the amplitude rather than the frequency of discharges. Ninomiya et al. (380) have proposed that the amplitude of discharges reflects alterations in the number of activated nerves within each discharge. It could be argued that a change in the mean amplitude of discharges could reflect the activation of different populations of nerves during stimuli. However, the enormous variation in the amplitude of discharges even between neighboring bursts (Fig. 1) suggests this is unlikely, at least under normal conditions. In anesthetized cats, baroreceptor activation by increasing blood pressure (a small amount) with norepinephrine produced a decrease in the frequency of discharges but little change in the amplitude of these discharges (319). However, chemoreceptor stimulation produced a selective increase in the amplitude of discharges. These observations support the hypothesis that these two components of SNA can be differentially controlled in response to different stimuli (314). The question arises then as to the location and mechanisms underlying this control. It is possible that under normal conditions, while not regulating the rhythmicity of sympathetic discharges, mechanisms in the spinal cord govern the number of preganglionic neurons activated by each descending stimuli. In support of this theory, a number of cell groups (e.g., paraventricular nucleus of the hypothalamus, A5, medullary raphe) have direct projections to the intermediolateral cell column and bypass the RVLM (465, 466). One hypothesis advanced in this review is that the network of cells involving the RVLM provide the basal level of nerve recruitment and determine the firing frequency based on the intrinsic rhythmicity and phasic input from arterial baroreceptors, but that inputs from cell groups with direct projections to the spinal cord provide an extra level of gain/recruitment of fibers (Fig. 6). The key feature of this proposal is that it provides for independent control over the frequency and amplitude of sympathetic discharges, e.g., where an increase in blood volume via cardiopulmonary reflexes may decrease the amplitude of SNA discharges without altering their frequency. A further extension of the hypothesis is that there is the ability to differentially affect SNA discharges to particular key organs, e.g., changes in blood volume affect renal SNA preferentially to SNA to other organs.

The concept of differential control over the amplitude and frequency of SNA has been strengthened by recent work by Ramchandra et al. (419) who measured renal and cardiac SNA in sheep in response to an increase in blood volume. They observed that volume expansion decreased overall SNA in cardiac and renal nerves but that the cardiac SNA decrease was due to a reduction in the discharge frequency while renal SNA fell due to a decrease in frequency and amplitude. Thus, not only can the amplitude and frequency of SNA discharges be differentially regulated to a single organ, but is also between organs. Of particular significance is their work on pacing-induced heart failure in which volume expansion caused no change in cardiac SNA and a small decrease in renal SNA, due entirely to decreased amplitude. These data indicate that differential control extends to selective changes in cardiovascular pathologies where SNA is chronically increased.

Interestingly, it appears that the observations of differential control of amplitude and frequency of SNA in animals had been preempted by observations on humans. Sundlöf and Wallin (468) showed that a 10-mmHg variation in diastolic pressure caused a twofold change in discharge amplitude but a fivefold change in the frequency of human muscle sympathetic activity. At that time, the implications of these findings for the control of SNA were not pursued, although more recent work (249) supports the concept of differential control, in particular in response to baroreceptor stimuli (251). It is pertinent to reflect that the most common method for quantifying SNA in humans is to record either the number of bursts per minute (burst frequency) or per 100 heartbeats (burst incidence) (329, 484, 489, 491). One difficulty with this approach is that changes in the recruitment of nerves, i.e., amplitude of bursts will not be adequately accounted for. While the absolute sympathetic burst amplitude will be a function of electrode proximity to nerve fibers in human recordings, the distribution of the burst amplitudes appears to be similar in repeated peroneal nerve recordings in the same subject (470). Overall, it is likely that some index of changes in burst amplitude when measuring SNA in humans would be useful.

Although it has been established that the timing of sympathetic discharges is quite closely regulated (24, 146), there is little information on the factors regulating the number of nerves recruited in each synchronized SNA discharge. If one plots the amplitude of a single discharge against the amplitude of the preceding discharge, no relationship between neighboring discharges can be identified, i.e., a large discharge is just as likely to be followed by a smaller discharge as by a large discharge (315). Furthermore, this variability between discharges does not seem to be affected by some stimuli. For example, although hypoxia increases the mean number of nerves recruited, the coefficient of variation between discharges is not altered (316). The amplitude of discharges follows a unimodal distribution (320). Although the intervals between discharges conform either to a burst every heart beat or every two to three heart beats, it appears to make no difference to the amplitude of a discharge whether it was preceded by a long period of no sympathetic activity or many high-frequency discharges.
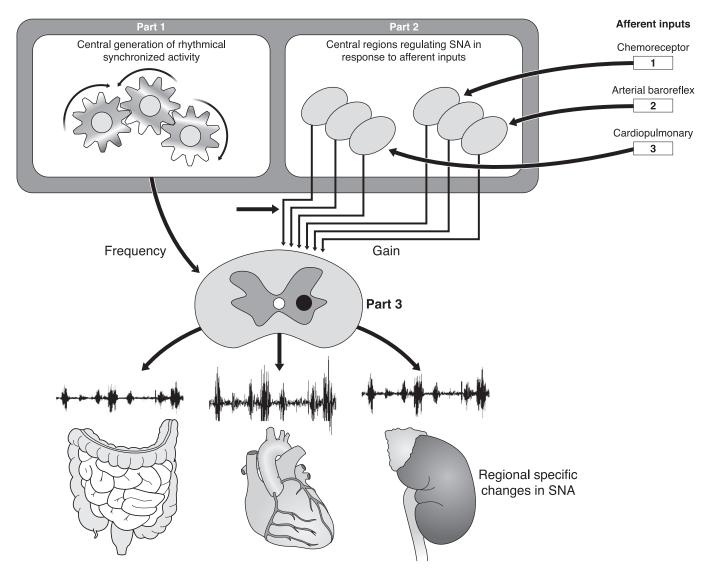
Part 1

Central generation of rhythmical synchronized activity

Part 2

Central regions regulating SNA in response to afferent inputs

Afferent inputs

Chemoreceptor

1

Arterial baroreflex

2

Cardiopulmonary

3

Frequency

Gain

Part 3

Regional specific changes in SNA

FIG. 6. Schematic of the proposed organization for the generation and regulation of SNA discharge properties to different organs. In *part 1*, a network of cell groups produces rhythmical discharges. This grouping involves the RVLM as a key element. In *part 2*, distinct central nervous system cell groups (e.g., PVN, A5 etc) receive afferent inputs from multiple sources (e.g., chemoreceptor, cardiopulmonary, arterial baroreflex, etc.). These inputs provide for differential regulation over SNA to particular organs (termed the tailored responder hypothesis). These inputs regulate the recruitment of nerves (gain) (*part 3*). The regulation of gain is independent of the generation of rhythmical activity and may interact at the level of the spinal cord or within the brain stem. The final result is an ongoing pattern of SNA where the timing of the discharges (rhythmicity) displays a high degree of coherence to different organs but where the mean level of activity and nerve recruitment are selectively adjusted in terms of the input from afferent inputs.

IX. IS THERE AN ADVANTAGE GENERATING SYNCHRONIZED ACTIVITY?

What advantage does it confer to cardiovascular control to have coordinated bursts of nerve activity? Evidence suggests that it is not just nerves to a single organ that display bursts, but activity traveling to organs such as the heart and kidney display a high degree of coherence in the timing of their bursts (154, 256). This suggests a common initiator for the synchronization of discharges, although there may be separate control over the overall level of SNA. This does not, however, reveal why activity

in individual nerves is coordinated to form synchronized activity. Indeed, it could be argued that the uncoordinated firing of the individual neurons would give the same level of control as the synchronized discharges, providing the overall level of activity was the same. This hypothesis is in some way supported by evidence that the blood vessels do not respond to the individual discharges with vasoconstriction (181, 229). Thus an average discharge rate between 2 and 6 Hz does not lead to a 2- to 6-Hz cycle of vasoconstriction and dilation in the vasculature.

While there are no direct studies indicating the advantage of synchronized discharges for cardiovascular

control, indirect evidence and theoretical studies suggest that such coordination leads to an increase in the gain of the system. That is, the signal comprising hundreds of nerve fibers activated synchronously, and in which the level of activation may vary in both frequency and amplitude domains, greatly increases the number of responses that can be configured to different stimuli. Birks (35) showed that electrical stimulation of preganglionic neurons with patterned stimulation rather than constant frequency increased the acetylcholine output of the terminals by as much as threefold.

It could be argued that synchronization simply reflects the nature of the inputs to the circuits generating sympathetic tone and serves no real functional purpose. However, there is some evidence that the coordinated nature of the discharges may lead to a coordinated release of neurotransmitter at the neuromuscular junction (23, 462). While the blood vessels may not constrict and relax with each discharge, they do respond to the coordinated mass release of neurotransmitter with sustained contraction (229). Andersson (16) tested whether electrical stimulation patterned into high-frequency bursts every 10 s induced greater vasoconstriction than continuous regular impulses (the total number of pulses being the same). Both types of stimulation were capable of evoking maintained constriction in cat skeletal muscles, but there was no effect of the pattern of stimuli unless the burst frequency was very high. However, Hardebo (196) took a more accurate approach by measuring the release of norepinephrine and tested whether the release would be greater with high-frequency burst stimulation rather than continuous low-frequency stimulation, again with the same total number of pulses. With regard to the rat caudal artery, burst stimulation at an average frequency of 6 Hz resulted in a 44% greater contractile response than using equally spaced stimuli. Furthermore, the norepinephrine release to each form of stimuli was also compared during electrical field stimulation of rat pial and caudal arteries as well as rabbit ear and basilar arteries. In all vessel segments studied, there was a greater release of norepinephrine when stimulation was in coordinated bursts, similar to that occurring in tonic SNA, rather than continuous trains of stimuli.

It appears that different frequencies of SNA can evoke different neurotransmitter responses. Neurotransmission was shown to be highly calcium dependent with electrical stimulation at low frequencies, but not during higher frequency stimulation (449). Additionally, high-frequency stimulation of the nerves in small mesenteric arteries of the rat mainly evoked the release of norepinephrine, while slower frequency stimulation involved an undetermined nonadrenergic transmitter (450). Similar responses were observed for the pig spleen, where the release of neuropeptide Y (NPY) was enhanced by electrical stimulation at frequencies below 2 Hz (399). Higher frequencies enhanced both NPY and norepinephrine release. The central ear artery of the rabbit also shows different responses to slow and fast frequency stimuli, low frequencies favoring a purinergic response and faster frequencies the norepinephrine component (250). These findings suggest that the different frequencies of SNA do not simply mean greater or lesser vasoconstriction in the innervated vasculature but may reflect different phenomena with different functional responses as a result of different neurotransmitters involved.

X. EFFECT OF SYMPATHETIC NERVE DISCHARGES ON THE VASCULATURE

The most common method for quantifying SNA is to average the signal over a period of time (e.g., 1–2 s); however, this ignores the rhythmical properties of SNA. Fluctuations in the level of SNA have been identified at the heart rate, at the respiratory frequency, and at a lower frequency, typically 0.1 Hz in humans (392), 0.3 Hz in rabbits (230), and 0.4 Hz in rats (53) (in blood pressure these are often referred to as Mayer waves). Slower oscillations in SNA, <1 Hz, result in a cycle of vasoconstriction and vasodilation within the vasculature, the amplitude of which generally decreases with increasing frequency (181). These slower frequencies result in oscillations in blood pressure and, via the baroreflex loop, in oscillations in heart rate. Experiments by Stauss and Kregel (457) using electrical stimulation of sympathetic nerves at different frequencies showed that the mesenteric vasculature was able to follow SNA frequencies up to 0.5 Hz, but not beyond 1.0 Hz. They subsequently performed electrical stimulation of the paraventricular nucleus of the hypothalamus at multiple frequencies to evoke oscillations in splanchnic nerve activity and mesenteric blood flow (459). These observations have also been confirmed for the renal vasculature (181), where the transfer function between SNA and renal blood flow reveals low-pass filter characteristics and a time delay between SNA and the renal blood flow response between 650 and 700 ms. Studies indicate that within the same species, differences exist in the frequency responses between vascular beds, such as the skin, gut, and kidney (177, 460). This differential responsiveness is also found between the medullary and cortical vasculature regions of the rabbit kidney (183). The ability of the vasculature to respond to faster frequencies of SNA with steady tone and to lower frequencies with an oscillation is indicative of an integrating-like phenomenon. Clearly, it results from a complex series of interactions between the characteristics of the neurotransmitter release and removal, second messenger pathways in the smooth muscle (i.e., the excitation-contraction coupling) (210, 211, 455), and interactions with the intrinsic regulatory systems of the vasculature such as

nitric oxide (456, 458). Studies on isolated rat vascular smooth muscle cells suggest that sympathetic modulation of vascular tone is limited by the α-adrenoceptor signal transduction with smooth muscle cells and not by an intrinsic inability of the cells to contract and relax at higher rates (456). For the vasculature to respond to such changes with vasoconstriction at similar time scales requires that sympathetic transmission at the α_1-receptor or other receptor (e.g., purinergic) sites be fast enough to transmit oscillations in this frequency range.

