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THE CENTRAL AUTONOMIC NERVOUS SYSTEM: Conscious Visceral Perception and Autonomic Pattern Generation

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■ **Abstract** The overall organization of the peripheral autonomic nervous system has been known for many decades, but the mechanisms by which it is controlled by the central nervous system are just now coming to light. In particular, two major issues have seen considerable progress in the past decade. First, the pathways that provide visceral sensation to conscious perception at a cortical level have been elucidated in both animals and humans. The nociceptive system runs in parallel to the pathways carrying visceral sensation from the cranial nerves and may be considered in itself a component of visceral sensation. Second, structures in the central nervous system that generate patterns of autonomic response have been identified. These pattern generators are located at multiple levels of the central nervous system, and they can be combined in temporal and spatial patterns to subserve a wide range of behavioral needs.

INTRODUCTION

Although the basic plan of the peripheral components of the autonomic nervous system has been known since the late nineteenth century, and its neurotransmitters were characterized more than 50 years ago, the organization of central control of the autonomic nervous system has only become clear in the past two decades, and several aspects remain controversial. Rather than attempt to review the entire subject, much of which has not progressed substantially since other comprehensive reviews were published (Saper 1995, Loewy & Spyer 1990), this review focuses on two key elements of the central autonomic system that remain controversial: how visceral sensory information reaches conscious appreciation and how patterns of autonomic response are generated by the brain. We attempt to put these areas into historical perspective and to provide a theoretical framework for considering current and future advances.

HOW DOES VISCERAL SENSORY INFORMATION REACH CONSCIOUS APPRECIATION?

Historical Perspective

The mechanisms for emotional expression were explored in the nineteenth century by Charles Darwin in his classic work, *The Expression of the Emotions in Man and Animals* (Darwin 1873). Although perhaps not as influential as his better-known work on natural selection, Darwin used the same approach of observation of animals in natural situations to demonstrate that different patterns of facial expression were common in animals of different species, including humans, who were facing similar behavioral situations, including anger, fear, happiness, and jealousy (Figure 1). These observations had profound effects on subsequent thought concerning the mechanisms of emotion and their obvious autonomic concomitants. First, Darwin legitimized the use of animal models for human emotional and autonomic expression. Subsequently, the use of animal experimentation became an accepted approach to understanding the physiological basis for such responses. A second consequence of Darwin's arguments was his recognition that autonomic responses were an intrinsic part of the emotional process. Although Darwin took pains to emphasize that he did not have the tools to address emotional autonomic responses, he explicitly recognized Claude Bernard's work on the subject, and thus prepared the field for later workers.

As tools for measuring autonomic responses improved, physiologists and psychologists in the 1880s began to approach the problems of emotional expression by evaluating autonomic alterations that accompany them. The Danish physiologist Lange (1885) proposed that autonomic responses occurred as reflex reactions during behaviors, and that the basis for emotional sensation was the perceptions that arose from such cardiovascular adjustments (e.g., flushing during embarrassment, pelvic blood flow during sexual arousal, elevated blood pressure and heart rate during anger, etc.).

There was considerable debate at the time whether cardiovascular sensation could account for the entire range of sensory experience associated with emotion. William James, professor of psychology at Harvard University, proposed a variation on Lange's model, usually called the James-Lange theory (James 1884). In this view, emotional experience was the sum product of the entire range of autonomic responses that accompany behavior (not just the cardiovascular response). Hence, the James-Lange theory allowed for additional sensory experiences reaching conscious perception, such as queasiness from abdominal sensations, or breathlessness during a panic attack.

This theory was criticized by Cannon (1929), who recognized his debt to Darwin in identifying patterns of motor response during emotions but sought to carry that approach forward by observing patterns of autonomic response in different emotional states (see "How are Different Patterns of Autonomic Output Generated?" below). Cannon argued that visceral sensation itself could not account

Figure 1 Comparisons of animal and human faces exhibiting snarling (*upper row*) or pleased (*lower row*) facial expressions. The similarity of facial musculature engaged in these expressions across different species provided evidence for Darwin's hypothesis that neural control of emotional response involved common pattern generators in different mammals. These observations also provided support for the use of animal models to study emotional expression. Reproduced from Darwin (1873) with permission.

for the full range of emotional experience. He pointed to experiments of nature or medical conditions in which the spinal cord or the vagus nerves had been transected in humans, who retained most if not all of their emotional sensation. Hence, Cannon argued for a central system for emotional experience and behavior that was separable from the brain system for appreciation of visceral sensation.

The first hints of a forebrain sensory representation devoted to visceral sensation came from experiments in the mid-twentieth century in which the newly developed tool of evoked potentials was used. Stimulation of the proximal end of the cut cervical vagus nerve allowed neurophysiologists to map the fields in

the forebrain in monkeys, cats, and rats that received vagal afferent input (Dell & Olson 1951, Bailey & Bremer 1938, Ogawa et al. 1990, Yamamoto et al. 1980). These experiments demonstrated a region of vagal receptive cortex, corresponding in each species to the insular cortex.

The importance of the vagal sensory cortex to conscious appreciation of visceral sensation became clear in studies performed by the neurosurgeons Wilder Penfield and Theodore Rasmussen in the 1950s (Penfield & Faulk 1955, Penfield & Rasmussen 1950), in which they used electrical stimulation to map the cerebral cortex in patients undergoing neurosurgical procedures. The surgery was done under local anesthesia so patients could report their responses to the surgeon when he stimulated different cortical areas. This approach allowed the surgeons to produce functional maps of the cerebral cortex in individual patients, and these were used as a guide during subsequent surgery to resect tumors, arteriovenous malformations, or sites of epileptic electrical activity.

As Penfield moved his stimulating electrode ventrally along the primary sensory cortex, he identified a region extending just beyond the tongue somatosensory area into the opercular cortex overlying the insula, where electrical stimulation produced taste sensation. When he moved his electrode further into the insula, his subjects reported that stimulation produced oropharyngeal, esophageal, or even gastrointestinal sensation. In his classic maps, Penfield positioned the gastointestinal tract as part of his sensory homunculus, running ventrally from the tongue sensory area into the operculum and insula.

