Differential control of sympathetic outflow

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Morrison, Shaun F. Differential control of sympathetic outflow. Am J Physiol Regulatory Integrative Comp Physiol 281: R683–R698, 2001.—With advances in experimental techniques, the early views of the sympathetic nervous system as a monolithic effector activated globally in situations requiring a rapid and aggressive response to life-threatening danger have been eclipsed by an organizational model featuring an extensive array of functionally specific output channels that can be simultaneously activated or inhibited in combinations that result in the patterns of autonomic activity supporting behavior and mediating homeostatic reflexes. With this perspective, the defense response is but one of the many activational states of the central autonomic network. This review summarizes evidence for the existence of tissue-specific sympathetic output pathways, which are likely to include distinct populations of premotor neurons whose target specificity could be assessed using the functional fingerprints developed from characterizations of postganglionic efferents to known targets. The differential responses in sympathetic outflows to stimulation of reflex inputs suggest that the circuits regulating the activity of sympathetic premotor neurons must have parallel access to groups of premotor neurons controlling different functions but that these connections vary in their ability to influence different sympathetic outputs. Understanding the structural and physiological substrates antecedent to premotor neurons that mediate the differential control of sympathetic outflows, including those to noncardiovascular targets, represents a challenge to our current technical and analytic approaches.

baroreceptor reflex; chemoreceptor reflex; thermoregulation; arterial pressure; cutaneous circulation; adrenal medulla; brown adipose tissue; periaqueductal gray; renal sympathetic nerve; vasoconstriction

RECOGNITION OF THE IMPORTANT role of the autonomic nervous system (ANS) in coping with life-threatening challenges led to the earliest concepts of the sympathetic nervous system as a monolithic effector, activated to globally enhance organ function and substrate availability for fight or flight and to protect cerebral perfusion in the event of significant injury. In contrast, the parasympathetic component of the ANS is engaged in the aftermath of such challenges to coordinate recovery, a reduction in energy utilization, and replenishment of energy stores. However, compared with our ancestors, modern lifestyles have all but eliminated the danger of predatory aggression, and we rarely engage the central autonomic networks developed by evolutionary pressure to cope with the most stressful challenges to homeostasis. In their stead, we are faced with the increasing awareness and prevalence of diseases such as hypertension, obesity, cardiac arrhythmia, heart failure, and diabetes, in which altered development or control of the ANS can play a significant role. Within this framework and, importantly, with the availability of more powerful and precise electrophysiological and anatomic techniques, research on the regulation of autonomic outflow has eclipsed earlier views with an organizational model that emphasizes the differential central control of sympathetic outflows to functionally specific targets and the hierarchical interactions among defined populations of neurons that produce the patterns of autonomic efferent activity supporting behavior and reflex responses. The focus has evolved toward an understanding of the central
neural networks generating and controlling the levels of ANS activity to specific tissues, including those with noncardiovascular functions, with the recognition that the fight-or-flight response is just one of many options in an extensive repertoire of effector activation states in which the central autonomic network may exist. Investigators are challenged to determine how the differential neural responses in physiological experiments or the patterns of activity-dependent and organ-specific labeling seen in anatomic studies might reflect the mechanisms affecting the coordinated series of autonomic changes supporting specific behaviors or mediating reflex responses.

This review describes research results providing anatomic and physiological evidence for central autonomic networks that allow for the selective control of the sympathetic outflow to individual tissues and thus for the expression of patterned autonomic responses. Investigation of the central neural mechanisms underlying differential autonomic responses is an ongoing area of autonomic neuroscience that has contributed to our understanding of the basis for organ specificity of autonomic responses. Neuronal tracing techniques, activity-dependent markers, and immunocytochemical approaches have been used to characterize neurons in the central and peripheral pathways to different tissues that provide the structural substrate for their differential sympathetic regulation. Comparisons of the centrally evoked and reflex responses of multiple autonomic effectors, in some cases recorded simultaneously, have demonstrated heterogeneity among the responses of functionally distinct outputs. Patterns emerge from these data that suggest multiple, interacting, but modality specific, hierarchical systems involving neurons in the hypothalamus, midbrain, and medulla that regulate groups of target-specific output pathways each comprising premotor neurons [and potentially their accompanying oscillator (63)], the preganglionic neurons they excite, and the ganglion cells innervating a particular tissue. The axonal branching patterns of neurons in such systems, antecedent to premotor neurons, could provide the basis for coordinating the changes in sympathetic outflows to an array of target-specific output pathways of related function. Although the characteristics and responses of the sympathetic outflows to the blood vessels and heart have been most extensively studied (45), nearly every tissue in the body receives a sympathetic innervation. Thus, although we have considerable information on the central regulation of systemic perfusion pressure, the organization of neural circuits specifically controlling many other modalities, such as temperature, circulatory volume, plasma osmolarity, blood glucose, energy balance, and reproduction, remains to be elucidated.

**ANATOMIC BASIS FOR TISSUE-SPECIFIC AUTONOMIC REGULATION**

Langley (104) divided the autonomic outflow from the central nervous system to the cardiovascular and visceral tissues into parasympathetic and sympathetic components based on their spinal origins as well as the differential effects on various tissues of nerve stimulation and application of adrenergic and cholinergic agents. The results of Cannon’s (29) functional studies led him to propose that parasympathetic efferents mediate more precise, target-focused responses than did sympathetic efferents that were considered to have more widespread effects. The tissue specificity of parasympathetic ganglion cells and thus the ability to provide selective regulation of various autonomic functions would appear manifest by the general anatomic arrangement in which parasympathetic ganglion cells are located within the innervated tissue and are excited by long preganglionic axons projecting from the central nervous system.