XI. EFFECT OF SYMPATHETIC NERVE DISCHARGES ON THE HEART

The ability of the heart and vasculature to respond quickly to changes in sympathetic activity (frequency responsiveness) is quite different despite evidence that the pattern of sympathetic outflow to the heart and organs such as the kidney is similar (381). The heart rate response to sympathetic nerve stimulation is slower than that of the vasculature. With regard to steady-state changes in SNA, the heart rate response is characterized by a time delay of 1–3 s followed by a slow increase with a time constant of 10–20 s. In the frequency domain, the heart rate response is characterized by a low-pass filter system with a cutoff frequency of ~0.015 Hz coupled to a 1.7-s time delay (30). The slow development of the heart rate response has been attributed to the slow norepinephrine dissipation rate and/or to the sluggishness of the adrenergic signal transduction system (281). Administration of the neuronal uptake blocker desipramine significantly slowed the heart rate response to sympathetic nerve stimulation, suggesting that the removal rate of norepinephrine at the neuroeffector junction is a rate-limiting step that defines the frequency response (368). This is in contrast to the vasculature, where the reuptake blocker did not affect the frequency response (32). Mokrane and Nadeau (353) identified two components in the heart rate response to SNA. With low intensities of sympathetic activation, the β-adrenergic response was faster than at higher intensities of nerve stimulation. There is evidence that vagal and sympathetic influences on the heart, while antagonistic with regard to heart rate, do appear to interact in a dynamic fashion. In particular, sympathetic stimulation combined with vagal stimulation increased the gain of the response and thus appears to extend its range of operation (242, 243). The regulation of cardiac function by the autonomic nervous system has been recently reviewed by Salo et al. (429).

XII. VASCULAR CAPACITANCE AND SYMPATHETIC NERVE ACTIVITY

Vascular capacitance is strongly influenced by SNA. The compliance of the veins is many times higher than arteries; thus total vascular capacitance is largely driven by venous capacitance. It is often overlooked that the venous circulation receives considerable sympathetic innervation, and with ~70% of the blood volume (394) can play a significant role in the acute cardiovascular responses to sympathetic activation. It is thought that changes in sympathetic nerve firing to the arteries and veins of any particular organ are similar. However, small veins and venules have been shown to be more sensitive to sympathetic activation than arterioles (216). In particular, electrical stimulation of sympathetic nerves depolarizes the venous smooth muscle cells more than arteriolar smooth muscle cells, and the contraction is greater and earlier in veins than in arteries. The splanchnic venous bed in particular is densely innervated by the SNS and represents the most important active capacitance bed in the body (171, 425). The splanchnic circulation, as one-third of the total blood volume, is the largest single reservoir of blood available for augmenting circulating blood volume (193). Venoconstriction in the splanchnic circulation results in a significant shift of blood towards the heart, increasing diastolic filling, and thus increasing cardiac output (172, 173).

Reduced vascular capacitance has been found consistently in humans with hypertension (428), which would be expected to redistribute blood stored in the splanchnic organs to the central circulation. It has recently been proposed that some models of hypertension that involve sympathetic activation (i.e., salt and angiotensin II-mediated hypertension; see sect. XIV) may be associated with an increase in blood pressure through an action of SNA on venous smooth muscle (252, 253). In rats on a high-salt diet plus infusion of angiotensin II, central venous pressure and mean circulatory filling pressure (MCFP) as an index of venous smooth muscle tone were measured. Angiotensin II plus high dietary salt intake resulted in an increase in MCFP but not changing blood volume throughout the 14 days of the study. MCFP is the pressure measured in the vasculature immediately after cardiac arrest, after pressures in all parts of the circulation are equal (190). The major determinants of MCFP are compliance of the venous system and blood volume (505). This increase in MCFP with angiotensin and salt was abolished by acute ganglionic blockade or celiac ganglionectomy, suggesting the increase in venomotor tone was sympathetically driven.

As reviewed by King and Fink (252), reduced vascular capacitance has been documented in human and animal models of hypertension. The increase in venous constriction and subsequent decrease in whole body venous capacity is thought to be neurogenically driven in many experimental models such as DOCA salt hypertension, spontaneously hypertensive rats (SHR), and Goldblatt hypertension (138, 330). In human hypertension, blood volume is not generally increased; however, there is a reduc-

tion in vascular capacitance which leads to an increase in the "effective blood volume," i.e., proportionally less blood volume residing within the veins. Since vascular capacitance is strongly controlled by the SNS and is predominantly influenced by compliance of the venous system, increases in venomotor tone driven by SNA may be important mediators in cardiovascular disease development and are certainly worthy of further research. While reduced vascular capacitance would be expected to acutely redistribute blood stored in the splanchnic organs to the central circulation, it should be noted that it is debated whether this would lead to a sustained increase in the central circulation without attendant alterations in the renal pressure natriuresis relationship (355). Furthermore, it is controversial whether an increase in MCFP is a causal mechanism leading to hypertension rather than an associated event. The use of mathematical models shows some potential in delineating the relative roles of various vascular compartments (3, 188).

XIII. DIFFERENTIAL CONTROL OF SYMPATHETIC OUTFLOW

The central nervous system receives a myriad of afferent inputs that are integrated and processed to generate efferent SNA response patterns. The central pathways and the patterning of SNA to various target organs have only been characterized for a few reflexes, in particular, the arterial baroreflex (see Ref. 185 for review). However, baroreceptor afferents provide only a small fraction of the signals to the brain that influence cardiovascular homeostasis. Other signals include chemoreceptors, cardiopulmonary receptors, inputs from higher brain centers, cardiac and renal afferents, and hormonal mediators to name a few. The aim of this review is not to detail the volumous wealth of information on central pathways, neurotransmitters, and cell groups involved in mediating sympathetic reflexes but rather to focus on the connections between central pathways, afferent reflexes, and disease states in the overall control of SNA.

Baseline SNA is driven by a network of neurons in the rostral ventrolateral medulla (RVLM), the hypothalamus, and the nucleus of the solitary tract (NTS) (88). In addition, cortical, limbic, and midbrain regions modulate ongoing SNA (168). Researchers measuring SNA in animals or humans often refer to SNA as if it is a generalized output of the central nervous system (CNS). However, there is good evidence both from direct recordings of regional nerve activity and from anatomical tracing of circuits within the CNS that the control of SNA is highly differentially regulated. This concept has been referred to as organotrophy or topography (185, 335, 408, 410), where separate groups of CNS neurons and pathways are associated with the regulation of SNA to specific organs.

Although it appears that every sympathetic preganglionic neuron receives some input from the same general areas of the hypothalamus, brain stem, and spinal cord (228, 469), it is apparent that these regions contribute unequally to the various sympathetic outflows. As reviewed by Guyenet (185), sympathetic outflow under strong baroreceptor control is regulated through the RVLM, whereas the cutaneous circulation is regulated through the rostral ventromedial medulla and medullary raphe (36, 37, 226). Within the RVLM there are a group of epinephrine-synthesizing cells (C1) that appear to be a key site regulating SNA to most target organs except the skin (52). One aspect of the organotrophic concept is that separate subgroups of RVLM neurons preferentially control SNA to skeletal muscle, splanchnic circulation, heart, and kidneys (59, 80, 335, 338).

One relevant observation is that when bursts of SNA occur, the timing and discharge characteristics share a high degree of commonality between SNA to different organs. For example, a series of bursts seen in lumbar SNA is likely to mirror that in renal SNA. Yet when a stimulus such as blood volume expansion is applied, the mean level of renal SNA declines, but lumbar SNA is unchanged (416). It appears that the underlying frequency of bursts of SNA has not changed, but rather the number of recruited nerves appears to decline. This differential control has been further extended to renal and cardiac SNA (419). This supports the concept of an independence in the control over the frequency of discharges and their amplitude (reflecting the relative number of nerves recruited) as discussed above. It is hypothesized that there is a high degree of commonality in the central nervous system pathways involved in generating sympathetic discharges, but other regions regulate the number of recruited nerves resulting in variations in the amplitude of discharges. As discussed in the above section on the amplitude and frequency of sympathetic discharges, these regions may include the paraventricular nucleus of the hypothalamus, A5, and medullary raphe which have direct projections to the spinal cord. SNA to many organs is under a high degree of baroreflex control, and yet to other organs is only weakly affected by changes in blood pressure, e.g., to the skin (378, 379). SNA to the skin generally displays a low level of mean SNA, typified by infrequent bursts, yet when bursts do occur, they have a high degree of coherence with SNA discharges to other organs. Possibly they are exposed to the same central generation processes but that the number of nerves recruited is being held at a low level by other factors. This hypothesis is illustrated in Figure 6.

An additional way to view SNS control of the cardiovascular system is as a "tailored responder"; that is, the central nervous system receives inputs from a host of afferent sources (e.g., baroreceptors, higher centers, blood volume, etc.). These are processed to produce

changes in SNA that effectively restore homeostasis without compromising other functions, i.e., the response matches the stimuli. Differential regulation of SNA occurs under many conditions with presumably the primary aim of redistributing blood flow. For example, an abrupt lowering of blood pressure results in baroreflex-modulated increases in SNA to many organs, e.g., muscle, renal, and gut, utilizing organs that at rest receive a large portion of cardiac output and thus to which changes in flow will exert a larger effect on total peripheral resistance. In contrast, a stimulus such as an alteration in plasma osmolarity and/or blood volume produces a different pattern of changes in SNA with a preferential alteration in renal SNA (416). Similarly, chemoreceptor activation in the rabbit produces a rise in renal and splanchnic SNA, a decrease in cardiac SNA, and overall no change in blood pressure (222). The tailored responder hypothesis (illustrated as part of Fig. 6) provides a substrate for understanding how differential activation occurs in cardiovascular diseases.

XIV. WHAT REGULATES THE LONG-TERM LEVEL OF SYMPATHETIC NERVE ACTIVITY?

SNA has a tonic baseline level of activity that is adjusted up and down in response to a variety of afferent inputs, e.g., arterial baroreceptors, chemoreceptors, cardiopulmonary receptors, etc. These adjustments occur rapidly (i.e., within 1 s in response to changes in blood pressure), over longer times scales of minutes in response to changes in blood volume, and over much longer time scales in response to alterations in hormonal levels or chronic stimuli (e.g., stress). What factors determine the underlying baseline level? Is it simply the summation of all short-term afferent reflexes that exert a constant input to the CNS, or are there a different set of controllers or even a set point (389) for the level of SNA to different organs? This information is pertinent considering the host of cardiovascular diseases associated with increases in the mean level of SNA. Although many of these diseases are also associated with impaired afferent reflexes, there may be other factors that have led to the increase in the underlying mean level of SNA to different organs. This section considers some of the factors implicated in the long-term control of SNA.

A. Arterial Baroreflexes

It has long been thought that arterial baroreflexes do not play a role in the long-term control of SNA and arterial pressure. The basis for this is evidence that the reflex adapts, or "resets," in response to maintained changes in pressure. Resetting was first suggested by McCubbin et al.

(342), who observed that the receptor firing rate of baroreceptors was much lower at equivalent pressures in chronically hypertensive rather than in normal dogs. It has since been shown that resetting is not necessarily a chronic phenomenon and may occur in response to brief exposure to sustained pressures. Shifts in the operating range of the receptors in the direction of the prevailing pressure have been reported within seconds to minutes after a change in pressure activity (67). Munch et al. (363), using an in vitro preparation of the rat aortic arch, showed that when a step rise in arterial pressure was maintained, single fiber baroreceptor activity declined exponentially with a time constant of 3–4 min. Reports of resetting over an even shorter time frame have been reported (54), but whether this is not just a hysteresis effect is unclear. Resetting of the reflex may not be limited to resetting of the arterial pressure-afferent baroreceptor activity, but could occur as a result of changes at the level of the afferent, central, or efferent sections of the baroreflex.

In cases of atherosclerosis or hypertrophy of the vessel walls, it is possible to see how baroreceptor resetting occurs. Chronic resetting can often be attributed to structural changes in the vessel wall, with a decrease in the wall compliance that leads to decreased strain and consequently decreased baroreceptor afferent activity (17). Acute resetting on the other hand is observed in the absence of structural changes in the vessel wall and is the equivalent of the adaptation process seen with many sensory neurons. The acute resetting described in many experiments involves preparations that have not been exposed to sheer stress, pulsatile pressures, and neural and hormonal influences that they would be exposed to in conscious freely moving animal. Each of these influences may independently modulate baroreceptor activity (66). In interpreting results from such experiments, we must ask if such conditions are representative of the input the system experiences in day-to-day living.