It is important to note that although Penfield's subjects volunteered a variety of descriptions about their visceral sensory experiences, none of them felt complete emotional responses from stimulation in the insular region. This experience was in contradistinction to experiments in which depth electrodes were used to stimulate the medial temporal lobe, also in patients with underlying epilepsy (Gloor et al. 1982). These patients instead reported emotional reactions, such as feelings of fear, or complex experiential phenomena with attendant emotions (such as seeing an old boyfriend, hearing a song on a guitar, or balancing on the edge of a fountain) with stimulation of the amygdala or hippocampal formation. Thus, although the visceral sensory cortex does relay information to medial temporal lobe structures where it may be integrated with emotional experience, it is unlikely that the insular cortex itself functions as an emotional integrator, or that visceral sensation is equated by the brain with the emotional experience that often accompanies it.

The mechanisms by which such conscious perceptions arise from activity of the internal organs remain poorly understood. We review the underlying anatomy and physiology of the visceral sensory pathways in a systematic way and attempt to arrive at a modern synthesis for understanding the conscious appreciation of visceral sensation. Note that we do not consider mechanisms of visceral sensory input in reflex pathways or even in highly coordinated and complex responses (e.g., digestion, cardiovascular response to muscle activity) that do not reach the level of conscious perception. For this information the reader is referred to the classic reviews by Sato & Schmidt (Sato & Schmidt 1973, Sato et al. 1997)

on somato-autonomic reflexes and the thorough reviews in the volume by Loewy & Spyer (1990).

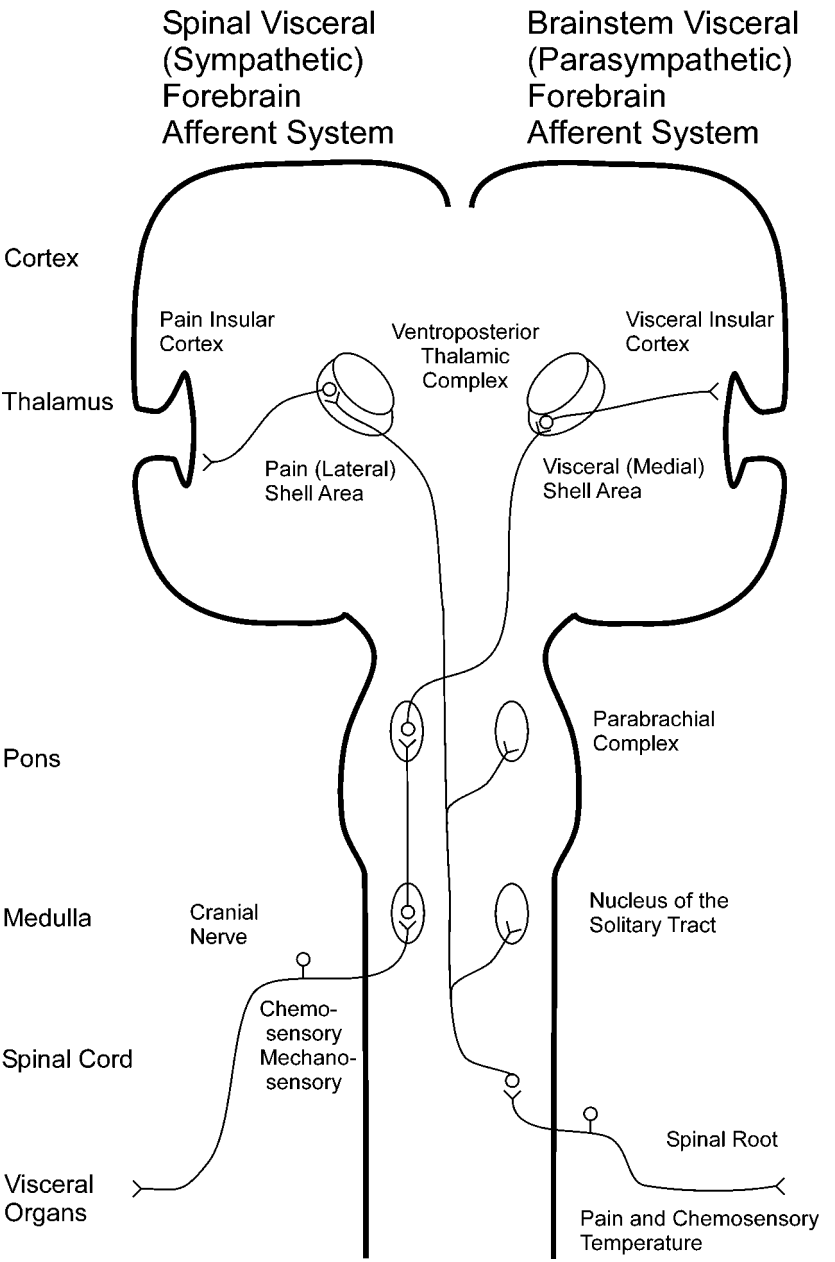
Two main sensory systems provide information to the brain about the state of the internal organs. The afferents provided by the cranial nerves, sometimes called the parasympathetic afferent system, carry mainly mechanoreceptor and chemosensory information. By contrast, afferents that arrive via spinal nerves, often called the sympathetic afferent system, convey mainly sensations related to temperature and impending or ongoing tissue injury, of either mechanical, chemical, or thermal origin (Figure 2, see after section on the gustatory system). We first consider the cranial nerve afferent system and then review the spinal afferent system, mainly in the context of its relationship to the cranial nerve system.

The Cranial Nerve (Parasympathetic) Visceral Sensory System

Visceral sensory information enters the brain via four cranial nerves: the trigeminal nerve, which conveys internal face and head visceral sensation; the facial nerve, which provides visceral sensory information (taste) from the tongue; the glossopharyngeal nerve, which conveys visceral sensory input (including taste) from the hard palate and upper part of the oropharynx as well as the carotid body; and the vagus nerve, which provides visceral sensation (including taste) from the lower part of the oropharynx, as well as supplying the larynx, trachea, esophagus, and thoracic and abdominal organs, with the exception of the pelvic viscera (Kerr 1961, Altschuler et al. 1989, Contreras et al. 1982). The pelvic viscera are innervated by nerves from the second through fourth sacral spinal segments. Although their patterns of spinal cord termination have been studied in detail (Morgan et al. 1981), what little is known about their central pathways or projections is similar to other spinal visceral afferent pathways, which are covered below.