Improved anatomic approaches have complemented physiological studies, indicating the fine detail to which functionally specific responses can be evoked by parasympathetic efferents. In examining the vagal innervation of the heart, chronotropic and dromotropic effects were found to be mediated by distinct ganglia within the cardiac fat pads (61), and this arrangement has been extended to the inotropic effects as well (60). Retrograde tracing and immunohistochemistry have provided evidence that these ganglia are, in turn, innervated by populations of vagal cardiac preganglionic neurons that can be distinguished on the basis of location and neurochemical inputs (59, 114, 115). Target specificity has also been demonstrated for cranial parasympathetic ganglia innervating the lacrimal and parotid glands and the iris and ciliary body (105).

**Do sympathetic ganglion cells innervate only one target tissue?** Although the axons of sympathetic ganglion cells are, as a rule, markedly longer than those of their parasympathetic counterparts and thus would have more opportunity for branching, the results of many studies support a model in which sympathetic ganglion cells innervate a single tissue type and thus provide the minimal structural basis necessary for generation of functionally specific sympathetic responses. Using retrograde transport from separate tissues, different distributions were found for ganglion cells innervating the kidney and the spleen (123) and for superior cervical ganglion neurons that project to the submandibular salivary glands, eyes, and pineal gland (111). With the use of immunohistochemical techniques to identify afferent terminals to sympathetic ganglion cells and thus the ability to provide selective regulation of various autonomic functions, would appear manifest by the general anatomic arrangement in which parasympathetic ganglion cells are located within the innervated tissue and are excited by long preganglionic axons projecting from the central nervous system.

**Are sympathetic preganglionic neurons (SPNs) target specific?** Recent experiments in which the transsynaptic retrograde tracer, pseudorabies virus, has been injected into either the rat pinna or the eye resulted in specific segmental distributions of labeled pregangli-
Autonomic preganglionic neurons have both neurons. SPNs controlling cardiac function in the rat (2). Analysis has been used to indicate a unique identification of noradrenergic adrenal medullary chromaffin cells, but neuropeptide-positive SPNs send terminals to the vicinity of stellate ganglia, but not to the adrenal gland (67). Calbindin-containing SPNs project to superior cervical and stellate ganglia, but not to the adrenal gland (67). Calretinin-positive SPNs send terminals to the vicinity of noradrenergic adrenal medullary chromaffin cells, but not those synthesizing epinephrine (53). Similar analysis has been used to indicate a unique identification of SPNs controlling cardiac function in the rat (2).

Anatomic differentiation of inputs to preganglionic neurons. Autonomic preganglionic neurons have both excitatory and inhibitory inputs, arising from spinal interneurons and from brain stem and hypothalamic sites. “Sympathetic premotor neuron” will be used to describe those supraspinal neurons that synapse directly on SPNs to provide the excitatory input that maintains their basal discharge and through which reflex and evoked responses in SPNs are effected. Regarding the central anatomic substrate for functionally specific autonomic responses, the question arises whether populations of tissue-selective premotor neurons provide unique driving inputs to their respective target groups of tissue-specific preganglionic neurons. Although the physiological data described below strongly suggest that this is the case, several complicating factors have prevented a direct anatomic answer to the question. Due to the intermixing of preganglionic neurons within the intermediolateral column of the spinal cord (89), it is not possible to apply classical retrograde tracers to populations of functionally homogeneous preganglionic neurons. The situation is improved by the recent advent of the pseudorabies viral tracing technique, which has been used in separate experiments to identify premotor neurons regulating the autonomic efferents to peripheral tissues with different functions (147, 156, 158). The target-specific differences that have been observed in the intensity and in the temporal and spatial qualities of the labeling at different central sites (158) are suggestive of underlying distinctions in the relative importance of the inputs from these areas to SPNs controlling different targets. However, the fact that relatively few tissues have been studied with this technique and the inherent limitations on the interpretation of the resulting data (particularly the infection of functionally different populations of sympathetic efferents innervating the different tissue types in the injection site) have thus far restricted the identification of tissue-specific premotor neurons. Application of two histochemically distinct viruses at different sites in the same experiment has the potential to reveal individual neurons that regulate the sympathetic outflow to more than one target tissue. Although this approach has resulted in double-labeled neurons in hypothalamic and brain stem sites (90), it is not possible to determine from a single time point whether such labeling resulted from direct infection of the neuron by viruses from two populations of preganglionic neurons or whether one of the infections may have resulted, for instance, from a virus in the axonal branches of a different population of brain stem sympathetic premotor neurons.

**PHYSIOLOGICAL EVIDENCE FOR DIFFERENTIAL AUTONOMIC REGULATION**

Characterization of functionally distinct populations of peripheral autonomic outputs. Characterization of the physiological and reflex response properties of individual pre- and postganglionic axons or nerve fascicles in the sympathetic nerves of humans and experimental animals has been used to segregate sympathetic efferents into distinct categories related to the potential target tissues they regulate. This has been accomplished by correlating changes in efferent discharge with some unique behavior of an end-organ tissue in the distribution of the effenter being recorded. These are important data. The ability to establish a different characteristic pattern of reflex responses (see examples below) that define a functional fingerprint for the autonomic innervation of each target tissue is strong evidence that its autonomic regulation occurs via a unique, tissue-specific population of preganglionic and ganglion neurons (reviewed by Janig, Refs. 84, 86). In addition, with the exception of the preganglionic innervation of the adrenal medullary chromaffin cells, the end-organ target tissue of a central neuron in a sympathetic pathway can only be inferred from a correspondence between its behavior and one of the functional fingerprints that has been established for the peripheral innervations of a variety of tissues. Finally, because the majority of reflex- and behaviorally evoked responses is mediated via supraspinal networks and sympathetic premotor pathways, these results are consistent with a model of central autonomic regulation that includes tissue-specific populations of premotor neurons. It is the detailed descriptions of the response characteristics of functionally defined sympathetic postganglionic or parasympathetic preganglionic axons that will provide the principal source of information for the physiological identification of such antecedent (i.e., sympathetic preganglionic, premotor, etc.) neurons in target-specific pathways.