While there is clear evidence that the baroreflex resets when faced with a sustained change in arterial pressure, the question arises if this is really the type of stimuli that the baroreflex is exposed to in vivo. Everyday activities such as sleeping, exercise, and eating produce considerable changes in arterial pressure, and thus the input to the baroreceptors is never really constant. Lohmeier et al. (296) applied electrical stimulation to the carotid baroreceptors in normotensive dogs for 7 days and observed a sustained reduction in arterial pressure, plasma norepinephrine, and renin. This observation suggests that the baroreflex did not reset under the experimental conditions. However, the stimulus used was not in fact constant but rather a train of stimuli for 9 min followed by a 1-min off period. Thus it is possible that the baroreflex was never in a position to be able to reset because their input was being adjusted every 9 min. Rather than criti-

cize the technique as one that could not ascertain whether baroreflex resetting occurs, one could suggest that it better reflects the normal pattern of stimuli that the baroreflex would be exposed to in normal daily life. Lohmeier et al. (295) bypassed the pressure-encoding step of the baroreflex by direct stimulation of the baroreceptors using field stimulation of the carotid sinus wall, and thus we can only conclude that the central component of the baroreflex does not reset under such conditions of chronic intermittent stimuli. It remains unclear whether the afferent limb of the baroreflex or the baroreceptors themselves would reset when exposed to a pressure which on average was raised, but showed continuous fluctuations around the higher level. More recently, Lohmeier et al. (292) have shown that 1 wk of baroreceptor activation in dogs with obesity-induced hypertension reduces arterial pressure and plasma norepinephrine concentrations. These findings indicate that baroreflex activation can chronically suppress the sympathoexcitation associated with obesity and abolish the attendant hypertension with this disease state. However, the ability of baroreceptor activation to abolish all forms of hypertension is not confirmed. In an angiotensin II model of hypertension in dogs, there was only a modest impact on the blood pressure, although there was a decrease in plasma norepinephrine (291).

The initial concept from the work of Lohmeier et al. (293) was that much of the chronic reduction in arterial pressure with chronic baroreceptor activation was due to suppression of renal SNA and attendant increments in renal excretory function. However, comparing a group of renal denervated versus renal nerve intact dogs during a 1-wk period of bilateral baroreceptor activation showed similar reductions in arterial pressure (293). Activation of the baroreflex was associated with sustained decreases in plasma norepinephrine concentration (~50%) and plasma renin activity (30–40%). Thus the presence of the renal nerves is not an obligate requirement for achieving long-term reductions in arterial pressure during prolonged activation of the baroreflex. This suggests that chronic baroreceptor stimulation induces decreases in SNA to many organs. Interestingly, they repeated the electrical activation of the carotid baroreflex for 7 days in the presence of chronic blockade of $\alpha(1)$- and $\beta(1,2)$-adrenergic receptors (294). During chronic blockade alone, there was a sustained decrease in the mean arterial pressure of 21 mmHg and an approximately threefold increase in plasma norepinephrine concentration, attributed to baroreceptor unloading. In comparison, during chronic blockade plus prolonged baroreflex activation, plasma norepinephrine concentration decreased to control levels, and mean arterial pressure fell an additional 10 ± 1 mmHg. Thus these findings suggest that inhibition of central sympathetic outflow by prolonged baroreflex activation lowers arterial pressure in part by previously unde-

fined mechanisms, possibly by diminishing attendant activation of postjunctional $\alpha(2)$-adrenergic receptors.

The underlying technology in these studies was developed with the aim of providing a device capable of producing chronic reductions in arterial pressure in humans who are resistant to pharmacological treatment for their hypertension. A recent clinical trial of patients in whom the device was chronically active for 12 mo revealed significant sustained reductions in blood pressure (434, 478). The fall in systolic blood pressure averaged 39 mmHg. These data strongly support the concept that chronic baroreceptor activation can produce, under some conditions, large sustained reductions in blood pressure. These reductions have been proposed to reflect chronic changes in SNA. It is unfortunate that SNA has not been measured before and after chronic baroreceptor activation in either animals or humans. Most recently, the changes in the spectral components of heart rate were examined in these subjects, and significant alterations were observed that were consistent with inhibition of sympathetic activity and increase of parasympathetic activity in patients (504). Clearly, there is much work to be undertaken to identify the mechanisms underlying these reductions. What is the role of the renin-angiotensin system in mediating the responses? Is the magnitude of the reduction in SNA similar to all organs or differentially reduced? Why did renal denervation (293) not attenuate the ability of the stimulation device to reduce blood pressure? Does this suggest that baroreflex-induced suppression of SNA cannot effectively counteract the powerful hypertensive effects of angiotensin II?

The possibility that chronic baroreceptor stimulation can sustainably lower long-term levels of SNA to different organs opens the prospect of device-based treatment of other diseases associated with chronic sympathetic activation. In dogs with heart failure induced by pacing, chronic baroreceptor stimulation was associated with greater survival rates compared with nonstimulated dogs (516). Additionally, concentrations of plasma norepinephrine and angiotensin II were lower in dogs receiving baroreceptor activation therapy. This effect on angiotensin II levels, presumably via reductions in renal SNA-mediated renin release, is a further positive outcome of chronic baroreceptor activation. Given the recent failure of some pharmacological treatments for heart failure (74), the ability to regulate levels of SNA in the long-term via chronic baroreflex modulation using an implantable device may provide opportunities for novel therapies to be developed.

Other studies suggest that arterial baroreceptors may be important in long-term regulation of arterial pressure under conditions of increased salt intake. Howe et al. (218) reported that increasing dietary salt intake resulted in hypertension in sinoaortic-denervated but not baroreceptor-intact rats. Osborn and Hornfeldt (388) 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 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 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 rats. These data support the hypothesis that arterial baroreceptors play a role in long-term regulation of arterial pressure under conditions of increased dietary salt intake.

Thrasher (475) developed a surgical method to produce chronic unloading of arterial baroreceptors in dogs where one carotid sinus and the aortic arch baroreceptor nerves were eliminated and the carotid sinus from the remaining innervated region 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 subsequently increased by an average of 22 mmHg above control. Removal of the ligature to restore normal flow through the carotid resulted in normalization of arterial pressure. While SNA was not directly recorded, indirect evidence was provided that sympathetic drive was increased during the 5-day 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 indicates that the excretory ability of the kidneys was altered. Initially the exciting aspect of the Thrasher model was that the chronic unloading of baroreceptors may "increase" SNA. Many of our current experimental interventions produce decreases in SNA. Thus an animal model that produces increases in SNA may be more reflective of the human condition of neurogenic hypertension with its associated increases in SNA to different organs. Subsequently, the model was extended for a 5-wk period of carotid baroreceptor unloading (474). Blood pressure was initially increased ~25 mmHg for the first week of unloading, then ~17 mmHg for the second week,

then ~10 mmHg for the remaining weeks. Plasma norepinephrine levels were increased for the first 2 wk of unloading but were thereafter not different from control. Thus it appears that the model is associated with a significant level of attenuation over time. Whether this is due to chronic resetting or some other adaptation (e.g., structural adaptation) is unclear, although the growth of new vessels was observed in the carotid sinus area. In our laboratory we have attempted to replicate this model in the rabbit. While transient increases in blood pressure could be achieved, pressure always returned to baseline levels within 48 h (F. McBryde, personal communication). Problematically, the increases in pressure were also observed in sinoaortically denervated animals, suggesting the increase in pressure may have been a response to cerebral underperfusion in this species.

B. Angiotensin II

High angiotensin II levels are observed in ~25% of hypertensive subjects (324). It has long been proposed that there is a relationship between angiotensin II and SNA. Sympathoexcitation induced by circulating angiotensin II in experimental animals was first demonstrated over three decades ago (135). Angiotensin II receptor binding sites are found in discrete areas of the forebrain and brain stem that are involved in the control of SNA (9–11). In particular, binding is found in the nucleus of the solitary tract and the rostral and caudal regions of the ventrolateral medulla (9–11), and microinjection of angiotensin II or antagonists into these regions alters sympathetic nerve activity. All these sites are critical nuclei involved in the arterial baroreflex pathway. Thus angiotensin could exert its action on sympathetic nerve activity via modulation of the baroreflex pathway. This is pertinent given the above evidence that the arterial baroreflex pathway has the ability to chronically regulate SNA under some conditions.

Patients with chronic angiotensin-dependent renovascular hypertension have generally demonstrated higher sympathetic levels, correlated with circulating angiotensin II concentrations (159, 233). Direct short-term recordings of splanchnic nerve activity in conscious rats reveal a significant increase in SNA during angiotensin II infusion (303). Other methods for indirectly assessing global sympathetic control of blood pressure often indicate increased SNA. Ganglionic blockade, adrenergic receptor blockade, and centrally acting sympatholytic drugs all cause a much larger fall in blood pressure in angiotensin II-infused animals than in normotensive controls (83, 254, 283, 303). However, the increase in SNA with angiotensin is not without debate, as measurements of peripheral plasma catecholamine to index SNA levels during angiotensin II suggest sympathetic activity does not change (63,

254), whereas lower renal norepinephrine spillover levels suggest sympathetic activity is decreased during angiotensin II hypertension (63).

Using direct long-term recordings of renal SNA and blood pressure in rabbits, Barrett et al. (27) explored the relationship between increased angiotensin II levels, SNA, and baroreflexes. A 1-wk period of angiotensin II infusion in the rabbit caused a rapid sustained increase in arterial pressure (~18 mmHg). Surprisingly, there was a sustained decrease in renal SNA throughout the whole angiotensin II infusion, not an increase as the previous literature described above would suggest. Cessation of the angiotensin II infusion caused blood pressure and renal SNA to return to control levels. One explanation for the decrease in renal SNA is that the increase in blood pressure associated with the angiotensin II resulted in a sustained baroreflex-mediated reduction in renal SNA. The heart rate baroreflex displayed evidence of the classical resetting, with a rightward shift in the curve. However, there was no evidence of resetting for the renal SNA baroreflex relationship; rather, the resting point moved down the curve. Upon ceasing the angiotensin II infusion, all baroreflex parameters returned to control values. It was proposed that the sustained decrease in renal SNA during angiotensin II infusion is baroreflex mediated. This was subsequently confirmed in arterial baroreceptor-denervated rabbits who underwent the same angiotensin II infusion protocol and revealed no alteration in renal SNA (25). Interestingly, these animals achieved the same magnitude increase in blood pressure as baroreceptor-intact animals, suggesting that the reduction in renal SNA was not ameliorating the overall blood pressure responses. In support of the proposal that some levels of angiotensin II increase blood pressure without increasing SNA, a dose of angiotensin II that was slowly pressor in the sheep, was associated with vasoconstriction in the main vascular beds but did not alter SNA (as assessed by ganglionic blockade) (215).

Lohmeier et al. (297) 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 renal SNA. It was proposed that this decrease in renal SNA 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 same angiotensin model in dogs shows evidence of sustained activation of central pathways involved in the arterial baroreflex pathway (299). Immunohistochemistry for Fos-like (Fos-Li) proteins determined long-term activation of neurons in the NTS, caudal ventrolateral medulla (CVLM), and RVLM after acute (21 h) and chronic (5 days) infusion of angiotensin. There was a two- to threefold increase in Fos-Li immunoreactivity in the NTS and CVLM, but no increase in RVLM neurons. This is to be expected as baroreceptor suppression of sympathoexcitatory cells in the RVLM is mediated by activation of neurons in the NTS and CVLM. Lesions at either the area postrema in the hindbrain or the subfornical organ in the forebrain attenuate angiotensin II-based hypertension and indicate that there are also direct central sympathoexcitatory actions of angiotensin II, offering further support for the action of angiotensin on brain regions involved in cardiovascular control (77, 78, 137).

Early studies on the relationship between angiotensin II and SNA predominantly examined the action of angiotensin II in isolation. However, more recent work now considers that it is the link between angiotensin II and dietary salt intake that is a central factor in driving the level of SNA. The broad concept as outlined by Osborn et al. (387) is that "moderate" elevations in angiotensin II levels increase blood pressure through a modest increase in SNA to specific regions, but that this effect can be potentiated by a high-salt diet. In studies in dogs with chronic angiotensin II administration, the rate of angiotensin II infused was calculated to increase plasma levels of angiotensin II to three times normal, i.e., a moderate increase (290, 298, 299). Recently, the depressor response to ganglionic blockade was used to assess pressor sympathetic drive in rabbits on different infusions of angiotensin II (20 or 50 ng·kg^{-1}·min^{-1}) (339). Consistent with the above studies, the higher dose was associated with a rapid increase in blood pressure and evidence of sustained sympathoinhibition. Yet the lower dose of angiotensin II was associated with a slow onset of hypertension, reaching the same level of pressure as the higher dose but taking 7–10 days. While there was evidence of sympathoinhibition in this group, in a further group with the addition of dietary salt (0.9% NaCl in drinking water) there was no such decrease in SNA. Thus it is possible that different doses of angiotensin II produce distinct profiles of hypertension and associated changes in sympathetic drive, and increased dietary salt intake disrupts the normal sympathoinhibitory response to angiotensin II-based hypertension. Interestingly, renal denervation did not affect the blood pressure responses to a high "pressor level" angiotensin II-induced hypertension (55), suggesting that the sympathetic activation to the kidney is not critical for the development of hypertension and could involve sympathetic activation to other organs such as the splanchnic circulation. Simon and co-workers (2, 447, 448) additionally suggest that when angiotensin II is administered, in initially subpressor doses, there may be trophic stimulation of vascular tissue, resulting in restructuring of extracellular matrix, and that this may precede hemodynamic changes.