VISCERAL AFFERENTS FROM ALL FOUR CRANIAL NERVES TERMINATE TOPOGRAPHICALLY IN THE NUCLEUS OF THE SOLITARY TRACT The abbreviation NTS, which is commonly used, stands for the Latin term, *nucleus tracti solitarii*. Other corruptions of the Latin term are frequently seen, such as *nucleus tractus solitarius* or *nucleus tractus solitarii*. The visceral sensory axons form a bundle, the solitary tract, which is analogous to the spinal trigeminal tract or Lissauer's tract and conveys sensory fibers along the length of the NTS.

Studies of the distribution of these sensory nerves along the length of the NTS show that they terminate in a strongly topographic pattern (Altschuler et al. 1989). The rostral tip of the NTS, which is in close proximity to the tongue region of the spinal trigeminal nucleus, is innervated by axons concerned with taste (a chemosensory modality) from the anterior two thirds of the tongue. Gustatory fibers from the posterior third of the tongue and the surrounding posterior oropharynx end more caudally in the rostral NTS (Contreras et al. 1982). At the level where the NTS begins to shift dorsomedially, to abut the floor of the fourth ventricle, fibers from the esophagus terminate in a tight cluster, the central NTS subnucleus (Altschuler



et al. 1989). Axons from parts of the vagus nerve that innervate progressively more caudal parts of the gastrointestinal tract end more caudally in the medial part of the NTS.

Axons from cardiovascular structures, including the carotid body and aortic arch baroreceptors, terminate within the dorsomedial part of the NTS, from just rostral to the level of the obex caudally through the commissural subnucleus of the NTS (Panneton & Loewy 1980, Ciriello 1983). Respiratory chemoreceptors are distributed in a similar pattern, but laryngeal, bronchial, tracheal, and pulmonary mechanoreceptor afferents synapse in the lateral part of the NTS, including the ventrolateral, interstitial, intermediate, and commissural nuclei (Kalia & Richter 1988).

THE PARABRACHIAL NUCLEUS IS THE MAJOR RELAY FOR ASCENDING VISCERAL INPUTS FROM THE NTS TO THE FOREBRAIN Because all of the cranial visceral afferents are relayed via a single cell group, the NTS, it is possible to study their further processing in the brain by examining the outputs from the NTS (Ricardo & Koh 1978, Beckstead 1980). In general, the most massive site for termination of fibers from the NTS is the parabrachial nucleus. The parabrachial nucleus consists of at least 13 separate subnuclei, which in turn provide extensive projections to a wide range of sites in the brainstem, hypothalamus, basal forebrain, thalamus, and cerebral cortex (Fulwiler & Saper 1984, Chamberlin & Saper 1994, Bester et al. 1997, Moga et al. 1990, Herbert et al. 1990), some of which are augmented by smaller direct projections from the NTS. Because this is a complex topic and conscious appreciation of visceral sensation depends upon the visceral sensory cortex (see below), we focus on the ways in which information from the NTS and parabrachial nucleus may reach the visceral sensory thalamus and hence the cerebral cortex.

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Figure 2 A schematic drawing illustrating the spinal (sympathetic) and brainstem (parasympathetic) visceral sensory pathways to the thalamus and cerebral cortex. Note that the spinal afferent pathway crosses in the spinal cord; it projects bilaterally in the brainstem to the nucleus of the solitary tract and the parabrachial nucleus, but only ipsilateral projections are shown for clarity of illustration. Spinal visceral afferents relay in the lateral part of the "shell" of the ventroposterior thalamic complex, along with other spinothalamic afferents, especially nociception. The pathway taken by visceral afferents conveyed in the facial, glossopharyngeal, and vagus nerves relays in the nucleus of the solitary tract and the parabrachial nucleus, then crosses to innervate the medial part of the shell of the contralateral ventroposterior thalamic complex. The brainstem visceral sensory pathway terminates in the anterior part of the insular cortex, in comparison with the spinal pathway, which terminates more caudally in the insular area.

THE GUSTATORY SYSTEM PROVIDES A MODEL FOR VISCERAL SENSORY ACCESS TO CONSCIOUS APPRECIATION To understand the relays responsible for conscious perception of visceral stimuli, it is instructive to consider the pathways that convey taste, a special visceral sensory modality that is appreciated in detail at a conscious level. As Herrick (1905) first pointed out in fishes, taste afferents from the NTS relay through the parabrachial region. In mammals inputs from the rostral part of the NTS are widely distributed in the parabrachial nucleus, including the medial subnucleus, external medial subnucleus, and ventral lateral subnucleus (Norgren 1978, Ricardo & Koh 1978). Large lesions of the parabrachial nucleus eliminate salt appetite, prevent conditioned taste avoidance in rats (Flynn et al. 1991), and cause deficits of taste discrimination in humans (Sato & Nitta 2000, Comvarros et al. 2000, Kokima & Hirano 1999, Onoda & Ikeda 1999, Nakjima et al. 1983). However, the location within the parabrachial nucleus of neurons that give rise to conscious taste perception has been controversial.