The use of single-fiber recordings is a key aspect of the physiological differentiation of functional classes of efferent autonomic axons and their antecedent central regulatory pathways. The complexity of most organs, in that they are comprised of multiple tissues (a minimum of a vascular and a parenchymal component), predicts that their autonomic innervations will be comprised of many, functionally differentiated populations of axons. Thus whole nerve recordings, even those...
made from autonomic nerves in the immediate proximity of the organ they innervate, will represent a summation of the basal activities and evoked responses of a functionally heterogeneous group of efferent axons. This is an analogous situation to that described above in which the neurons in central pathways identified with retrograde transport of viral tracers will include a conglomerate of those controlling the autonomic efferents to each of the tissues in the original infection zone of the virus injection. Some prominent examples in which this situation complicates the interpretation of data from nerve bundle recordings are 1) the multiple functions represented within the renal nerves (49, 106); 2) the existence of many fiber types within the adrenal nerves, including not only preganglionic axons to the two types of medullary chromaffin cells (128, 141) but also postganglionic inputs to adrenal cortical cells and blood vessels, vagal efferents, and sympathetic and vagal afferents (31, 34, 80, 136, 141, 169); 3) the vascular and adipo-cytine innervation within sympathetic nerves to brown adipose tissue (28, 127); and 4) the wide distribution of fibers in the rat splanchnic nerve and the cat lumbar splanchnic nerves to vascular, gastrointestinal, reproductive, and adipose targets (85).

The meticulous studies carried out over many years in the laboratory of Wilfrid Janig (84, 85) have provided a significant portion of the information available on the behavior of a variety of peripheral sympathetic efferents in the cat and rat lumbar and cervical sympathetic outflows. They have characterized sympathetic efferent channels as 1) vasoconstrictors to muscle and viscera, 2) cutaneous vasoconstrictors, 3) sudomotor, 4) pilomotor, 5) “inspiratory” potentially innervating vessels of the nasal mucosa, 6) pupillomotor, and 7) motility regulating for the gastrointestinal system and for the reproductive system. The extensive studies of Gunnar Wallin and colleagues (16, 51, 87) provided considerable data indicating a strong correlation between the functional fingerprints of muscle and skin sympathetic outflow in experimental animals and those determined from recordings of human sympathetic nerve activity. Although there are many tissues, such as the heart, adipose, pancreas, spleen, thymus, thyroid, pineal, gastrointestinal, reproductive, etc. whose autonomic functional fingerprints cannot be determined in humans and for which only limited data are available from experimental preparations, the growing appreciation of the role of alterations in autonomic regulation in a variety of disease states may stimulate research that will expand the characterization of these autonomic outflows as well.

The sympathetic innervation of the adrenal medullary chromaffin cells, which secrete either epinephrine or norepinephrine (44, 75), provides an example of target specificity at the level of the preganglionic neuron. Anatomically, terminals of calretinin-containing cat adrenal SPNs terminate in the vicinity of noradrenergic chromaffin cells, whereas those adrenal SPNs without calretinin are located preferentially among adrenergic chromaffin cells (53). Physiologically, adrenal SPNs can be segregated into two populations. Those with long-latency responses to stimulation of the rostral ventrolateral medulla (RVLM) and little sensitivity to the baroreceptor reflex are strongly stimulated by the glucopenic agent 2-deoxy-d-glucose (2-DG), indicating their role in regulation of adrenal epinephrine secretion, which is markedly increased by 2-DG (Fig. 1). Conversely, adrenal SPNs with short-latency responses to RVLM stimulation and which can be completely inhibited by baroreceptor reflex activation are unaffected by administration of 2-DG and are presumed to control adrenal norepinephrine release (128).

These data provide direct evidence for the distinct functional organization of the central networks governing the release of the two catecholamines from the adrenal medulla that had been suggested by differences in the catecholamine secretion previously observed in response to physiological challenges and experimental stimuli (56, 146, 157, 161, 165, 166).

DIFFERENTIAL AUTONOMIC RESPONSES TO REFLEX INPUTS

**Baroreceptor reflex.** Baroreceptor reflex-mediated inhibition is a hallmark of sympathetic outflows regulating muscle and visceral vasoconstrictor targets, the kidney, and the heart, as would be expected inasmuch as the performance of these tissues contributes directly to determining the level of arterial pressure. Strong stimulation of vagal parasympathetic input to the heart accompanies the sympathoinhibitory responses to pressor stimuli (57, 96). One criterion that is often used to assess the sensitivity of a particular sympathetic outflow to modulation by the baroreceptor reflex is the synchrony between the bursts in nerve activity and the arterial pressure wave (cardiac cycle). This analysis is based on the premise that the baroreceptor reflex pathway is briefly stimulated during the systolic pressure rise, which often exceeds 40 mmHg, resulting in a reduced probability of sympathetic discharge during a portion of the cardiac cycle and an entrainment of the sympathetic bursts to the frequency of the heart rate.