Recently, a direct telemetric approach was used in rabbits to record renal SNA during high dietary salt intake (340). Throughout a 6-day period of high salt, blood pressure and renal SNA were not significantly altered despite significant reductions in plasma renin activity. The lack of suppression of RSNA during high dietary salt suggests that either there has been a decrease in responsiveness of the renin-secreting cells of the juxtaglomerular apparatus to adrenergic stimuli, or nonneural mechanisms are wholly responsible for the inhibition of the RAS under the condition of elevated salt intake in the rabbit. A conceptual framework for how different levels of angiotensin II produce different sympathetic responses is represented in Figure 7.

The involvement of SNA in angiotensin II-dependent hypertension may also involve alterations in the gain of the sympathetic neuroeffector; that is, for a given level of SNA, the changes in blood flow or renin release show
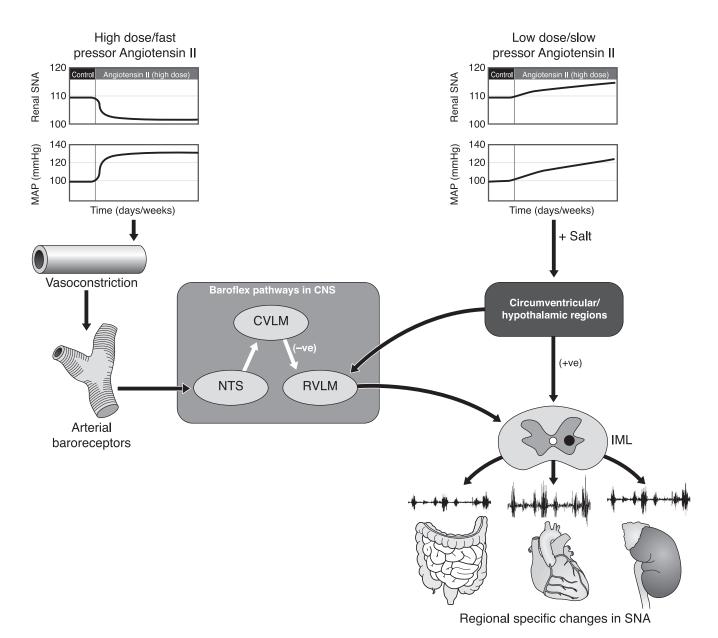
FIG. 7. Schema representing the ability of different levels of angiotensin II to affect SNA. At higher levels of angiotensin II (*left*), there is a direct vasoconstrictor effect and immediate rise in blood pressure. This results in a baroreflex-mediated suppression of SNA. This effect does not appear to diminish with time, suggesting a potential ability of angiotensin II to prevent normal baroreflex resetting (possibly via CNS interactions). The converse situation is represented on the *right*, where lower levels of angiotensin II occur in conjunction with high dietary salt. The raised angiotensin is not immediately pressor but acts on circumventricular organs and/or hypothalamic regions within the CNS to cause increases in SNA to various organs, e.g., renal. It is likely that the changes in SNA are differentially regulated to different organs. The remarkably dose-dependent effects of angiotensin II on size and direction of SNA responses have likely contributed to the many inconsistencies in results reported by different laboratories.

enhanced responsiveness to stimuli. With the use of electrical stimulation of the renal nerves, the responsiveness of total renal blood flow (417) or cortical blood flow did not appear to be enhanced in angiotensin II-dependent hypertension, but the medullary blood flow response was (57). Furthermore, there was a blunting of the relationship between renal SNA and renin release in hypertensive rabbits. It is recognized that electrical stimulation does not adequately reflect the naturally occurring SNA; however, Evans et al. (128) subsequently recorded SNA using hypoxia as the stimuli. They observed in hypertensive rabbits that the renal functional responses (glomerular filtration rate, urine flow, and sodium excretion) to hypoxia were similar to normotensive animals. Interestingly, they observed that the hypoxia-induced increases in renal norepinephrine spillover tended to be less in hypertensive rabbits and that renal DHPG overflow (a marker for neuronal reuptake and metabolism of norepinephrine) was greater in hypertensive rabbits. Overall, it appears unlikely that enhancement (increased gain) of neural control of renal function occurs in angiotensin-dependent hypertension.

Clearly, further studies are warranted to explore the relationship between angiotensin II and chronic levels of SNA. It is fair to point out that some studies in humans do not support a link between angiotensin II and SNA (as reviewed by Esler et al., Ref. 115). On the basis of the differences in the blood pressure profiles obtained (fast or slow pressor) with administration of angiotensin II, it does appear that there are two distinct actions. In the example of a high plasma level of angiotensin II, the resulting rapid vasoconstriction and subsequent increase in blood pressure appears to be consequently sympathoinhibitory via the arterial baroreflex pathway. This effect dominates at levels of angiotensin II associated with a rapid increase in arterial pressure and could also be in the early phase of angiotensin II-based hypertension. One must keep in mind that angiotensin II also has numerous direct renal actions that certainly are critical in the development of hypertension. This ability of angiotensin II to chronically interact with baroreflexes may be specific to angiotensin II as chronic infusion of other pressor agents such as phenylephrine or norepinephrine, while resulting in an initial increase in blood pressure, showed an "escape" of pressure back to control levels within 48 h, possibly suggesting baroreflex resetting (S.-J. Guild, personal communication). However, in addition to vascular actions, angiotensin II may exert a chronic action on the CNS to restore SNA or even increase SNA to different organs above baseline levels. This effect may dominate where the increase in arterial pressure has a slower onset and/or occurs with lower levels of angiotensin II. Thus the central direct actions of angiotensin II and the actions via vasoconstrictor-mediated activation of arterial baroreflexes may interact in an antagonistic fashion,

or may utilize nonbaroreflex pathways to exert control over SNA (Fig. 7). Recently, Davern and Head (89) explored brain regions responding to chronic elevated angiotensin II using fos-related antigens to detect prolonged neuronal activation. They observed that regions of the area postrema and amygdala were activated transiently after acute angiotensin, but not responsive after 3 days or more of angiotensin II. Neurons in the NTS, caudal ventrolateral medulla, and lateral parabrachial nucleus were activated in the early period of angiotensin II, but were not responsive by 14 days. The circumventricular organs of the lamina terminalis and subfornical organ showed sustained but diminishing activation over the 14-day period, consistent with sensitization to angiotensin II and downregulation of AT_1 receptors. However, the downstream hypothalamic nuclei that receive inputs from these nuclei, the paraventricular, supraoptic, and arcuate nuclei, showed marked sustained activation. These findings suggest that there is desensitization of circumventricular organs but sensitization of neurons in hypothalamic regions to long-term angiotensin II infusion. This study is important as it highlights the marked differences between acute effects of angiotensin II in regions known to be involved in the integration of baroreceptor inputs, and the more chronic effects on forebrain circumventricular organs and associated downstream neuronal pathways.

C. Blood Volume

Acute changes in circulating blood volume are an important regulator of renal SNA. Cardiopulmonary low-pressure baroreceptors at the venous-atrial junctions of the heart either fire phasically in time with the cardiac cycle or more tonically, depending on their location. Collectively, they provide information to the brain about the central venous pressure and force of atrial contraction (184). They appear sensitive to fluctuations in venous volume of <1% (207). The normal response to increased blood volume is a selective increase in cardiac SNA and reduction in renal SNA (239), with little or no change in SNA to other organs (416). These responses travel via vagal afferents to the CNS (21). This reflex is dependent on neurons in the paraventricular nucleus (PVN) (198, 300, 301). Neurons in the PVN show early gene activation on stimulation of atrial receptors (409), and a similar differential pattern of cardiac sympathetic excitation and renal inhibition can be evoked by activating PVN neurons. Cardiac atrial afferents selectively cause GABA neuron-induced inhibition within spinally projecting vasopressin-containing neurons in the PVN that project to renal sympathetic neurons (317, 411). A lesion of these spinally projecting neurons abolishes the reflex (301). The parvocellular neurons of the PVN also project to a number of extrahypothalamic sites in the brain stem involved in

cardiovascular regulation (444). The direct spinal projection from PVN neurons is of particular interest, for it has been hypothesized that this projection allows for modulation of the descending input from RVLM neurons (315). The rhythmic drive generated within the cell groups of the brain stem may be modulated to adjust the neuronal recruitment (Fig. 4).

The central pathways for regulating blood volume appear reasonably well characterized, yet alterations with different disease states or how long-term regulation is effected are poorly understood. Given evidence that in heart failure the cardiopulmonary reflex is blunted (508), and that there is reduced activity in the PVN (284), it would seem a fruitful area for future research (see Ref. 87 for review). One possibility is that the neural pathway subserving the control of blood volume plays much more of a dominant role in the regulation of blood pressure via SNA than has previously been considered. Bie et al. (34) challenge the notion that it is arterial pressure that is the important signal to invoke the action of the pressure diuresis/natriuresis mechanism in blood pressure control during alterations in salt intake. They present evidence from studies in both humans and dogs that acute salt loading, via saline infusion, causes a diuretic response that occurs without rise in blood pressure and thus the diuresis must be due to the increased volume rather than a change in pressure (33, 354). Interestingly, they also observed that the acute sodium-driven decrease in plasma renin levels without change in arterial pressure or glomerular filtration rate was unaffected by $\beta(1)$-receptor blockade. This area clearly requires further investigation as previously it has been considered that the renal nerves are the main controller of renin secretion in the absence of a change in arterial pressure or glomerular filtration rate (100).

D. Osmolarity

In animal models of water deprivation, elevated osmolarity is associated with increased lumbar SNA (440). Acute increases in osmolarity appear to decrease splanchnic and renal SNA (502), but more prolonged water deprivation for 48 h increased renal SNA (441). In humans, increasing plasma osmolarity by ~10 mosM using a hypertonic saline infusion resulted in initial increases in muscle SNA and plasma norepinephrine levels, as opposed to an isotonic infusion that resulted in a decrease in SNA (132). This increase was relatively short in duration (~20 min) despite further increases in osmolarity. When smaller increases in osmolarity were used (~3 mosM), this did not result in changes in baseline muscle SNA (68). Osmotic regulation of SNA is important for maintaining blood pressure during water deprivation (49, 463). The mechanism involves angiotensin II and glutamatergic excitatory inputs to the paraventricular nucleus (142). In

terms of the central pathways for regulating SNA to different organs in response to changes in osmolarity, it appears that osmosensitive sites within the lamina terminalis such as the organum vasculosum are key regions (344). This in turn links through the PVN and its direct spinally projecting pathways to differentially influence sympathetic outflow to various organs (464). Elevated osmolarity is not only seen during dehydration but is also proposed to be involved in the salt sensitivity of blood pressure, where small dietary-induced increases in salt and associated plasma osmolarity may drive regional sympathetic outflow (48). Elevated dietary salt intake has been reported to significantly raise plasma sodium concentrations in both humans and rats (131, 203). Brooks et al. (50) propose that when salt intake increases, this acts via the renal baroreceptor and macula densa to result in a reduction in angiotensin II which in turn may decrease SNA to different organs via a central action (as outlined above in the section on angiotensin II). It is appropriate to indicate that the studies suggesting a chronic relationship between plasma osmolarity and SNA are based on acute measures of changes in sympathetic activity (generally renal SNA) in response to acute changes in plasma osmolarity. One of the difficulties in delineating the mode of action is that increased plasma osmolarity is generally associated with the development of thirst, and the resulting increase in fluid intake may restore osmolarity but result in increased blood volume and a cardiopulmonary and arterial baroreceptor stimulus.

Drinking water alone increases muscle SNA (439) and plasma norepinephrine levels as much as such classic sympathetic stimuli as caffeine and nicotine (235). This effect profoundly increases blood pressure in autonomic failure patients and in older normal subjects. Interestingly, the increase in muscle SNA was absent after drinking an isotonic solution (51), indicating that the cardiovascular responses to water are influenced by its hyposmotic properties. It is unclear why hyperosmotic and hyposmotic stimuli appear to have similar effects on muscle SNA. However, it is likely that central osmotic control mechanisms are capable of generating multiple, and potentially opposite, sympathetic responses depending on the magnitude and duration of the stimulus. Given that the simple and essential act of drinking water has noticeable influences on the sympathetic nervous system, it is likely that osmolarity does influence the long-term level of SNA to different organs independent of changes in blood volume.