One approach to identifying the parabrachial region responsible for taste perception has been to determine the inputs to the thalamocortical taste system. The taste cortex has been mapped in rodents and primates by single-unit recording of neurons that respond to the application of gustatory stimuli applied to the tongue. The taste cortex in primates includes the inner, upper lip of the opercular cortex (closest to the insula) and the adjacent anterior insular region (Pritchard et al. 1986, Scott et al. 1986, Yaxley et al. 1990, Ito & Ogawa 1991, Baylis et al. 1995, Scott & Plata-Salaman 1999, Ito et al. 2001). In rodents a homologous taste area is found just dorsal to the rhinal sulcus, just rostral to where it is crossed by the middle cerebral artery (Kosar et al. 1986a, Cechetto & Saper 1987). The dysgranular field of the insular cortex in rats corresponds to this functionally defined region. The thalamic relay nucleus for the taste cortex is the most medial part of the ventroposterior parvicellular nucleus [VPpc, sometimes called the ventroposterior medial parvicellular nucleus (VPMpc) and sometimes ventromedial basal nucleus (VMb)] (Kosar et al. 1986b, Flynn et al. 1991, Cechetto & Saper 1987). Studies of lesions in humans have demonstrated that the representation of taste at a cortical or thalamic level is contralateral to the tongue (Onoda & Ikeda 1999a). Hence, by studying the contralateral brainstem inputs to the VPpc it should be possible to determine the brainstem relay for conscious appreciation of taste.

The inputs to the medial part of the VPpc have been examined using both anterograde and retrograde tracing studies in rodents (Cechetto & Saper 1987, Yasui et al. 1989, Bester et al. 1999). Retrograde transport studies are complicated by the fact that the small size of the VPpc makes it almost impossible to confine tracer injections to this nucleus, and hence the adjacent intralaminar and midline nuclei are virtually always involved by the injections (Cechetto & Saper 1987, Yasui et al. 1989). Retrogradely labeled neurons were found on the ipsilateral side of the brain in a wide range of parabrachial subnuclei, including the medial, external medial, and ventral lateral groups. However, on the contralateral side of the brain there were few labeled neurons in the medial and ventral lateral parabrachial subnuclei, whereas the external medial subnucleus contained about three to four

times as many retrogradely labeled neurons as on the ipsilateral side. Hence, the projection from the external medial subnucleus is the only parabrachial-thalamic projection that is predominantly contralateral.

Anterograde tracing studies demonstrated a pattern of labeling consistent with these findings (Bester et al. 1999; D. F. Cechetto & C. B. Saper, unpublished). Efferents from the medial and ventral lateral subnuclei innervated predominantly the midline and intralaminar nuclei on the ipsilateral side, with a smaller contralateral projection, and only a light projection to the VPpc. By contrast, after tracer injections into the external medial nucleus, the bulk of the projection was to the contralateral VPpc, with only a light ipsilateral projection and relatively few axons in the intralaminar and midline nuclei.

This point is made most clearly by examining the pattern of immunostaining for calcitonin gene-related peptide (CGRP) in the thalamus (Yasui et al. 1989). Among the thalamically projecting neurons in the parabrachial complex, only the external medial subnucleus contains CGRP. The CGRP terminal field from this projection clearly outlines the VPpc in rats. De Lacalle & Saper (2000) recently described a similar CGRP projection in human brains.

Norgren and colleagues (Beckstead et al. 1980, Norgren 1984) have put forward an alternative view of the ascending taste pathway in primates. They noted that following injections of tritiated amino acids into the most rostral pole of the NTS in monkeys, they could trace a direct projection to the ipsilateral VPMpc and that only their more caudal NTS injections labeled substantial projections to the parabrachial nucleus.

On the other hand, in humans lesions of the dorsolateral pons, including the parabrachial nucleus, cause an ipsilateral taste deficit, whereas thalamic lesions cause a contralateral taste deficit (Sato & Nitta 2000, Combarros et al. 2000, Kojima & Hirano 1999, Onoda & Ikeda 1999, Nakajima et al. 1983). Thus, the ipsilateral projection from the NTS to the thalamus described by Beckstead and colleagues (1980) in monkeys is unlikely to account for conscious taste perception, and the parabrachial relay to the contralateral thalamus seems to be a critical component of taste perception in humans.

OTHER VISCERAL SENSORY MODALITIES ARE ORGANIZED IN A TOPOGRAPHIC PATTERN THAT PARALLELS THE TASTE PATHWAYS The thalamocortical localization of other visceral sensory modalities has been studied most carefully in rats, in which Cechetto & Saper (1987) systematically mapped cardiovascular baroreceptor, carotid chemoreceptor, pulmonary inflation, gastric stretch, and taste responses in the insular cortex. These experiments identified a topographic pattern of visceral sensory responses in the dysgranular and granular insular region of rats. As in the NTS, taste was located most rostrally; taste neurons were found mainly in the dysgranular insular field. Neurons responding to gastrointestinal sensation were found just caudal to the taste area, and most were in the more dorsal granular insular field. There was some overlap of the locations of neurons responding to taste and to gastrointestinal inputs, and occasional cells responded to both modalities.

Neurons responding to cardiovascular and respiratory afferents were located further caudally in the insular region. Again, there was spatial overlap of the neurons responding to these modalities, and occasional neurons responded to both types of inputs. Retrograde tracer, injected from the recording pipettes at the precise sites of the cortical visceral sensory responses, demonstrated a topographic input from the VPpc into the insular cortex, with the most medial tip of the VPpc innervating the dysgranular taste cortex, the midpart of the VPpc sending inputs to the rostral granular gastrointestinal insular sensory field, and the most lateral part of the VPpc supplying the more caudal granular cardiovascular part of the insular visceral sensory cortex. Preliminary recordings of responses of single neurons in the thalamus to these different stimuli confirmed the medial to lateral topography of the VPpc (D. F. Cechetto & C. B. Saper, unpublished observations). Electrical stimulation of the homologous region in the human thalamus produces sensations both of taste and of gastric fullness (Lenz et al. 1997), suggesting that the special (taste) and general visceral relay nuclei are similarly organized in humans.