Pulse-synchronous discharges have been observed in the muscle vasococonstrictor nerves of the cat and humans (17, 48, 66, 87), renal nerve of the cat and rat (50, 95, 102, 122, 137), cardiac and splenic nerves of the cat (95, 122), and the lumbar and splanchnic nerves of the rat (70, 131). Similarly, the discharge of adrenal SPNs controlling the chromaffin cells that secrete norepinephrine is strongly modulated by baroreceptor input (128). However, as illustrated in Fig. 2, averages of sympathetic nerve activity triggered with the R-wave of the electrocardiogram indicate that there is relatively little pulse-synchronous modulation of the activity of most cutaneous vasococonstrictor nerves in cat, rat, or humans (17, 66, 87, 91, 137) or of sympathetic sudomotor fibers in humans (112). This relative absence of a baroreceptor influence on sympathetic outflows related to thermoregulation is also supported by the lack of a cardiac frequency-related component in

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the autospectrum of the sympathetic outflow to rat brown adipose tissue (127). Similarly, the spontaneous discharge of epinephrine-regulating adrenal SPNs is relatively insensitive to arterial baroreceptor input (128).

Testing the ability of increases (or decreases) in arterial or carotid sinus pressure to induce an inhibition (or excitation) of sympathetic discharge has yielded qualitatively similar results: skeletal muscle vasconstrictor nerve activity in cat and human (22, 52, 125, 144); pelvic visceral vasconstrictor nerve activity in cat (125); splenic, renal, and cardiac nerve discharge in the cat (137, 138); lumbar, renal, and splanchnic nerve activity in the rat (131, 148); and adrenal nerve activity and adrenal norepinephrine-controlling preganglionic neurons in the rat (33, 103, 128, 134, 148) are very sensitive to baroreceptor-mediated inhibition, whereas most of the sympathetic fibers innervating the skin exhibit a markedly weaker baroreceptor responsiveness (22, 125, 137), as do the sympathetic outflow to brown adipose tissue and the epinephrine-regulating adrenal SPNs (128, 132). Extending the hypotensive stimulus to the decompensatory phase of hemorrhage elicits a dramatic inhibition in renal sympathetic outflow and a large increase in adrenal sympathetic nerve activity and epinephrine secretion (33, 100, 154, 159, 160). These responses are significantly dependent on cardiac vagal afferent input to the nucleus of the solitary tract, from which similar differential responses can be elicited through activation of purinergic receptors (149, 150).

**Arterial chemoreceptor reflex.** The immediate cardiovascular response to stimulation of arterial chemoreceptors with hypoxia or reduced blood flow through the
carotid or aortic bodies is an increase in sympathetically mediated vasoconstriction to reduce tissue oxygen consumption and to increase arterial pressure and augment cerebral oxygen availability. Cardiac vagal activation is also present (98), possibly reducing coronary oxygen consumption through bradycardia. Differential responses to chemoreceptor reflex stimulation have been demonstrated in the sympathetic nerves controlling muscle and visceral vasoconstriction vs. those to the skin. Stimulation of the arterial chemoreceptor reflex with systemic hypoxia, CO₂-saturated saline, or sodium cyanide excited the preganglionic cervical sympathetic nerve and the postganglionic sympathetic innervation of skeletal muscle and pulmonary vasculature and to the kidney in the cat (22, 82, 93, 98, 152), the splanchnic nerve in the rabbit (83), and the renal and splanchnic sympathetic outflows in the rat (50, 99). Chronic moderate or acute severe hypoxia also elicited an increase in rat cardiac sympathetic outflow, the latter accompanied by a rise in adrenal epinephrine secretion (92). In contrast, cutaneous postganglionic neurons are inhibited (Fig. 3) by arterial chemoreceptor reflex stimulation in the cat, dog, and rabbit (22, 23, 83).

The influence of central respiratory generating networks on those controlling sympathetic outflow is significantly stronger in muscle and visceral vasoconstrictor sympathetic discharge than in that of cutaneous sympathetic efferents, although this differential respiratory modulation is expressed more in the cat than in the rat or human. With the use of a phrenic nerve discharge to monitor the central respiratory cycle, a strong respiratory modulation has been observed in the cardiac vagal outflow (51) and in the amplitude of the bursts in the sympathetic nerves to the kidney in the cat and rat (4, 95, 137, 139), to the skeletal muscle in the cat and human (10, 51, 66, 94), to the cardiac nerve in the cat and rat (4, 95, 139), and to the lumbar, adrenal, cervical, and splanchnic nerves in the rat (74, 126, 139). Although such modulation is absent in the majority of cutaneous sympathetic fibers recorded in the cat (66, 137), it is present in the rat (72, 91) and human (73, 87) cutaneous sympathetic outflow.

**Thermal stimuli.** Autonomic thermoregulatory responses are directed toward changes in the level of 1) heat conservation through circulatory adjustments focused on modifying cutaneous blood flow and through changes in sudomotor and pilomotor activity and 2) heat production through influences on thermogenic mechanisms. Secondary effects, from arterial and cardiopulmonary baroreceptor reflexes for instance, would be expected during some thermoregulatory responses, as in those requiring a large increase in cutaneous blood flow. Thus direct thermoregulatory responses are mediated by differential changes in the sympathetic outflows to the skin and tissues involved in thermogenesis, relative to muscle and visceral vasoconstrictor nerve activity.