XV. CHRONIC SYMPATHOEXCITATION

A. Obesity

Management and treatment of obesity-related hypertension poses a formidable challenge, with recent data

suggesting that up to 70% of newly diagnosed hypertensive cases are attributable to obesity (356). A recent review of the relationship between obesity and blood pressure by Davy and Hall (93) suggests that "rather than a special case, obesity hypertension should be considered the most common form of essential hypertension." Obesity-induced hypertension is associated with increased extracellular fluid volume and cardiac output (192). This implies that obesity leads to dysfunction of the mechanisms regulating extracellular fluid volume, with emerging evidence implicating increased sympathetic nervous system activity. Initially it was suggested that overall SNA was low in human obesity, contributing to weight gain through the absence of sympathetically mediated thermogenesis (276). However, microneurographic recordings in obese hypertensive subjects subsequently demonstrated increased muscle SNA (162), with a doubling of norepinephrine spillover from the kidneys (125, 483). Removal of the renal sympathetic nerves appears to blunt obesity-related hypertension in dogs (240). There is also evidence of suppression of cardiac SNA in the early stages of obesity (426), consistent with the CNS ability to differentially regulate sympathetic outflows chronically. Interestingly, muscle SNA levels decline with significant weight loss (14) or were found to be increased 15–20% in healthy, nonobese males with modest weight gain (155). It has been suggested that visceral obesity rather than subcutaneous obesity is an important distinction linking obesity and sympathetic neural activation in humans (13, 14). In terms of changes in the pattern of SNA, there is evidence that obesity is associated with increased numbers of nerve fibers recruited (evidenced as increases in the amplitude of sympathetic bursts) rather than an increase in the firing rate of the same nerves (127, 268, 270). This was different from normal-weight hypertensives, which had increased firing probability and higher incidence of multiple spikes per heartbeat. In earlier sections on amplitude and frequency, the possibility was raised that quite different CNS processes are involved in regulating the firing and recruitment of sympathetic nerves, and thus it is possible that different pathologies may affect these components, either via a direct central action or via an afferent reflex pathway.

In obesity hypertension, abnormal kidney function is initially due to increased tubular sodium reabsorption, which causes sodium retention and expansion of extracellular and blood volumes (192). The rightward shift in the renal pressure-natriuresis relationship results in sodium reabsorption, fluid retention, and blood pressure elevation. One interpretation of this effect is that the obese individual requires higher levels of blood pressure to maintain sodium and fluid homeostasis. There are several potential mechanisms that could mediate the sodium retention and hypertension associated with obesity, including sympathetic nervous system activation, renin-an-giotensin-aldosterone system activation, and compression of the kidney. The mechanism(s) by which weight gain elicits sympathetic neural activation remains unclear. Landsberg (274) initially hypothesized that the increase in SNA with weight gain serves the homeostatic role of stimulating thermogenesis to prevent further weight gain. Other proposed mechanisms linking obesity with SNS activation include baroreflex dysfunction, hypothalamic-pituitary axis dysfunction, hyperinsulinemia/insulin resistance (275), and hyperleptinemia (86).

Leptin is almost exclusively produced by adipose tissue and acts in the CNS through a specific receptor and multiple neuropeptide pathways to decrease appetite and increase energy expenditure. Leptin thus functions as the afferent component of a negative-feedback mechanism to control adipose tissue mass. Plasma leptin levels are elevated in human obesity (311). Chronic sympathoexcitation may be driven by high leptin levels derived from adipose tissue, as acute administration of leptin increases renal and lumbar SNA in rats (201, 202). Additionally, it has been proposed that obesity is associated with resistance to the metabolic actions of leptin but preservation of its renal SNA and arterial pressure effects, leading to hypertension (415). In humans, plasma leptin levels in lean and obese men are correlated with measures of whole body and regional norepinephrine spillover (110, 111). Leptin gains entry to the CNS through a high affinity to transporters in the hypothalamus and choroid plexus (511). In addition, the CNS is a site of synthesis for leptin (19, 112). Leptin in turn acts at OB receptors found in many neuronal subtypes in the lateral hypothalamic area, hypothalamic arcuate, and PVN to initiate satiety. As described elsewhere in this review, the PVN of the hypothalamus in particular is a major site for the integration and regulation of sympathetic outflow. Increases in body fat, and therefore plasma leptin concentration, may induce central leptin resistance. Thus appetite is maintained at an inappropriately high level, leading to an imbalance in caloric intake and energy expenditure and therefore a loss of energy homeostasis. Leptin resistance has been observed in obese human patients (109) and animal models of obesity (412, 413). More recently, brain leptin receptor gene expression was not found to be impaired in human obesity (112).

It has been suggested that a component of sympathetic activation in obesity might originate from reduced gain of the arterial baroreflex. In humans, baroreflex control of heart rate appears to be blunted in obese normotensive compared with lean hypertensive subjects (95, 452). Early measurements of MSNA also indicate SNA-baroreflex function was blunted in obese subjects (163), although more recent studies by the same group contradict this (166). Baroreflex gain of splanchnic SNA is reduced in anesthetized adult obese Zucker rats (438). This deficiency occurs after the onset of obesity. Overall, the degree

to which baroreflex sensitivity measured in this way reflects the long-term influence of the baroreflex on SNS outflow in obesity hypertension remains unclear.

B. Sleep Apnea

There is mounting evidence that sleep-related breathing disorders play an important pathophysiological role in cardiovascular disease. This is notable in the setting of obstructive sleep apnea, where breathing is interrupted primarily by upper airway narrowing or collapse, in the face of continued respiratory effort. Sleep apnea has a high prevalence not only in the general population but also associated with hypertension and stroke. Central sleep apnea is associated with a lack of output from the central respiratory generator in the brain stem and manifests as periods of apneas and hypopnea without discernible breathing efforts. Central sleep apnea is intimately and more specifically linked to heart failure (although this association is not exclusive). Nevertheless, both types of sleep apneas do share some commonalities and can occur in the same individual. Importantly, sympathetic activation is thought to be a key mechanism linking sleep apnea to cardiovascular disease (373, 374).

Sleep apnea has historically been linked to heart disease, since improvement in cardiac function is often associated with a reduction of sleep apnea frequency and may suggest a bidirectional importance to their relationship. It is certainly likely that the repetitive surges in SNA to different organs associated with chemoreceptor activation are likely to be a significant deleterious factor in heart failure. The greater mortality rate reported in sleep apnea patients with heart failure compared with heart failure patients without sleep apnea may be linked to arrhythmogenesis mediated by sympathetic activation and hypoxemia (277).

Repeated nocturnal episodes of upper airway blockade result in periodic asphyxia and increased muscle SNA and blood pressure as a result of chemoreceptor activation (371, 454). The sympathetic responses to acute hypoxia may be altered over time, and enhanced chemoreflex activity could play a role in the pathogenesis of chronic sympathoexcitation (170, 220). Subjects with obstructive sleep apnea not only have altered chemoreceptor reflexes but also arterial baroreflex control over muscle SNA (371). Over time, this periodic nocturnal sympathetic activation appears to evolve into a rise in the mean daytime level of SNA even when subjects are breathing normally and both arterial oxygen saturation and carbon dioxide levels are also normal (62, 370). It should be noted that sympathetic activation is certainly not the only factor in the long-term consequences of sleep apnea. Rather, there is a plethora of deleterious events including alterations in nitric oxide, endothelin, oxidative stress, interleukins,

leptin, and insulin. It is pertinent, however, that sympathetic activation appears to be an early marker of the initiation of a pathological cascade. The importance of preventing the increase in SNA to different organs is underlined by observations from animal studies in which an increase in blood pressure due to obstructive sleep apnea could be prevented by renal and adrenal denervation (22, 139).

Recent animal studies using models of chronic intermittent hypoxia indicate significant changes in the regulation of the cardiovascular and respiratory system including enhanced sensitivity of peripheral chemoreceptors (398, 407), increased long-term facilitation of respiratory motor activity (343), and augmented expiratory activity (513). Overall, it has been suggested that intermittent hypoxia alters the respiratory pattern generation as well as the central modulation of sympathetic outflow (512).

The mainstay therapy for obstructive sleep apnea is continuous positive airway pressure (CPAP), which results in acute and marked reductions in nocturnal muscle SNA and blunts the blood pressure surges during sleep. Imadojemu et al. (220) observed normalization of the sympathetic response to acute hypoxic stimulation. CPAP reduces daytime sleepiness, which was also correlated with reductions in muscle SNA (105). Long-term CPAP treatment appears to chronically decrease muscle SNA (369).

C. Mental Stress

There is uncertainty as to the role life-style plays in setting the long-term level of SNA to different organs and thus in the development of cardiovascular disease. White-coat hypertension (a condition associated with increased blood pressure in the clinic environment, and presumably stressful environment) is associated with increased SNA (377, 453). Whether these people are hyperresponsive to emotional or other stimuli, or have other underlying pathologies, remains to be established. Long-term studies of human populations, such as cloistered nuns living in secluded and unchanging environments, reveal blood pressure does not rise with age as expected (477). Large-scale studies also link hypertension development with chronic mental stress in the workplace (423, 461). Blood pressure has been shown to be elevated soon after migration, presumably due to stress (406). The role of the SNS in these events has been difficult to isolate given the large number of confounding factors. While stress reduction techniques such as meditation or yoga produce a modest reduction in blood pressure in hypertensive subjects, this is outranked by weight reduction and regular exercise (103).

D. Hypertension

Hypertension is a causative factor in the development of heart failure, renal failure, and stroke. While it is often reported that "the causes of hypertension are unknown," this denies that there have been an enormous number of publications on the etiology of hypertension. The multifactoral nature of the disease means it is hard to bring the vast array of information into a cohesive framework. This review has already dealt with many of the underlying issues involved in regulating blood pressure through discussion of factors regulating the long-term level of SNA, such as angiotensin II and arterial barore-flexes. It has also covered diseases known to be involved in the initiation of hypertension, in particular obesity and sleep apnea. Thus this section focuses on the mechanisms by which SNS interacts with blood pressure in the long term.

In human hypertension, analysis of regional SNA (norepinephrine spillover or microneurography) has demonstrated in many cases activation of sympathetic outflows to the heart, kidneys, and skeletal muscle vasculature particularly in younger borderline hypertensive subjects (15, 123, 158). Normotensive young men with a family history of hypertension have greater rates of norepinephrine spillover than those without a family history (136). Importantly, there is a disproportionate increase in sympathetic activity to the heart and kidneys in hypertension, with approximately half of the increase in norepinephrine being accounted for by increased SNA to these organs (117, 118). The increase in cardiac norepinephrine spillover is additionally complicated by evidence that neuronal norepinephrine reuptake is decreased in hypertension (435). However, the sympathoexcitation occurring in hypertension is by no means as clearly delineated as it is in heart failure. When large numbers of subjects with essential hypertension are studied, a range of muscle SNA values are observed (237). Microneurographic recordings indicate that even if there is a rise in baseline muscle SNA in hypertension, it is modest and with substantial overlap with individuals who have normal blood pressure (Fig. 8). This overlap of data from normotensive subjects is also seen with cardiac and renal norepinephrine spillover values in hypertensive groups and in part reflects the multifactoral causes of the disease state for which SNA is one of many factors. While the mean levels are significantly different between the two groups, it is clear that many hypertensive individuals have norepinephrine spillover values that are well within the normal range (435). It may be that the increase in muscle SNA is specific for different forms of hypertension. In primary aldosteronism (351), adrenal pheochromocytoma, or renovascular hypertension (157), SNA has been found to be similar to that of age-match normotensive controls. It has been proposed that neurogenic mechanisms are dominant in the patho-
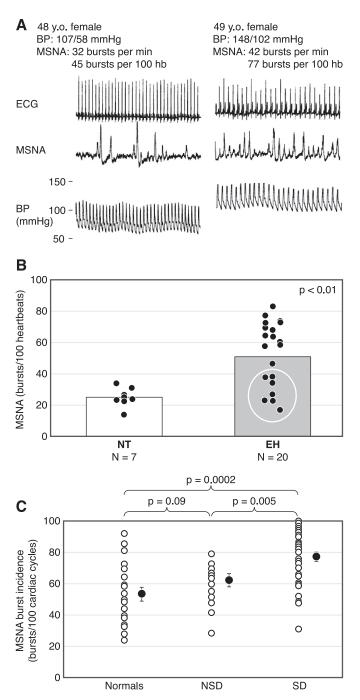
FIG. 8. A: neurograms of MSNA from a normotensive subject and one with borderline hypertension illustrating the apparent increase in frequency of sympathetic discharges. B: mean and individual data obtained from the group of subjects. While the mean level was significantly elevated in the borderline hypertensive group (EH), approximately one-third of these subjects (indicated by the oval circle) had levels of MSNA that were within the range of values seen in the normotensive (NT) group. [A and B adapted from Schlaich et al. (435).] C: variation in MSNA between subjects with treated heart failure with (SD) an without (NSD) sleep-disordered breathing compared with age-matched healthy control subjects. Although MSNA was increased significantly when apnea coexists with heart failure, it is clear that the large variation between control subjects means that significant overlap exists between subjects groups. Unlike signals such as blood pressure, heart rate, and other biochemical markers, a normal range for MSNA levels appears difficult to define. Thus values obtained from the control group of subjects must be used to define the normal range. [C from Floras (141), with permission from Elsevier Ltd.]

genesis of ~40% of patients with essential hypertension (158, 426).