Single unit recordings from monkeys support a similar topographic organization of visceral sensory cortex in primates. The taste area in primates actually occupies two separate representations: a primary taste area in the inner lip of the rostral opercular cortex extending into the insular region, which constitutes a dysgranular insular field; and a taste association area in the orbitofrontal cortex, which also receives olfactory inputs (Pritchard et al. 1986, Scott et al. 1986, Yaxley et al. 1990, Ito & Ogawa 1991, Baylis et al. 1995, Scott & Plata-Salaman 1999, Ito et al. 2001, Ongur & Price 2000). One study of single neurons in the insular area of awake monkeys reported responses to stimulating the cervical vagus nerve, suggesting a general visceral input to the insular region caudal to the taste area (Radna & MacLean 1981). Recent functional magnetic resonance imaging studies in humans demonstrated increased blood flow in the insular cortex, just caudal to the gustatory cortex, with visceral stimuli such as air hunger, maximal inspiration, valsalva maneuver, or physical manipulations such as hand grip or cold application to the forehead or hands, which elevate blood pressure and heart rate (King et al. 1999, Harper et al. 2000, Banzett et al. 2000). Taken as a whole, these studies suggest that the insular cortex of primates, including humans, contains a visceral sensory representation. The more rostral representation of taste, compared with general visceral modalities, also suggests that the topographic ordering of visceral sensations are preserved throughout the system, from the visceral sensory "homunculus" in the NTS all the way through to the cerebral cortex.

OTHER POSSIBLE ROUTES BY WHICH VISCERAL SENSORY AFFERENTS MAY REACH THE CEREBRAL CORTEX In addition to the NTS-parabrachial-thalamic-cortical relay, the NTS and parabrachial nucleus project to other targets that might provide access to cortical appreciation of visceral sensation. One possible route is a direct projection from the parabrachial nucleus to the cerebral cortex (Saper 1982). This pathway originates from neurons in the medial part of the medial parabrachial subnucleus, in a region that receives gustatory visceral afferents. Some of these

direct parabrachio-cortical axons innervate the insular visceral sensory field (the dysgranular and granular cortex), but most project to the agranular insular cortex and the lateral prefrontal cortex, regions in which the neurons do not respond to discrete visceral stimuli (Saper 1982, Allen et al. 1991). Hence, this direct parabrachio-cortical pathway probably does not play a major role in conscious visceral perception, but it may instead serve a secondary role, e.g., as an arousing influence, perhaps to direct behavior towards a food source.

The NTS also projects to a number of other sites with forebrain projections, which therefore could potentially contribute to visceral perception, including the ventrolateral medulla, the hypothalamus, and the amygdala/bed nucleus of the stria terminalis (Ricardo & Koh 1978). A small percentage of neurons in the ventrolateral medulla project to sites such as the locus coeruleus, lateral hypothalamus, and midline thalamic nuclei, each of which has direct but diffuse cortical projections (Otake et al. 1994, Woulfe et al. 1990, Aston-Jones et al. 1986, Saper 1985). Neurons in the lateral hypothalamus that project diffusely to the cerebral cortex also could potentially relay inputs directly from the NTS. However, because these projections are diffuse, they are more likely to be important in arousal than in conveying specific sensory information. Other basal forebrain targets of the NTS, such as other hypothalamic targets or the bed nucleus of the stria terminalis and the central nucleus of the amygdala, do not have direct cortical projections and hence probably do not contribute in a major way to conscious appreciation of visceral sensation.

SUMMARY Current evidence suggests that, in mammals from rats to humans, the pathway by which cranial nerve visceral afferents reach conscious appreciation involves a relay from the NTS to the ipsilateral external medial parabrachial nucleus. This cell group, many of whose neurons contain the peptide CGRP, then relays visceral afferents to the contralateral VPpc, which in turn innervates a dysgranular and granular anterior insular sensory field that acts as a visceral sensory cortex. This pathway appears to maintain its organotopic ordering, in roughly the same pattern as in the NTS, at a cortical level. There is less evidence for the maintenance of this topopraphic ordering at thalamic and parabrachial levels, but it is likely that the viscerotopic map is maintained throughout the system. Visceral sensations may then be relayed to other structures, including the medial temporal lobe, where they may become part of a more complex emotional experience. However, discrete visceral sensations appear to depend upon the integrity of the visceral sensory cortex and thalamus.

The Spinal (Sympathetic) Visceral Afferent System

Sensory afferents from the internal organs also enter the central nervous system via the spinal nerves, and these inputs have been called sympathetic visceral sensory afferents. This term is confusing, however, as visceral sensory afferents (e.g., concerned with muscle chemosensation during exercise) may arise at all spinal levels, not just the thoracic levels at which sympathetic preganglionic neurons are

found (Kalia et al. 1981). In addition, dorsal horn sensory neurons that respond to visceral organs may be located at spinal levels quite distant from the level at which the visceral sensory afferents enter the spinal cord (e.g., dorsal horn neurons that respond to cardiac pain are found from at least the C2 to the T5 spinal levels) (see Blair et al. 1982, Chandler et al. 2000). Conversely, pelvic sensory afferents from spinal segments S2–4 are important for the regulation of sacral parasympathetic outflow, but there is little evidence that the information they convey is handled differently from inputs entering at other spinal levels. Thus, we consider spinal visceral afferent systems as a whole.

Our concepts concerning which spinal visceral afferents reach conscious perception are shaped by reports from patients with spinal cord transections, in whom the contribution from spinal as opposed to cranial nerve visceral inputs can be most readily observed. In general, visceral afferents that enter via spinal nerves convey information concerned with temperature as well as nociceptive visceral inputs related to mechanical, chemical, or thermal stimulation (Adelson et al. 1997, Ammons 1992), and the spinal afferents seem to be the principal source for these modalities reaching conscious perception. For example, patients with spinal transection may have a vague sense of vagally mediated fullness after eating a hot meal, but they do not report abdominal warmth or discomfort of acid reflux or colicky pain owing to a distended or obstructed viscus; the absence of these sensations in patients with spinal transection presents a continuous danger to survival (Strauther et al. 1999, Juler & Eltorai 1985). It is possible to show that these sensations do arrive at the spinal cord but are not relayed to the brain, because spinal reflexes due to visceral afferents remain active in patients with spinal cord transections and in fact may be exaggerated. For example, spinal patients often become aware of an overdistended bladder when they experience episodes of diffuse sympathetic activation, including sweating and hypertension (Silver 2000, Giannantoni et al. 1998).