Exposure to a warm (43°C) environment activated sudomotor sympathetic activity in humans while suppressing cutaneous vasoconstrictor fiber discharge (16). Similarly, heating the spinal cord in anesthetized rabbits and dogs produced an inhibition of cutaneous sympathetic nerve activity accompanied by an excitation of the cardiac and splanchic nerve activities (42, 153). Peripheral thermal receptor stimulation (heat) elicits an increase in rat renal sympathetic nerve activity (50), resulting in a fall in renal blood flow. Conversely, a cold (15°C) environment stimulates activity in human cutaneous vasoconstrictor efferents while inhibiting sudomotor sympathetic outflow (16). Exposure to cold stimulates sympathetic nerve activity to rat brown adipose tissue, but has only a minor effect on splanchnic sympathetic discharge, at least some of which may arise from sympathetic axons regulating thermogenesis in mesenteric brown adipose tissue depots (127). Spinal cooling activated cutaneous, as well as splanchnic, sympathetic discharge in rabbits and dogs, but evoked little change in cardiac sympathetic activity or heart rate (42, 153). A decrease in cardiac...
sympathetic outflow during cold exposure was also seen in rats (165). Although cold-stimulated increases in plasma norepinephrine could arise from both sympathetic terminals and adrenal chromaffin cells, the absence of a change in plasma epinephrine during cold exposure (58, 163) and a fall in adrenal norepinephrine content (163) are consistent with the differential stimulation of adrenal norepinephrine release in response to cold exposure (165).

**Nociceptor stimulation.** Peripheral nociceptor stimulation, such as that produced by pinching the skin, evokes a strong excitation of muscle and visceral vasoconstrictor sympathetic outflow but a prompt reduction in cutaneous vasoconstrictor efferent discharge in cat (88). An equally strong differential response, but in the opposite direction, is evoked by painful trigeminal stimuli in the anesthetized rabbit. The “trigeminal depressor response,” evoked by stimulation of the trigeminal nerve or pinching the facial skin, involves a reduction in splanchnic, renal, and skeletal muscle sympathetic outflow and a simultaneous increase in that to the cutaneous vessels (101, 167). Cutaneous vasoconstriction has also been demonstrated in anesthetized humans during surgical incision (113, 151). Ischemic injury evoked a suppression of cardiac sympathetic discharge and a stimulation of adrenal epinephrine secretion (164). Recent experiments have suggested an involvement of sympathetic premotor neurons in the rostral medullary raphe in the control of cutaneous blood flow as a potential neural substrate contributing to the differential responses in cutaneous vs. muscle and visceral vasoconstrictor sympathetic outflow. Activation of raphe neurons, independent of those in the RVLM, produced a large increase in the sympathetic outflow to the cutaneous vascular bed in the rat tail and the rabbit ear, with little effect on the visceral vasomotor outflow to the kidney or mesentery (20, 143). Inhibition of neurons in the raphe selectively prevented the cutaneous constriction in the rabbit ear during trigeminal stimulation, whereas inhibition of RVLM neurons was necessary to block the mesenteric vasoconstriction from stimulation of abdominal vagal afferents (19).

**Hypoglycemia.** A fall in blood glucose, sensed by central and hepatic glucoreceptors, stimulates an autonomic response directed primarily at restoring levels of circulating glucose through stimulation of hepatic glycogenolysis and inhibition of insulin-sensitive glucose uptake. Secondary effects include a reduction in body temperature and a restriction of muscle blood flow, both of which would reduce glucose utilization. Experimentally, hypoglycemia is achieved with injections of insulin. Alternatively, reflex pathways to correct hypoglycemia are activated by the glucopenia produced by the administration of 2-DG, which blocks cellular glucose metabolism. Because insulin can have direct effects on sympathetic nerve activity, euglycemic control studies are required to interpret the results of insulin-induced hypoglycemia.

In humans, muscle sympathetic nerve activity and the sudomotor component of skin sympathetic activity are stimulated by acute hypoglycemia, whereas the vasoconstrictor component of skin sympathetic activity is reduced (15, 55, 78). The increase in sweating and cutaneous vasodilation would contribute to a fall in body temperature, as would the inhibition of sympathetic outflow and thermogenesis in rat brown adipose tissue evoked by administration of 2-DG (54, 79). Indirect evidence has also been presented in humans and dogs for an increased sympathetic outflow to the liver during hypoglycemia (24, 133), which would contribute to glycogenolysis and an elevation in blood glucose. Hypoglycemia stimulates a large increase in adrenal sympathetic nerve activity and epinephrine secretion in rats and humans, but decreases or has little effect on renal and cardiac sympathetic outflows (24, 32, 55, 78, 110, 124, 135, 142, 162, 166, 168). The release of adrenal catecholamines is differentially affected by hypoglycemia, which is a much stronger stimulus for the secretion of epinephrine than of norepinephrine (128, 163).

**DIFFERENTIATION OF PREMOTOR NEURONS CONTROLLING SPECIFIC TARGET TISSUES**

The prominent role of supraspinal circuits, in particular the premotor neurons, in the functional organization of the autonomic reflexes described above gives strong support to the view that the differential reflex responses observed in sympathetic nerves controlling different target tissues are a reflection of the existence of tissue-specific populations of premotor neurons. As alluded to above, the characterization of these neuronal populations will be dependent on the precision with which functional fingerprints of the autonomic outflow to specific tissues can be defined. The requirement for antidromic activation from the spinal intermediolateral nucleus and the likely necessity to determine the neuronal responses to a series of reflex or centrally evoked stimuli represent significant impediments to obtaining these data. Current evidence, albeit indirect, for functionally specific populations of sympathetic premotor neurons has been derived from two approaches: correlation of the activity of individual neurons with that in multiple, simultaneously recorded nerve bundles and monitoring the differential responses in multiple nerves during activation of subsets of premotor neurons. These studies have been performed in the RVLM and the raphe, which are among the brain regions identified anatomically as the principal sources of direct premotor input to SPNs (156).