How do increases in SNA to different organs translate into hemodynamic changes leading to the development and maintenance of hypertension? Perhaps not surprisingly, this is a matter of considerable debate. Although it is generally accepted that the established phase of hypertension is associated with increased total peripheral resistance and normal cardiac output, the relationship of these variables during the early stages of hypertension is less clear. Long-term regulation of arterial pressure is closely linked to blood volume homeostasis through the "renal-body fluid feedback mechanism." The central foundation of this model is that blood pressure is determined by the equilibrium point of a curve relating arterial pressure and renal excretion, often referred to as the renal function curve. A key feature of the renal-body fluid feedback control system is pressure natriuresis, the ability of the kidneys to respond to changes in arterial pressure by altering the renal excretion of salt and water. A primary shift in this renal function curve to a higher pressure results in blood volume expansion. It is hypothesized that this sets in motion the whole body autoregulation response, which is characterized by an initial increase in cardiac output and a subsequent increase in total peripheral resistance followed by the return of cardiac output to near normal levels (186, 187, 189). While changes in cardiac output or resistance in other parts of the body may acutely alter arterial pressure, it is often considered that without a change in renal excretory function, any such change in arterial pressure will be short-lived as any change in pressure is rapidly compensated by an increase in urine output (192). As advanced by Guyton and colleagues (186, 187, 189), the pressure natriuresis relationship plays a critical role in the maintenance of stable body fluid balance and therefore blood pressure, and it has been suggested that an alteration in this relationship is a critical step in the development of hypertension. At the time Guyton proposed this model, our understanding of the influence of the sympathetic nervous system was minimal, although Guyton did clearly state that it was likely to be important. One mechanism by which renal SNA could increase blood pressure chronically is by alteration of the pressure natriuresis relationship. Long-term low-dose infusions of norepinephrine directly into the renal artery cause the retention of sodium and water and produce sustained increases in arterial pressure (82, 422), whereas renal denervation resets the pressure natriuresis curve to a lower pressure (176). The vast majority of studies have used denervation to ascertain the relevance of renal SNA and in this denervation delays the onset or reduces the magnitude of hypertension (224, 255, 367, 482, 500). The renal nerves innervate both afferent and efferent arterioles, juxtaglomerular apparatus, and the proximal tubule (100, 302), and thus changes in renal SNA play an important role in regulating renal blood flow, glomerular filtration rate, renin release, and urinary sodium and water excretion (318). A series of studies have identified that the renal medullary circulation plays a role in long-term blood pressure control and is less sensitive than cortical blood flow to renal SNA (114, 183). Indeed, medullary blood flow appears to be refractory to increases in endogenous renal sympathetic nerve activity within the physiological range in all but the most extreme cases. Subtle chronic changes in the neural regulation of medullary or cortical blood flow could, in turn, lead to salt and water retention and hypertension.

On the basis of the above information, it would appear that the renal nerves and their effect on renal function and pressure natriuresis relationship can play a leading role in the development of hypertension. It would therefore be a reasonable assumption that renal denervation would greatly attenuate or even abolish the chronic increases in blood pressure in experimental models involving increased SNA. It is therefore surprising that when using the chronic baroreceptor stimulation model to lower arterial pressure in normotensive dogs, renal denervation did not further reduce blood pressure (293), although in the absence of the renal nerves, there was greater sodium retention during baroreflex activation than when the renal nerves were present. Thus, in the absence of the renal nerves, the additional sodium retention could cause greater activation of redundant natriuretic mechanisms, such as atrial natriuretic peptide, that would enhance pressure natriuresis. One interpretation of this is that the renal nerves are not critical in lowering blood pressure with this form of stimulation and that the primary effect of the stimulus is via a nonrenal action such as lowering total peripheral resistance. How can we reconcile this with the Guytonian model that the kidney is central to the long-term regulation of blood pressure? Osborn and colleagues (386, 387) advance the concept that the early hemodynamic pattern in hypertension may be being driven by differential sympathetic activation to various organs. They propose a sympathetic action on venous capacitance or to other nonrenal beds is able to drive the initiation of hypertension without requiring a shift in the pressure natriuresis relationship. Furthermore, they argue that the Guyton model is restrained by its dependence on the renal body fluid balance relationship. They do not dismiss the concept that pressure natriuresis occurs, but that it is central to the control of blood pressure around control levels. They suggest that the weakness of the Guytonian model is its dependency on the regulation of blood volume. Clearly, there is much research required in this area. However, it is important to consider that in the vast majority of cardiovascular diseases, there is a disproportionate increase in renal SNA compared with SNA to the muscle (326, 435). If the renal nerves do regulate pressure natriuresis, then it is reason-

able to propose that where elevations in renal SNA occur, one mechanism by which it could produce chronic changes in blood pressure is via an action on the kidney.

Recently, a bold new treatment targeting the renal nerves for drug-resistant hypertension has undergone initial human trials (264). Patients received percutaneous radiofrequency catheter-based treatment to bilaterally ablate the renal nerves. Both systolic and diastolic pressure were significantly reduced up to 12 mo after the procedure, and renal norepinephrine spillover, measured 15–30 days after radiofrequency ablation, was decreased 47% from baseline, indicating a significant reduction in renal SNA efferent traffic. More recently, a study of a single male indicated a significant reduction in muscle SNA 3 mo after the ablation and an even greater reduction after 12 mo (436). This suggests that the reduction in renal SNA feeds back to lower global SNA. In support of this, whole body norepinephrine spillover was also reduced. This reduction may be affected by the presumed reduction renin release and thus lower angiotensin II levels which may modulate SNA via central pathways as described above (see sect. XIVB). These data are potentially exciting on multiple fronts: 1) it supports the notion that in the human the renal nerves do play a long-term role in the regulation of blood pressure, and 2) it indicates that targeting solely the renal nerves can lead to a sustained reduction in blood pressure. This is important as it supports the concept of future drug therapies that may target the CNS pathways involved in regulating selectively renal SNA and the need to understand more about the factors regulating specifically renal SNA. Finally, as described in this review, there are multiple cardiovascular diseases in which norepinephrine spillover data indicate a selective increase in renal SNA. If the safety and efficacy of the procedures are borne out, it is likely that a broader patient group, e.g., heart failure and sleep apnea, could benefit from this procedure. One caveat is that with the procedure the renal afferent nerves have also been removed and their contribution to the reduction in blood pressure remains to be established.

The potential involvement of sympathetic overactivity has been neglected in subjects with renal failure in this population despite accumulating experimental and clinical evidence suggesting a crucial role of sympathetic activation for both progression of renal failure and the high rate of cardiovascular events in patients with chronic kidney disease (437). Recent evidence indicates increases in muscle SNA but not SNA to the skin (160, 396). Afferent signals from the kidney, detected by chemoreceptors and mechanoreceptors (100, 259, 260), feed directly into central nuclei regulating SNA (393, 501). Thus renal failure either in conjunction with hypertension or independently may be another factor in the development of sympatho-excitation seen in these patients.

In his recent book on essential hypertension, Paul Korner (262) argues strongly for a primary role of the CNS in the development of hypertension. He suggests that there are two syndromes of hypertension in which the sympathetic nervous system is involved: hypertensive obesity and stress-and-salt-related hypertension. In his schema, factors including genes and the environment impact primarily through the CNS, and therefore, its outputs such as SNA to different organs are driving the changes in renal and cardiovascular function. Overall, this concept places the brain as the central controller of blood pressure rather than the kidney. Korner (262) takes a rather critical view of the Guytonian model, doubting that the "whole body autoregulatory concept" is able to explain the increase in total peripheral resistance (TPR) seen in hypertension. Korner argues that the increase in TPR could be equally explained by increased overall SNA and that the brain receives a huge variety of afferent inputs that are integrated and ultimately processed to generate a differential efferent SNA response to different organs.

E. Heart Failure

The hallmark of heart failure is neurohormonal activation in response to decreased cardiac output and underperfusion of tissues. International guidelines for the treatment of heart failure and myocardial infarction (MI) focus on reducing the severity of the neurohormonal activation (64, 433, 476). Unless patients are hypotensive, β-blockers and ACE inhibitors are generally administered within 24 h post-MI, in addition to clot-dissolving agents (345, 390). Norepinephrine spillover techniques reveal a preferential activation of cardiac SNA, as much as 50 times above normal (122, 199). This elevation is approximately equivalent to the rate of norepinephrine release observed in the healthy heart during maximal exercise. The increased spillover of the neurotransmitter from the heart is largely attributable to increased nerve activity as it is accompanied by increased overflow of the norepinephrine precursor DOPA, indicating cardiac SNA is increased rather than alterations in norepinephrine reuptake (245, 246). With regard to muscle SNA recordings, most studies show mean levels of muscle SNA are elevated in heart failure (165); however, there are also some subjects who have normal muscle SNA levels. Observations of normal levels of muscle SNA in heart failure patients seem to be more associated with nonischemic dilated cardiomyopathy rather than ischemic myopathy (383). In part, some of this discrepancy between norepinephrine measurements and muscle SNA measurements may be attributed to differential activation. Cardiac norepinephrine is elevated more than kidney, gut, or liver norepinephrine spillover, while SNA to the lungs appears normal (199). There is some evidence to suggest that SNA

to the heart is preferentially activated in the early stages of heart failure, whereas activation of renal and muscle SNA is observed in the later stages (427). Overall, the increases in SNA to the heart and kidney appear to account for more than half of the increase in total norepinephrine spillover observed (199). It is pertinent to note that after cardiac transplantation, neurochemical studies have indicated a normalization of sympathetic outflow (427).

The degree of sympathoactivation appears to be a good indicator of long-term prognosis. Specifically, it appears better than other commonly measured indexes of cardiac performance such as cardiac index, pulmonary wedge pressure, or arterial pressure (75). The experimental observations of increased cardiac SNA underpin the therapeutic intervention of β-adrenergic blockade in heart failure. Mortality is reduced 30–60% by β-adrenergic blockade (391). The importance of understanding the changes in SNA to specific organs was underlined in a study correlating long-term survival with total norepinephrine spillover or specifically renal norepinephrine spillover (400). The level of renal but not total sympathetic activation was found to be a strong predictor of survival. Although targeting the SNS in heart failure is now mainstream treatment, it remains unclear whether all methods to reduce SNA to different organs are beneficial. The Moxonidine Congestive Heart Failure Trial (MOXCON) was designed to evaluate the role of central imidazoline receptor stimulation with moxonidine on survival; however, this was associated with an increase in mortality despite an 19% decrease in plasma norepinephrine (76). While it may be argued that the dose of moxonidine was too large (3.0 mg/day; several times greater than those used for treating hypertension 0.4–1.2 mg/day), it is clear that more research is required into the mechanisms controlling SNA to different organs in this condition.

It has been postulated that the increase in cardiac SNA is the most damaging aspect of the sympathoactivation in heart failure (497). The increase in cardiac SNA is linked to abnormal calcium cycling and calcium leakage in the failing myocardium, contributing to the decrease in myocardial contractility (279, 421). The likelihood of spontaneous depolarization, arrhythmia development (248), and sudden death (247) is increased through the enhancement of spontaneous inward currents through L-type calcium channels. Rapid increases in cardiac SNA are associated with ventricular arrhythmias (348), coronary occlusion, and damage to myocytes associated with the resulting high norepinephrine levels (325). Conversely, there are changes in the cardiac sympathetic nerve terminals which suggest that the sympathetic innervation declines during the development of heart failure (208). In addition to the damaging effects of increased cardiac SNA, the increase in SNA to the kidneys also clearly exacerbates heart failure through impaired renal function

and an ability to appropriately maintain fluid balance. It has been observed that renal denervation prior to the MI in rats improved cardiac performance (384). In particular, the renal denervated group had lower end-diastolic pressures, greater fractional shortening, and improved sodium excretion compared with the intact group. One may speculate that the positive actions of renal denervation were through improved renal function and reduced angiotensin II. Although overall SNA did not appear to be altered, it is possible that cardiac SNA was in fact lower through a reduction in angiotensin II levels. Overall, these studies support the concept that the direct recordings of renal or cardiac SNA in animal models is likely to reveal mechanisms producing sympathoexcitation in heart failure.

The fundamental processes underlying the sympathetic activation in heart failure remain uncertain, yet a number of likely factors have been identified. These factors include alterations in the levels of circulating hormones acting on circumventricular organs, reflex changes in response to altered afferent inputs, e.g., from cardiopulmonary and/or arterial baroreceptors or chemoreceptors, and changes in the central generation and control of sympathetic outflow in response to a variety of inputs.