PRIMARY PATHWAYS TAKEN BY ASCENDING SPINAL VISCERAL AFFERENTS The primary pathways taken by ascending spinal visceral afferents are controversial. Although most spinal visceral afferents are thought to converge with musculoskeletal and cutaneous afferents and ascend via the spinothalamic and spinoreticular tracts (Foreman 1999, Weiss & Chowdhury 1998), there is some evidence for ascending fibers taking a dorsal column trajectory. A few visceral fibers enter the dorsal columns directly (Knuepfer & Schramm 1985), but most terminate either in lamina I or in the deep layers of the dorsal horn (IV and V) or the intermediate gray matter (layers VII and X), where a few may reach as far as the preganglionic neurons in the intermediolateral column (Kuo et al. 1983; Roppolo et al. 1985; Sugiura et al. 1989, 1993).

Some cells in layer X, around the central canal, send ascending afferents concerned with visceral pain (e.g., colorectal distention) through the dorsal columns (Willis et al. 1999). These neurons are particularly numerous at sacral levels, and their axons ascend along the medial septum of the dorsal columns. In addition, smaller numbers of cells in layer X at thoracic levels project to the dorsal column

nuclei, by sending their axons along the intermediate septum. These afferents synapse in the dorsal column nuclei, and the postsynaptic neurons project to the contralateral ventroposterior thalamic complex. A majority, although not all, ascending afferents concerned with pelvic visceral pain appear to take this pathway; the importance of this route for other visceral afferents is not as clear (Willis et al. 1999).

Neurons from laminae I, IV, and V that respond to visceral stimuli generally also receive nociceptive inputs from cutaneous sensory fields (Foreman 1999). Hence, from the level of the of the first synapse in the spinal cord, the ascending visceral sensory pathways from these laminae converge with and are therefore essentially identical to the classic spinoreticular and spinothalamic tracts.

CONVERGENCE WITH CRANIAL NERVE VISCERAL SENSORY PATHWAYS A key feature of these ascending pathways is that they provide collaterals that converge with the cranial nerve visceral sensory pathways at virtually every level (Mehler et al. 1960, Saper 2000). For example, neurons in laminae I, V, VII, and X innervate the nucleus of the solitary tract (Menetrey & Basbaum 1987; Gamboa-Esteves et al. 2001a,b), and there is also a projection from viscero ceptive neurons in laminae I, V, and VII of the spinal dorsal horn to the ventrolateral medulla (Ammons 1988). Some of these afferents may be responsible for autonomic reflex responses to visceral stimuli, including visceral pain.

As many as 80% of lamina I spinothalamic axons in rats send collaterals to the parabrachial nucleus (Hylden et al. 1989), and recordings in monkeys from spinal dorsal horn neurons that receive visceral sensory input show that many can be antidromically activated from parabrachial nucleus (Foreman 1999). The spinal inputs to the parabrachial nucleus are rather complex, with afferents to different subnuclei arising from distinct laminae and levels of the spinal cord (Cechetto et al. 1985, Feil & Herbert 1995, Bernard et al. 1995, Panneton & Burton 1985). Many of these afferents end in subnuclei that primarily innervate the medulla, hypothalamus, or amygdala and hence for reasons discussed above are not likely to contribute to conscious appreciation of visceral sensation (Chamberlin & Saper 1994, Moga et al. 1990). However, other afferents end in the internal lateral parabrachial subnucleus, which provides a diffuse input to the intralaminar thalamic nuclei and may be involved in arousal responses to visceral stimuli (Cechetto et al. 1985, Feil & Herbert 1995, Fulwiler & Saper 1984, Bourgeais et al. 2001). Modest numbers of spinal afferents also terminate in the external medial nucleus (Feil & Herbert 1995, Bernard et al. 1995) and hence may contribute to conscious appreciation of visceral sensation via the visceral sensory thalamic relay nucleus and cortex.

Smaller numbers of spinal nociceptive neurons in laminae I, IV, V, VII, and X directly innervate the hypothalamus, and a few even reach the amygdala and medial prefrontal cortex (Burstein & Potrebic 1993, Cliffer et al. 1991, Burstein et al. 1996). However, because none of these latter targets specifically innervates the visceral sensory thalamus or cortex, they are not likely to bring visceral sensation to the level of conscious perception.

Within the thalamus the spinothalamic tract provides a medial projection to the intralaminar nuclei, as well as a lateral projection to the ventroposterior thalamic complex. The terminal field for the lateral projection in rats, cats, and monkeys has been characterized as a "shell" area along the ventral and lateral margins of the complex, just lateral to the VPpc (Horie & Yokota 1990, Koyama et al. 1998, Kobayashi 1998; C.B. Saper, unpublished observations). In monkeys this region has been termed the posterior part of the ventromedial nucleus (Craig & Dostrovsky 2001, Blomqvist et al. 2000) and constitutes a calbindin-immunoreactive terminal field. The cortical projection from this region innervates the posterior insular cortex in monkeys, and in humans pain activates a homologous region just caudal to the primary visceral sensory cortex (Casey et al. 1996, 2001; Craig et al. 2000).

Neurons in the shell region in cats respond not only to cutaneous pain but also to visceral sensory stimuli (Horie & Yokota 1990). In humans neuronal responses to cardiovascular stimuli can be recorded in a similar region, and many of these neurons also have cutaneous sensory fields in the parts of the neck and arm associated with referred cardiac pain (Oppenheimer 1998). Thus, the spinal visceral sensory system is maintained as a component of the spinothalamic system all the way from the first synapse in the spinal cord to the thalamus.

SUMMARY In summary, a remarkable feature of the spinal visceral sensory system is its close relationship with the cranial nerve visceral sensory system at every level. At brainstem levels collaterals from the spinal system converge extensively with the cranial nerve sensory system in the nucleus of the solitary tract, ventrolateral medulla, and parabrachial nucleus. At the level of the forebrain the spinal visceral sensory system constitutes a posterolateral continuation of the cranial nerve visceral sensory thalamus and cortex (Saper 2000).