**Correlation of brain stem unit activity to sympathetic nerve discharge.** If the discharge of a sympathetic premotor neuron contributes to the synchronous activation (i.e., burst behavior) of a single, homogenous population of tissue-specific sympathetic ganglion cells, then the expectation would be for the discharge of that neuron to be more strongly correlated to the bursts of activity on the nerve that it influences than to those on nerves regulating other target tissues. Using this paradigm, Barman and colleagues (12) identified RVLM and raphe neurons with discharges that were more
tightly coupled to either the cardiac, renal, or external carotid nerves. This analysis is inherently complicated by the attempt to correlate unit activity with a group of sympathetic efferents that each regulate a target with a cardiovascular function: the potential for a variable degree of coupling among the supraspinal circuits that generate the activity in each sympathetic channel to cardiovascular target tissues (63) would make it more difficult to observe differences among the unit-to-nerve activity correlations. Additionally, sympathetic nerve bundles, such as the renal and cardiac, are likely to contain multiple populations of functionally specific axons (49). The use of partial coherence analysis (41) has been an improvement on the original approach, but the conclusions are still limited by the array of efferent nerves one has available in any particular experiment.

**Differential responses from altering the activity of RVLM neurons.** With the discovery of cardiovascular sympathetic premotor neurons in the RVLM, several laboratories began to address the question of whether there was a viscerotopic organization of premotor neuron populations within the RVLM. Inherent in finding a distinct tissue topography in the sympathetic responses elicited by microstimulation within the RVLM would also be evidence for functionally specific populations of premotor neurons, thereby establishing that the "private lines" regulating the myriad of autonomic influences on tissue function could be traced centrally from the sympathetic ganglion cells and preganglionic neurons to their antecedent premotor neurons. The focus of microstimulation experiments within RVLM has been on differentiating subregions that regulate different cardiovascular tissues.

Activation of neurons in restricted regions of the RVLM in the cat with microinjections of an excitatory amino acid has produced the following general results: neurons in pathways controlling the vasoconstrictor sympathetic outflow to muscle are located more laterally and caudally in the RVLM, those capable of increasing cutaneous sympathetic nerve activity were located more medially in the RVLM, and those activating renal, cardiac, and lumbar splanchnic nerves are found rostromedially (27, 46, 47, 108, 119). Although there were relatively large areas from which responses on more than one nerve were evoked, the finding of restricted regions of the RVLM from which responses in only one tissue could be recorded is consistent with the existence of sympathetic premotor neurons directed solely to the regulation of the SPNs for that tissue. In this scenario, responses evoked in multiple nerves would arise from the anatomic intermixing of populations of functionally specific premotor neurons in the RVLM. This and the relatively smaller anatomic size of the RVLM are likely explanations for the failure to find similar results in the rat (13, 14). Importantly, simultaneous changes in blood flow to hindlimb and forelimb could be produced independently of those to the kidney, suggesting that the variable being regulated at the level of the premotor neuron is related to the target tissue (skeletal muscle blood flow vs. renal resistance, in this example) rather than the anatomic location within the body (118). This organizational principle is supported by the finding of extensive axonal branching of individual sympathetic premotor neurons projecting to intermediolateral nucleus (IML) neurons, possibly SPNs whose ganglion cell targets innervate the same end-organ tissue, at multiple levels of the thoracic spinal cord (8, 129). Additionally, as with cardiac vagal preganglionic neurons in the nucleus ambiguus (59), the data indicating selective regulation by different populations of RVLM neurons of cardiac contractility, rate, and conduction (26) emphasize the degree of functional specificity residing within the autonomic premotor and preganglionic efferents. Although relatively few noncardiovascular efferent pathways have been examined, the failure to demonstrate an excitatory effect of RVLM neurons on sympathetic regulation of pupillary dilation, piloerection, sweat glands, retraction of the nictitating membrane, rat tail blood flow, and rat brown adipose tissue sympathetic activity (116, 120, 121, 127, 143) is consistent with a selective role for premotor neurons in the RVLM in regulating sympathetic functions related to the maintenance of tissue perfusion pressure. Experimental designs involving the stimulation or inactivation of large numbers of neurons cannot, however, rule out the possibility that individual RVLM neurons branch to innervate multiple populations of SPNs controlling different tissues. Thus, although the available evidence favors tissue-specific populations of sympathetic premotor neurons within RVLM, we do not yet have direct evidence for their existence. Indeed, although sympathetic premotor neurons displaying the functional fingerprint indicating a role in the regulation of vasoc constriction have been extensively studied (8, 25, 117, 131), the same rudimentary characteristics would be expected of those controlling a variety of other functions as well: venous compliance, cardiac performance, and renal glomerular filtration.