Hormonal activation is widespread in heart failure and includes the renin-angiotensin-aldosterone system, natriuretic peptides, adrenomedullin, endothelin, and vasopressin. While each of these has direct effects, they also have indirect actions on the SNS. In particular, the renin-angiotensin system, as outlined in section XIVB, is likely to be a major factor in the resultant sympathoactivation. Angiotensin II exerts a number of central chronic actions on SNA levels to different organs through the circumventricular organs. These actions may themselves directly result in increased SNA to different organs or they may modulate the inputs from other reflex pathways, e.g., arterial baroreflexes. Human studies show inconsistent effects on SNA with treatments targeting angiotensin II (97, 221). In experimentally induced heart failure, AT$_1$ receptor antagonists acutely decrease renal SNA and improve arterial baroreflex function (99, 365). May and colleagues (497) suggest that central angiotensin pathways may modulate the cardiac sympathoexcitation. There appears to be a selective cardiac activation with acute intracerebroventricular infusions of angiotensin II in conscious sheep (499). Angiotensin II levels are elevated in the cerebrospinal fluid in heart failure (517), and in the RVLM and NTS, there is increased mRNA and protein expression of the AT$_1$ receptor in rabbits in heart failure (148). Increases in AT$_1$ receptor expression have also been found in the PVN of animals with heart failure (517). The impact of these central changes appears significant as administration of the AT$_1$ receptor antisense oligonucleotide into the cerebral ventricles reduces baseline SNA in rats with heart failure, while having no effect in normal rats (509). More recently, it has been suggested that the

mechanism by which angiotensin II increases SNA is mediated by reactive oxygen species (147–149, 510). Enhanced superoxide production occurs in the RVLM of rabbits with heart failure and inhibition of superoxide production normalizes the responses to central angiotensin II administration (148). It does appear that increased redox signaling in central cardiovascular control regions is one mechanism in the neurocardiovascular dysregulation that follows MI. In mice, intracerebroventricular injection of an adenoviral vector encoding superoxide dismutase (Ad-Cu/ZnSOD) causes a significant decrease in the number of Fos-positive neurons in the paraventricular nucleus and supraoptic nucleus at 2 wk after MI compared with mice who received the control vector (286). The mechanisms by which superoxide results in increased SNA to different organs in heart failure is unclear, although it may involve alterations in a balance with nitric oxide. Decreases in neuronal nitric oxide synthase synthesis have been observed in the CNS of rabbits and rats with heart failure (397, 496). The concept is that because nitric oxide is sympathoinhibitory, a reduction in the levels of nitric oxide within the CNS would predispose cell groups involved in regulating SNA to different organs to become more excitable, leading to an increase in baseline SNA. In support of this, Gao et al. (150) recently showed in rabbits in heart failure that statin treatment upregulated neuronal nitric oxide synthase protein expression in the rostral ventrolateral medulla and improved baroreflex function. Thus statins appear to act in part through their ability to increase nitric oxide production (480) and so may provide an additional therapeutic approach for patients in heart failure (195). Recently, Lindley et al. (287) identified that MI induced increases in superoxide radical formation in forebrain regions (subfornical organ) and that the use of adenoviral vectors to produce long-term modulation of the redox state (via Ad-Cu/ZnSOD) abolished the increased superoxide levels and led to significantly improved myocardial function compared with control vector-treated mice. This was accompanied by diminished levels of cardiomyocyte apoptosis. These effects of superoxide scavenging in the forebrain paralleled increased post-MI survival rates and suggest that oxidative stress in the forebrain could play an important role in the deterioration of cardiac function following MI and underscores the promise of CNS-targeted antioxidant therapy for the treatment of MI-induced heart failure. In support of this concept, Pliquett and colleagues (404, 405) observed that statin treatment in rabbits reduced renal SNA and enhanced baroreflex function in heart failure.

Arterial baroreflex control over SNA has been shown to be impaired in animals (289, 518) and humans (161, 328) with heart failure, and this is thought to be a function of both baroreceptor abnormalities and changes in central neuronal processing of afferent signals. In particular, the arterial baroreceptors themselves may become desensitized (98). Desensitization would be expected to result in increased SNA to different organs, although the relevance of this is unclear as arterial baroreceptor-denervated dogs had levels of plasma norepinephrine similar to intact animals (44). Other studies, however, have found preserved arterial baroreflex control of muscle SNA in heart failure patients (97), and some researchers argue that baroreflex control over SNA is normal, but baroreflex control of heart rate is abnormal (140). In support of this, Watson et al. (498) recently observed that while baseline cardiac SNA was almost doubled in sheep in heart failure, baroreflex control over cardiac SNA appeared normal as distinct from the baroreflex control of heart rate which was significantly depressed. Zucker et al. (514) suggest that depression of arterial baroreflex function may in fact be an early phenomenon during the development of heart failure. It needs to be acknowledged that just because the relationship between arterial pressure and SNA to different organs shows an alteration in sensitivity, it does not automatically follow that this will result in an increase in the baseline level of SNA. Baroreflex gain refers to the sensitivity of SNA to changes in blood pressure. The problem is determining that the baseline level of SNA is increased, as many of the techniques for normalizing SNA set the baseline level to 100% and thus rescale the changes in response to stimuli from this set point (see sect. VII). It is possible that mechanisms leading to altered responsiveness of SNA are not the same mechanisms setting the underlying level of SNA.

In addition to altered arterial baroreflex function, it has been proposed that there is an increase in the sensitivity of several sympathoexcitatory reflexes in heart failure. The broad concept is that enhanced input from receptors, e.g., peripheral chemoreceptors and other afferent inputs, provide positive feedback that exacerbates the excitatory process in a vicious cycle. Ma et al. (305) stimulated the central end of the cardiac afferent nerves in dogs with heart failure and found a greater sympathetic response, indicating that the central gain of the reflex was enhanced. Similarly, the peripheral chemoreceptor response to hypoxia is enhanced in rabbits with pacing-induced heart failure (467). This enhancement has also been documented in patients with chronic heart failure and also appears to extend to increased central hypercapnic chemosensitivity (73). Alterations in the local production of substances such as bradykinin, nitric oxide, and prostaglandins have all been proposed to account for the enhanced responsiveness (45, 84, 382). Another chemosensitive sympathoexcitatory reflex thought to contribute to increased SNA is via cardiac afferent nerves. The baseline cardiac sympathetic afferent discharge rate was found to be increased in dogs with pacing-induced heart failure (493), and chemical or electrical activation of afferent nerves gave enhanced renal SNA responses (305,

494). It is possible that the heightened cardiac afferent reflexes interact centrally, e.g., at the NTS to depress arterial baroreflexes and enhance the arterial chemoreflex (151, 495). In support of this, blockade of cardiac afferents partially stabilized the decreased arterial baroreflex in rats in heart failure induced by MI (147).

Cardiopulmonary reflexes appear important in regulating sympathoexcitation in heart failure. Given that chronically increased blood volume is a central feature of heart failure, it is likely that alterations in cardiopulmonary reflexes must at least be complicit, if not central to the sympathoexcitation in heart failure. In humans with heart failure, acutely reducing cardiac filling pressures appears to reduce cardiac norepinephrine spillover (244). This is in contrast to the normal states where such a reduction would lead to an increase in SNA. In heart failure, upright tilt (241) and lower body negative pressure (134), which lower cardiac filling pressure, are associated with forearm vasodilation or attenuated vasoconstriction compared with the vasoconstrictor response in normal subjects (1). In humans in heart failure, the muscle SNA response was attenuated in response to stimuli that increased or decreased cardiac filling pressure without affecting blood pressure (97). The normal response to an increase in cardiac filling pressure via increasing blood volume is a reduction in renal and cardiac SNA, yet in sheep with pacing induced heart failure, there is little change in SNA to either organs (416, 420). Similarly, a reduction in cardiac filling pressure induced via hemorrhage was found to increase cardiac SNA ~180% in normal sheep but did not change SNA in the sheep with heart failure. Generalized desensitization to changes in cardiac filling pressure appears to be associated with reduced sensitivity of atrial vagal afferents, which have been shown to become less sensitive in dogs with chronic heart failure (515). Furthermore, there was a lack of activation of neural pathways in the brain such as the paraventricular nucleus of the hypothalamus that are normally activated by volume expansion (8). In rabbits with pacing-induced heart failure, the renal SNA response to an increase in blood volume was severely blunted, yet an exercise program over 3 wk substantially restored the cardiopulmonary reflex response (403).

As outlined in section XIII, there is good evidence that SNA to different organs is specifically controlled, yet few studies that have examined how this control may be altered in different pathologies. The research of May and co-workers (332, 418–420) is illuminating in this regard. Their studies with pacing-induced heart failure in sheep indicate that in the normal state the resting discharge rate in cardiac nerves was much lower than that seen in renal nerves. Furthermore, there were significant differences in the arterial baroreflex control to the two organs where cardiac SNA had greater gain than renal SNA and a different resting set point. In heart failure, there was a substantial increase in cardiac nerve discharge frequency, whereas with renal SNA, the frequency increased only slightly from its already high level. They also observed that the baroreflex gain for cardiac and renal SNA were unchanged in heart failure. It was suggested that the increased cardiac SNA in sheep in heart failure is in part baroreflex mediated in response to the lower arterial pressure and that the resting level of cardiac SNA is set to a lower level than renal SNA, but in heart failure, the resting levels of SNA to both organs are close to their maxima.

Floras (141) has recently reviewed the sympathetic activation in heart failure with reference to the implications for clinical treatment. He notes that the dominant model accounting for sympathetic activation assumes a generalized sympathetic activation as a result of ventricular systolic dysfunction and notes, as discussed throughout this review, that there is a selective activation to specific organs rather than generalized activation. Overall it is suggested that the sympathetic activation reflects the net balance in interactions between appropriate reflex compensatory responses to impaired systolic function (e.g., arterial baroreflexes) and excitatory stimuli as a result of impaired reflexes (e.g., cardiopulmonary). While pathways responsible for altered reflex control over SNA in heart failure are being elucidated, there remain some serious gaps in our knowledge over the progression to elevated SNA as heart failure develops. While SNA has been measured many times, in a variety of animal models of heart failure, a longitudinal study directly monitoring regional SNA levels before and after the induction of heart failure has yet to be performed. Such studies may be useful in determining if the mechanisms responsible for the sympathoexcitation differ between the early, middle, and late phases of heart failure.

F. Summation of Sympathetic Activation in Disease States

The above sections outline the sympathetic activation occurring in a number of disease states. However, it must be acknowledged that many of these do not occur in isolation; for example, heart failure is often the end result of hypertension coupled with obesity. Importantly, there is a direct summation of the sympathetic activation with multiple diseases (164) (Fig. 9). SNA, as assessed by microneurography, is least in lean patients with heart failure with normal blood pressure, intermediate in patients with heart failure and either obesity or hypertension, and highest in heart failure with obesity and hypertension. While some researchers have shown an impairment of arterial baroreflexes across each condition (164), as discussed, there are also more specific alterations with some diseases, e.g., obesity-induced changes in leptin that
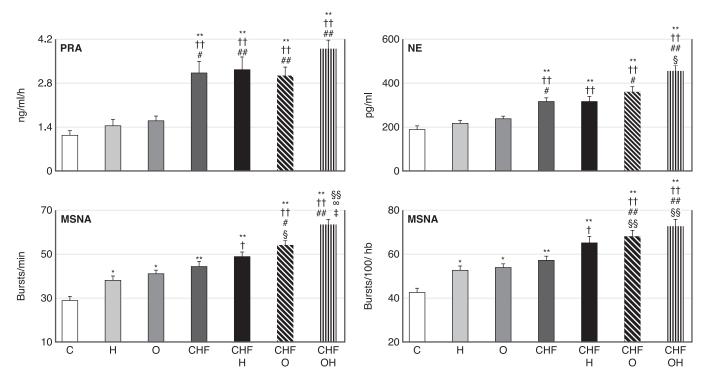
FIG. 9. Baseline plasma renin activity (PRA), plasma norepinephrine (NE), and MSNA (expressed as burst incidence over time and corrected for heart rate) values in control subjects (C) and in patients with hypertension (H), obesity (O), congestive heart failure (CHF), congestive heart failure and hypertension (CHFH), congestive heart failure and obesity (CHFO), and congestive heart failure combined with hypertension and obesity (CHFOH). Data are means ± SE. *$P < 0.05$, **$P < 0.01$ vs. C; †$P < 0.05$, ††$P < 0.01$ vs. H; #$P < 0.05$, ##$P < 0.01$ vs. O; §$P < 0.05$, §§$P < 0.01$ vs. CHF; ∞$P < 0.05$ vs. CHFH; ‡$P < 0.05$ vs. CHFO. These data highlight that there is a summative interaction between various cardiovascular diseases and an increasing level of SNA. [From Grassi et al. (164).]

may drive some of the sympathetic activation to different organs (202). In normal-weight individuals with essential hypertension, renal and cardiac SNA are increased, yet in obesity-related hypertension, although SNA to the kidney is increased, SNA to the heart is reduced (124, 483). Overall the summative effects may be expected to increase the patient's risk of death given the strong relationship between sympathetic activation and mortality (28, 75, 266). Further consideration should be given to the clinical use of β-adrenergic blockade whose value may be greatest in patients with heart failure with accompanying obesity or hypertension (121).