This relationship of pain with visceral sensation may seem surprising. However, pain is at its root a visceral sensory modality: the sensation that arises from mechanical or thermal stress that threatens tissue integrity. The tissue usually tested when examining a patient for pain perception is the cutaneous surface, which has resulted in the conceptualization of a spinothalamic system of cutaneous sensation representing pain and temperature, compared to the dorsal column system representing position sense and fine cutaneous discrimination. Another way to view the dichotomy is that discriminative sensations carried by the dorsal columns arise from a variety of tissues, both superficial and deep (including both skin deformation and joint receptors, for example), that are related to fine discrimination at body surfaces, muscles, and joints. These sensations are externally directed, i.e., they are concerned with exploring the external world and discerning the relationship of the body with external space. Nociceptive sensations, by contrast, are related to mechanical and thermal stresses of both deep and superficial tissues. Because they monitor tissue integrity, these sensations are internally directed, i.e., they are concerned ultimately with the state of the body itself, as opposed to its relationship with the external world. When viewed from this perspective, it is reasonable to describe pain per se as a visceral modality.

HOW ARE DIFFERENT PATTERNS OF AUTONOMIC OUTPUT GENERATED?

Historical Perspective

In addition to noting the marked similarities in facial expression in animals and humans experiencing related emotions, Darwin was aware that patterns of autonomic response also occur during different emotional states. For example, he noted that during rage "the action of the heart is much accelerated, or it may be much disturbed. The face reddens, or it becomes purple . . . or it may turn deadly pale" (Darwin 1873). He also commented upon changes in piloerection and sweating in different emotional states. However, despite the progress that he cited in autonomic physiology owing to the efforts of contemporary physiologists such as Claude Bernard, Darwin did not have adequate methods at the time to pursue this level of analysis.

Walter B. Cannon, the eminent physiology professor at Harvard Medical School in the first half of the twentieth century, was heavily influenced by Darwin's observations and spent much of his career examining the physiological responses associated with emotions (Cannon 1929). Cannon focused on the secretion of adrenal catecholamines, as assessed by bioassay, and also examined changes in blood sugar (which are associated with adrenal secretion) as measures of sympathetic response during emotional states.

Cannon chose as his model for evaluating sympathoadrenal responses a condition known as "sham rage." Dusser de Barenne (1920) had discovered in the early 1920s that following decortication, a cat could respond to such innocuous stimuli as stroking the fur with a generalized "rage" response, characterized by somatomotor activity including arching of the back, extension of the claws, hissing, and spitting. These animals would also display autonomic responses such as retraction of the nictitating membrane, elevations of blood pressure and heart rate, and increased adrenal secretion similar to those seen in an intact cat that is threatened. However, in the absence of a functioning cerebral cortex, Cannon characterized this state as sham rage (Cannon & Britton 1927, Cannon 1929).

Cannon hypothesized that the diencephalon was the origin of the coordinated emotional response. His student Philip Bard (1928) demonstrated by means of serial transections of the remaining neuraxis in decorticate cats that severing the connections from the diencephalon to the midbrain eliminated the coordinated sham rage response (Figure 3). These experiments provided the basis for placing a pattern generator for both the somatomotor and the autonomic responses associated with this "fight-or-flight" response in the diencephalon.

Perhaps as a consequence of the simple models and measures available to him, Cannon viewed sympathetic response as a generalized reaction to environmental stimuli, which he characterized as "stressful." Interestingly, this unitary conception of stress influenced Selye (1975), who later equated stress with conditions that elevate adrenal corticosteroid levels. Cannon's view of sympathoadrenal response

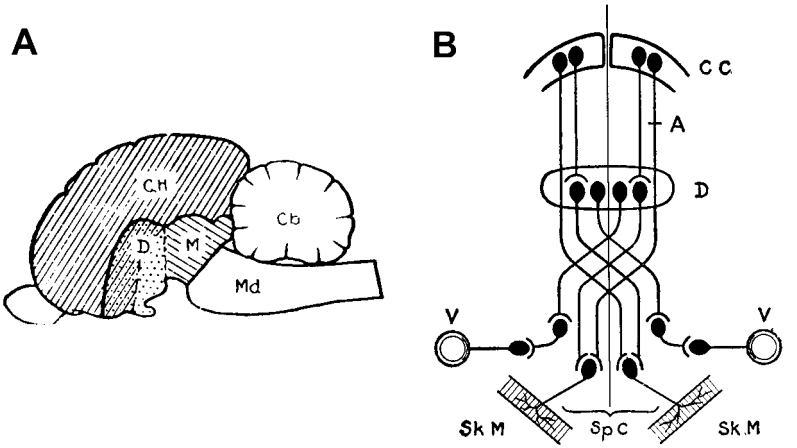

Figure 3 Two drawings from the work of Walter B. Cannon illustrating his ideas on the organization of sympathetic pattern generators. (*A*) The experiments of Cannon & Britton (1927) showed that after removal of the cortical mantle (CM) from a cat, even innocuous stimuli such as stroking the fur would result in fits of "sham rage," including all of the autonomic and somatomotor components of a rage attack. Subsequently, Cannon's student Bard placed transections through the diencephalon (D) and midbrain (M), demonstrating that a fully developed rage attack required the intact diencephalon. Md, medulla; Cb, cerebellum. (*B*) Cannon explained that although the cerebral cortex (CC) projects directly to the spinal cord (SpC) and controls skeletal muscle (SkM) responses, it also projects to the diencephalon, where it inhibits neurons that can produce patterned motor and autonomic responses. V, blood vessel. In the absence of cortical input, these diencephalic pattern generators become hypersensitive to other inputs, so that cutaneous stimuli that would ordinarily produce little if any response can result in a rage attack. From Cannon (1929) with permission.

as a monolithic reaction to a wide range of environmental stressors may have been a natural conclusion, given the limited range of autonomic functions he could measure in unanesthetized animals. However, subsequent work has demonstrated that sympathetic responses are highly patterned and differentiated.