**Effects of altering the activity of neurons in rostral medullary raphe.** The responses evoked from activation of the rostral medullary raphe in the rat and the rabbit, another locus of sympathetic premotor neurons (3, 107), provide evidence of a broader functional specificity: the populations of SPNs driven by raphe-spinal neurons are involved in thermoregulation and possibly energy balance, rather than the control of organ perfusion pressure, which may be the purview of RVLM premotor neurons. In studies on the central regulation of the sympathetic outflow to brown adipose tissue in the rat, disinhibition of neurons in the rostral raphe pallidus region produced large increases in brown adipose tissue sympathetic nerve activity, with only a small increment in splanchnic sympathetic nerve activity (127). The activation of brown adipose sympathetic outflow from raphe was independent of the activity of neurons in the RVLM (Fig. 4). Considering the significance of brown adipose tissue thermogenesis in the overall energy expenditure in small mammals, it seems likely that raphe neurons also play a role in regulating sympathetic outflows involved in metabolism and energy balance. Neurons in the rostral raphe
were also found to be a source of sympathoexcitatory drive to the cutaneous circulation in the rabbit ear (20) and in the rat tail (143), both of which contribute significantly to thermoregulation through their role in heat dissipation. In these cases as well, RVLM neurons were found to have little influence on the sympathetic control of these thermoregulatory circulations (19, 143). Although it seems likely that target-specific populations of sympathetic premotor neurons exist within the raphe-spinal projection, the identification of sympathetic premotor neurons controlling different thermoregulatory and metabolic tissues remains to be accomplished. Although neither the role of raphe-spinal neurons in thermoregulation in the cat nor the functional specificity of cat raphe sympathetic premotor neurons has been examined (although see Ref. 12), the finding of raphe neurons with projections to the IML, with strong baroreceptor modulation (129, 130) and with a role in the 10-Hz rhythm in sympathetic nerve activity (11), suggests that a cardiovascular regulatory function is represented within the population of raphe sympathetic premotor neurons in this species.

Summary. Current physiological data provide strong support for the existence of tissue-specific populations of sympathetic premotor neurons as an important structural and functional basis for the ability of the central nervous system to generate autonomic responses at selective sites in the body and to orchestrate complex autonomic patterns involving differential changes in the amplitudes of the sympathetic outflows to relevant targets. Although only two of the several anatomically segregated groups of sympathetic premotor neurons have been studied from a functional perspective, the results suggest an organizational model in which the basis for the anatomic clustering of different subpopulations of premotor neurons resides in the larger homeostatic function to which the regulation of their target tissues contributes. Thus RVLM premotor neurons regulate cardiovascular target tissues to control arterial pressure at an appropriate level to maintain nutritive tissue blood flow, whereas a population of rostral raphe-spinal sympathetic premotor neurons may selectively control sympathetic outputs involved in thermoregulatory and metabolic control. Within this model, it is expected not only that certain supraspinal loci will comprise unique sites for premotor neurons regulating particular tissues but also that some populations of SPNs will receive premotor inputs from more than one source. For instance, the increase in heart rate during exercise may arise from activation of cardiac sympathetic premotor neurons in the RVLM, whereas that occurring during brown adipose tissue thermogenesis may involve stimulation of premotor neurons in the rostral raphe that project to the same population of cardiac preganglionic neurons (30).

HIERARCHICAL ORGANIZATION OF DIFFERENTIAL SYMPATHETIC REGULATION

Given the evidence described above that sympathetic premotor neurons are functionally “dedicated” by virtue of their axonal projection pattern, one might ask whether the selective control of tissue-specific autonomic outflow is maintained at any organizational level that is central to the premotor neurons? Specifically, are neurons antecedent to premotor neurons functionally specific or are their axonal branches distributed to provide mechanisms for linking sympa-
thetic premotor output channels to effect simultaneous changes in different target tissues? Although these questions do pose a potential, albeit simplistic, framework for the neural substrates underlying patterned autonomic responses, a number of factors combines to complicate the experimental testing of such hypotheses. As with all such studies, there are significant limitations set by the number of outputs that can be simultaneously monitored and by the difficulty in distinguishing whether simultaneous activation of multiple outputs arises from stimulating 1) separate populations of neurons controlling each output or 2) a single group of neurons with axons that branch to innervate multiple, functionally specific efferent pathways. Regions containing sympathetic premotor neurons receive inputs from multiple sources, which may themselves be interconnected. Additionally, considerable evidence supports the existence of individual “oscillator” circuits that drive target-specific populations of premotor neurons (63) to generate the bursting activity characteristic of each sympathetic outflow. The interaction of inputs from more rostral sites with such brain stem oscillator circuits, the potential for coupling among oscillators for different outputs, and the presence of a significant inhibitory input to premotor neurons (71, 132) represent further complexities of the central autonomic networks.

Stimulation of the hypothalamus. A variety of differential autonomic responses has been documented from activation of the hypothalamus. The varied use of electrical vs. chemical stimuli; the activation of relatively large, functionally heterogeneous populations of neurons; and the existence of intrahypothalamic connections as well as descending pathways to the periaqueductal gray (PAG), the RVLM, and the spinal cord allow few conclusions on the pathways or, in some cases, the functional significance for these responses. Nonetheless, in the best light, the differential nature of the evoked responses does indicate a degree of separate regulation of the outputs being monitored, although likely reflecting only a portion of an organized homeostatic response involving an unknown number of additional effectors.

Sampling of plasma catecholamines during systematic stimulation through the cat hypothalamus revealed that markedly different ratios of adrenal epinephrine and norepinephrine secretion could be evoked, even from neighboring sites (56, 145). Although these data reveal little of the organization of hypothalamic networks influencing adrenal medullary function, they are consistent with the existence of separate descending pathways to the two groups of adrenal sympathetic premotor neurons controlling epinephrine- vs. norepinephrine-secreting chromaffin cells (128). In this regard, different hypothalamic regions contribute to the autonomic response to hypoglycemia and to hypothermia, which elicit differential release of adrenal catecholamines (163). Opposite responses can also be evoked in cardiac sympathetic nerve activity and muscle vasoconstrictor outflow in cat and in cardiac and renal sympathetic nerve activities in the rabbit by stimulation at certain hypothalamic sites (97, 140). Stimulation within neighboring sites in the lateral hypothalamus evoked differential responses in cardiac and in vasoconstrictor efferents to neck or to pharyngeal muscles (21). Although these responses resemble portions of the response to arterial chemoreceptor activation, it will remain for future investigation to identify the behavioral or reflex context for many of these data.