XVI. GENOMIC APPROACHES

In the last 15 years, many studies have shown that modification of the mouse genome may alter the capacity of cardiovascular control systems to respond to homeostatic challenges or even bring about a permanent pathophysiological state. Although the most common species for recording SNA is the rat, there have been a number of studies recording SNA in mice (200, 347, 358, 472). Although it is clearly a technical challenge to record SNA in the mice, the array of genomic approaches available in this species has the potential to offer new insights. Pre-

vious approaches to assessing the sympathetic nervous system in this species have used indirect methods such as ganglionic blockade and recording the subsequent reduction in blood pressure (90, 231). The limitations in obtaining adequate blood samples from a mouse appear to preclude the use of norepinephrine spillover techniques. With regard to the direct recording of SNA, one problematic aspect is that comparisons in the nerve signal will need to be conducted between different genetic strains. The available evidence suggests that in the mouse, unlike in humans, the autonomic balance is heavily dominated by the sympathetic nervous system and that parasympathetic contributions are only minor (231).

It is beyond the scope of this review to do justice to genomic approaches for understanding the sympathetic nervous system and cardiovascular control in general, and the reader is referred to several recent reviews/studies on this topic (81, 265, 285). Approaches such as the catecholamine enzyme or receptor gene knockout mice are particular examples that are specifically examining the influence of the sympathetic nervous system (12, 20, 347). The relative contribution of central and peripheral angiotensin II has been investigated using a transgenic mouse model with brain-restricted overexpression of AT_{1A} receptors. These mice are normotensive at baseline

but have dramatically enhanced pressor and bradycardic responses to intracerebroventricular angiotensin II or activation of endogenous angiotensin II production (106, 278). Given the interaction between angiotensin II and the SNS, as discussed in section XIVB, such approaches are likely to prove fruitful. A role for the sympathetic nervous system has been identified recently in the Schlager genetically hypertensive mice (90). These mice (BPH/2J) have reduced brain norepinephrine content but markedly greater neuronal activation in specific regions of the amygdala and hypothalamus, possibly related to greater levels of arousal and an altered circadian blood pressure rhythm that, based on sympathetic blockade, appears to be due to elevated SNA. This mouse model may be most relevant to human hypertensive patients who have a centrally mediated sympathetic excitability associated with circadian rhythms or perhaps to white coat hypertension. Rahmouni et al. (414) have developed knockout mouse models of Bardet-Biedl syndrome (BBS) that is characterized often by obesity. Recent studies suggest polymorphisms in certain BBS genes might increase the risk of obesity and hypertension in non-BBS individuals (29). The work of Rahmouni et al. (414) hypothesizes that defects in energy balance and central neurogenic mechanisms play a role in obesity and in hypertension associated with the deletion of *BBS* genes in mice. Most recently, do Carmo et al. (104) using melanocortin-4 receptor-deficient mice (MC4R) have attempted to separate obesity and hemodynamic changes as causes of renal injury. They observed that normotensive 52- to 55-wk-old MC4R−/− mice did not develop significant renal injury despite obesity and prolonged exposure to metabolic disturbances such as insulin resistance, hyperinsulinemia, hyperglycemia, hyperlipidemia, and hyperleptinemia, factors that are considered by many investigators to play a major role in the etiology of obesity-associated nephropathy. They suggest that obesity and associated metabolic abnormalities may not be a major cause of severe renal disease in the absence of hypertension. Elevations in arterial pressure may be necessary for obesity and related metabolic abnormalities to cause major renal injury. The lack of hypertension in the MC4R−/− mouse may be due to impaired sympathetic nervous system activation that normally mediates obesity-induced hypertension (471). Another genomic approach that deserves comment is the adenovirus-mediated gene transfer (288) to select brain regions involved in cardiovascular control (287). Transfecting the cytoplasmic superoxide dismutase (Ad-Cu/ZnSOD) to forebrain circumventricular organs has indicated that oxidative stress in this region plays a role in the deterioration of cardiac function following MI. Other groups have used gene transfer with a noradrenergic promoter in specific organs such as the heart to upregulate sympathetic neuronal nitric oxide synthase (94, 282).

XVII. INCREASED SYMPATHETIC ACTIVITY AS A TRIGGER FOR SUDDEN CARDIOVASCULAR EVENTS

It is well established that the onset of sudden cardiovascular events follow a circadian periodicity or are frequently triggered by physical or mental stress. The Los Angeles earthquake of 1994 saw a four- to fivefold increase in sudden cardiovascular deaths on that day (424). Since the SNS is also known to be active in sudden cardiovascular death, it is relevant to consider the potential role and mechanisms by which increased SNA to different organs may lead to sudden cardiovascular events. It should be acknowledged that there is a paucity of research in this area. It is not possible to distinguish between specific increases in cardiac SNA versus SNA-derived increases in release of epinephrine from the adrenal cortex. Morning peaks in acute MI, transient ischemia, and stroke are well documented (362, 503). For example, the risk of sudden cardiac death (SCD) increases by 70% between 7 and 9 a.m. compared with the rest of the day. Since SNA is elevated during this time period associated with assuming upright posture, SNA to different organs could be a trigger for SCD (85, 503). It is possible that the increase in SNA and associated vasoconstriction makes an atherosclerotic plaque vulnerable to rupture. From autopsy data it is estimated that one-third of SCD are caused by acute coronary occlusion by thrombus (91, 209, 366). An alternate hypothesis is that increased cardiac SNA promotes cardiac electrical instability and thus the development of arrhythmias.

Ventricular fibrillation and ventricular tachycardia (VF/VT) are often preceded by signs of sympathetic overactivity (395). Cardiac SNA has been found to increase within minutes of ischemia (312). Jardine et al. (232) recently explored the relationship between the activation of cardiac SNA and the emergence of VF/VT after induced MI in the sheep. In animals susceptible to subsequent VF/VT, they observed an increase in cardiac SNA before arrhythmia onset. No differences were observed in cardiac baroreflex sensitivity between resistant and susceptible sheep. Increases in cardiac SNA were independent of that which occurred later in all animals after MI. It is unknown if these increases are selective to cardiac SNA or could be observed in muscle SNA in humans; however, it does raise the possibility that acute increases in SNA may be predictors of VF/VT in the period immediately after MI.

It is possible that acute increases in SNA exert a damaging influence only in the presence of an underlying pathology. Chronically increased sympathetic activity appears to contribute to the genesis of structural changes, including left ventricular hypertrophy and arterial remodeling and treatments aimed at regressing

some of these abnormalities associated with cardiovascular disease appear more successful if this includes a reduction in SNA (238). It has been suggested that the progression and regression of left ventricular hypertrophy do not depend on the level of blood pressure alone, but also on the level of cardiac sympathetic drive (324, 359). The left ventricular hypertrophy associated with hypertension promotes reentrant arrhythmias, and increased cardiac SNA could increase their likelihood.

XVIII. TREATMENTS FOR CARDIOVASCULAR DISEASE THAT IMPACT ON SYMPATHETIC NERVE ACTIVITY

As was discussed earlier, sympathoactivation, in particular to the kidney and heart, appears to be a powerful indicator of prognosis in cardiovascular diseases. Some researchers, however, do not recognize the importance of maintaining acute sympathetic responsiveness to short-term stimuli such as exercise or posturally induced changes in blood pressure. The use of treatments designed to lower SNA chronically is likely to be rewarded with beneficial actions providing the short-term reflex control is maintained. α-Adrenoreceptor antagonists are effective antihypertensive agents, but there are concerns about their safety profile. In the ALLHAT trial, the α-blocker (doxazosin) arm was stopped prematurely because of an increased risk of cardiovascular events, particularly heart failure (92). Similarly, β-blockers are effective in obesity-associated hypertension (43) but do result in reduced energy expenditure leading to a small weight gain (402). In a recent large-scale trial (POISE study group) of over 8,000 patients undergoing noncardiac surgery, the use of the perioperative β-blocker metoprolol was found to reduce the incidence of MI, but increased the risk of strokes and death in the 30 days after the operation (178). These studies highlight the danger in assuming sympatholytic agents are not without risk.

Apart from the direct sympatholytic actions of $\alpha1$- and β-receptor antagonists in reducing blood pressure in hypertension, there are reports that other common treatments may lower blood pressure at least in part through an action on the SNS. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists (ARBs) may exert at least some of their action through a reduction in SNA to different organs. Angiotensin II has already been described (see sect. XIVB) as a potential long-term mediator of SNA to different organs. However, the clinical evidence for this interaction is weaker; Krum et al. (263) observed that angiotensin receptor blockade did not change either muscle SNA or whole body norepinephrine spillover in hypertensive patients. In heart failure, both reductions in SNA or no changes have been reported with ACE inhibitors (97, 167, 221). Grassi et al. (167) measured muscle SNA before and after 2 mo of ACE inhibition in heart failure patients and found no differences. They also observed no changes in baroreflex control of MSNA, suggesting that chronic ACE inhibition reduces blood pressure without altering short-term reflex control of SNA. Conversely, ACE inhibition or angiotensin II receptor blockade in a group of subjects with hypertensive chronic renal disease resulted in reductions of, but did not normalize, muscle SNA levels (376). It must be noted that this was a subgroup of hypertensive subjects with specific renal disease. Chronic kidney disease such as polycystic kidney disease is associated with sympathetic overactivity, which may be a factor in the initiation of the hypertension seen in these subjects (375).

Imidazoline receptor agonists have the potential for important cardiovascular benefits (133). The hypotensive action of these "second generation" centrally acting agents, such as rilmenidine and moxonidine, occurs mainly as a result of sympathetic inhibition. Both rilmenidine and moxonidine appear to act selectively at the I_1 receptor rather than at the α_2-adrenoceptor, which are both found in the RVLM. There is substantial evidence that the main site of action of these agents is the RVLM (65, 204, 333). In addition to the hypotension, rilmenidine facilitates cardiac vagal baroreflexes and inhibits cardiac sympathetic baroreflexes and diminishes the increase in renal sympathetic activity produced by environmental stress (204, 205). Rilmenidine also has peripheral actions such as in the kidney promoting natriuresis (236), and moxonidine increases the levels of atrial natriuretic peptide (61). Recent trials in type 1 diabetics or subjects with metabolic syndrome have yielded positive results for the imidazoline receptor agonists (96, 125, 191, 431). However, increased adverse events and mortality at high doses of moxonidine in subjects with heart failure (class II to IV) preclude the use of the drug in heart failure (76).

Current guidelines for the treatment of hypertension do not recommend specific antihypertensive agents for specific types of hypertension (72), and it has been argued that it matters less what is used to treat hypertension as long as blood pressure reductions are achieved (179). However, it can be argued that in pathologies in which SNA to different organs is likely to be elevated (e.g., obesity), there is strong justification for a combination of baseline treatment along with a treatment targeting lowering SNA to different organs.

XIX. FUTURE DIRECTIONS

The sympathetic nervous system has moved towards center stage in cardiovascular medicine. In the last 30

years, over 35,000 publications included the SNS as a key word. However, there are some serious gaps in our understanding of SNA that mean that our ability to derive novel clinical treatments for cardiovascular diseases based on targeting SNA remains in its infancy. The research outlined in this review underlines the importance of studying the SNS. The linkage between sympathoactivation and poor clinical outcomes for a range of cardiovascular diseases continues to drive new research. Human studies on this topic are naturally limited as to the interventions possible and are often by their nature observational rather than interventional. Their ability to inform on the fundamental origins of sympathoexcitation is limited, and this provides a major justification for animal-based studies. However, there is a great paucity of animal models in which the SNS can be chronically manipulated to mimic the human situation and often little direct evidence that SNA is increased in these models. For example, while SNA is increased in certain forms of hypertension, there is not a validated animal platform in which chronic sympathoexcitation has been well defined. Instead, the area suffers from disparate approaches, which are in turn exacerbated by differences in the duration and severity of the hypertension. There is clearly a need for an animal experimental platform to be identified in which the SNS changes are well-characterized along with end organ changes.

In summary a "wish list" of future studies/approaches includes the following.

1) Differential control: that we consider the SNS as a highly differentiated output from the CNS providing control over multiple end-organ functions. It is important to be specific about the end organ when referring to SNA and realize that SNA to one organ, e.g., muscle, is not necessarily indicative of SNA to all organs.

2) Quantifying SNA: that the research community adopt a consistent standard when reporting SNA (180).

3) Long term: while our knowledge of the CNS anatomy and processes regulating SNA to different organs has developed well over the last decade, much of the basis for this has been derived from short-term experiments lasting hours. If we are to truly understand the role of the SNS in the development of cardiovascular diseases, we need to take a fresh look at our experimental approaches to investigate the interaction with various hormonal systems and end-organ functions. It is imperative that a long-term view become central in future research projects.

4) Tailored responder: that we consider that the CNS produces quite specific responses in the pattern of sympathetic outflow (amplitude and frequency) even to the same target organ in response to different afferent stimuli.

5) Animal models: there is a need for the research community to develop better animal models and technologies that reflect the disease progression seen in humans.

A particular focus is required on models in which SNA is chronically elevated.

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