Historically, the hypothalamically evoked defense response, also referred to as the fight-or-flight or visceral alerting response, has often been described as a behavior involving differential control of sympathetic outflow (1, 76, 77). This view seems to have arisen from the finding that the cardiac stimulation, widespread visceral vasoconstriction, piloerection, and pupillary dilatation observed during the defense response are accompanied by a characteristic increase in skeletal muscle blood flow (43). However, the evoked increase in muscle blood flow is mediated by activation of a cholinergic (atropine sensitive) vasodilator pathway, with little evidence for a marked inhibition of adrenergic muscle vasoconstrictors (43, 81). Although the utility of studies examining the defense response in anesthetized animals has been questioned (18) and the prominence of a cholinergic vasodilator pathway is unclear in species other than the cat, experiments to identify the descending pathways for the hypothalamic defense response were a significant motivation for examining the role of the PAG in the organization of patterned autonomic responses (40).

Stimulation of the PAG. Detailed stimulation studies have delineated an organizational structure based on longitudinal columns within the PAG for circuits that are capable of coordinating a variety of complex autonomic, motor, and sensory modulating commands mimicking the fight-or-flight response (dorsal and lateral columns, Fig. 5A) as well as those seen during recovery from stress, activation of antinociception, or the vasovagal syncope that can accompany deep pain (ventrolateral columns) (7, 35, 109). The portions of the PAG columns from which autonomic responses are evoked have extensive, viscerotopically organized, descending projections to sympathetic premotor neurons in the RVLM (36, 37, 39). Differential activation of these pathways is likely to mediate the vasoconstrictor and tachycardic components of “active emotional coping” evoked from the dorsal and lateral columns of PAG and the vasodepressor and bradycardic responses of “passive coping” strategies mimicked by stimulation of ventrolateral PAG (5, 6, 38). These response patterns suggest that PAG neurons, by virtue of the topography of their inputs to the RVLM, provide a substrate for the parallel activation or inhibition of premotor neurons controlling an extensive array of cardiovascular targets.

Recent studies have also provided evidence that activation of sites in the defense region of PAG can evoke differential changes in visceral vs. skeletal muscle sympathetic outflows (64, 65). Under conditions allowing 10-Hz rhythms in these nerves, PAG stimuli that
elicited increases in cardiac and renal sympathetic nerve activities produced a prompt inhibition of vertebral nerve activity (Fig. 5B) and a prolongation of the phase angle between them. These findings have led to the proposal of a novel mechanism by which differential responses may be produced in functionally specific sympathetic outflows: if an input (such as that from PAG) to a network of coupled oscillators (in this case involving populations of premotor neurons in RVLM) shifts the phase relationship between the oscillators generating the bursts in different sympathetic nerves, then, by virtue of their coupling, the reduced synchrony could result in a decrease in the burst amplitude of one output relative to the other, including a complete inhibition if the shift in phase is of sufficient magnitude (62).

CONCLUSIONS

The demonstration that sympathetic outflows to different targets can be differentially affected by central stimulation and during reflex and behavioral responses reflects a much more complex structure to the central autonomic network than that necessary to affect the relatively simple global changes in sympathetic discharge that were the focus of early investigators. Anatomic and functional studies have indicated a structural foundation for differential sympathetic responses in the target specificity of the projections of ganglion cell axons and those of their preganglionic inputs. Although it has been more difficult to obtain direct evidence for dedicated, tissue-specific populations of sympathetic premotor neurons, the ability to elicit differential responses in different sympathetic outflows from stimulations at stereotyped sites within a single locus of premotor neurons (such as RVLM) or at sites within anatomically separate loci of premotor neurons (such as RVLM and raphe) is strongly supportive of such a model. Similarly, differential sympathetic responses to activation of a number of reflexes that involve changes in sympathetic premotor neuronal discharge are most easily explained through differential inputs to populations of functionally dedicated premotor neurons. The functional fingerprints of the sympathetic outflows to different tissues could provide the information needed for a response-based differentiation among premotor neurons controlling different tissues. Although current evidence is still sparse, the clustering of different populations of tissue-specific premotor neurons at a particular anatomic site may relate to a similarity in the overall function of the outputs being regulated by those groups of premotor neurons. Within the framework of this hypothesis, the premotor neurons located in the RVLM appear to be primarily involved in regulating cardiovascular target tissues involved in maintaining organ perfusion pressure and nutritive blood flow, in contrast to those in the rostral raphe nuclei that influence targets with thermoregulatory and metabolic functions. Will this model be supported by the differential nature of the responses evoked from other sources of premotor input to preganglionic neurons, such as the A5 region and the paraventricular nucleus of the hypothalamus?

Determining the substrate for tissue specificity within central autonomic pathways represents not only a significant advance in our understanding of the functional organization of sympathetic control net-
works, but also a stepping stone to identifying the mechanisms through which multiple, tissue-dedicated output systems are engaged to produce the constellation of changes in individual effector outflows that comprises a complete autonomic response or behavior component. On this threshold, we are challenged to put the information derived from patterns of differential, stimulation-evoked responses into functional contexts that will yield insight into the underlying organizational structure, operating principles, and response dynamics of the central autonomic network.

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