Patterns of Autonomic Response

DEFENSE REACTION For example, the pattern of sympathoadrenal response studied by Cannon has been described as a "defense reaction." It can be elicited by electrical stimulation in the lateral hypothalamus or periaqueductal gray matter, and hence has been studied in great detail in anesthetized animals (Hilton & Spyer 1980, Yardley & Hilton 1987, Arthur et al. 1991, Schadt & Hasser 2001). Although there is an increase in blood pressure and heart rate during the defense reaction, the use of miniature doppler flow probes has demonstrated sympathetically

mediated vasoconstriction and reduction in blood flow to cutaneous beds or to renal or splanchnic vessels but vasodilation and increased flow in vessels carrying blood to the hindlimbs. The hindlimb vasodilation may be due to activation of sympathetic cholinergic vasodilation in cats (i.e., still a product of diffuse sympathetic activation) (Morrison 2001), but in rats, which lack cholinergic vasodilation, the increased blood flow to hindlimb skeletal muscles is due to withdrawal of sympathetic vasoconstriction (Yardley & Hilton 1987). This pattern of response is clearly adaptive (i.e., it is useful to have maximal tissue perfusion available to the hindlimbs to provide energy to fight or flee and to reduce blood flow to other vascular beds in case of injury), but even the fight-or-flight response is not a uniform pattern of sympathetic activation as Cannon imagined.

Other studies of sympathetic nerve responses under a wide range of physiological conditions have demonstrated highly differentiated patterns of activity, consistent with the need for modulation of different organ functions. This topic has recently been reviewed in detail by Morrison (2001) and is therefore discussed only briefly here.

THERMOREGULATION Thermoregulation requires differential control of sudomotor versus cutaneous vasoconstrictor and pilomotor sympathetic outflow, i.e., during heating sweating is required, whereas during cooling it is necessary to reduce cutaneous blood flow and increase heat retention of the fur by piloerection. At the same time, it is necessary to dilate deeper vascular beds to increase heat retention. This patterning has been identified in humans, in which studies of single sympathetic fibers in peripheral nerves can distinguish sudomotor, cutaneous vasoconstrictor, and muscle vasoconstrictor fibers (Janig & McLachlan 1992). In rats recordings have been made from tail artery and brown fat sympathetic afferents (Johnson & Gilbey 1994, Rathner & McAllen 1999, Morrison et al. 1999). Because the tail skin in rats is not covered by fur, it radiates heat efficiently and thus is used as a thermoregulatory organ. Brown adipose tissue contains massive numbers of mitochondria and high levels of uncoupling protein, which allow the mitochondria to burn calories to produce heat rather than synthesize ATP. The level of this thermogenic activity is under sympathetic control via the $\beta 3$ adrenergic receptor (Hamann et al. 1998). Exposure to cooling increases sympathetic discharge to both brown adipose tissue and the tail artery (Morrison 2001). During fever responses owing to immune system activation, body temperature is increased by sympathetic responses similar to those seen during cooling (see Zhang et al. 2000 for review).

METABOLIC CHALLENGE Metabolic challenges also produced highly patterned responses. Hypoglycemia, which can be reproduced by challenge with insulin or 2-deoxyglucose, causes increased sympathetic outflow to the liver and adrenal glands (resulting in increased gluconeogenesis), muscle vascular beds (thus reducing glucose utilization), and sweat glands (thus lowering body temperature and hence metabolic rate) (Niijima 1975, Sacca et al. 1977, Brodows et al. 1975, Medvedev et al. 1988). At the same time there is a decrease in sympathetic

discharge to brown adipose tissue and cutaneous blood vessels (thus promoting cooling) and little effect on cardiac or renal sympathetic outflow.

DEHYDRATION Dehydration is associated with an increase in adrenal, renal, and cardiac sympathetic activation, all of which are necessary to support blood pressure (Gharbi et al. 1999). However, there is a reduction in sweating, thus conserving fluid volume (Grucza et al. 1987, Baker 1989).

SENSORY STIMULI Sensory stimuli produce a wide range of patterned autonomic responses, owing to local spinal reflexes as well as spino-bulbo-spinal pathways (Sato & Schmidt 1973, Sato et al. 1997). As a result, pain can produce different patterns of response depending upon the location of the stimulus. Painful cutaneous stimuli to the body, for example, cause increases in sympathetic outflow to the heart and adrenal glands, as well as causing vasconstriction of cutaneous, renal, and mesenteric beds (Shimoda et al. 1998, Yamaguchi et al. 2001). On the other hand, trigeminal stimuli or deep stimuli, such as muscle pain, may provoke a fall in blood pressure and decreased sympathetic outflow to the heart, visceral, and muscle vascular beds (Keay et al. 2000). Vestibular stimulation also produces a differentiated pattern of sympathetic response, which includes increased blood flow to the hindlimbs but decreased perfusion of the face and forelimbs (Kerman et al. 2000).

Evidence for Organotopic Organization of Neuronal Pools that Generate Patterned Sympathetic Responses

One approach to identifying the origins of the different patterns of autonomic activation in varying physiological states has been to look for topographic organization of the premotor cell groups. Finding an organotopic map, along the lines of the somatic sensory or motor systems, would not necessarily identify the sources of pattern generation, but it would facilitate the search for inputs that result in patterned responses (e.g., finding the motor homunculus in the primary motor cortex did not solve the problem of motor pattern generators, but it did help elucidate the organization of motor control).

RETROGRADE TRACER STUDIES Early experiments were unable to identify a somatotopic patern of organization in the central sympathetic regulatory system. Because sympathetic preganglionic neurons for many target organs tend to be located at specific spinal levels, e.g., pupillary neurons at T1–2, cardiac neurons at T2–5, adrenal neurons at T7–11, tail artery vasoconstrictor neurons at T13–L1, etc., (see Tucker & Saper 1985 for review), it was tempting to speculate that inputs to the sympathetic preganglionic neurons might be topographically ordered. However, regardless of which spinal level was injected, retrograde transport of tracers from different spinal levels of the sympathetic preganglionic column identified the same set of central structures, including the paraventricular nucleus, the retrochiasmatic

area, the lateral hypothalamus, the parabrachial nucleus, the A5 area, the rostral ventrolateral medulla, the medullary raphe, and the nucleus of the solitary tract (NTS) (Tucker & Saper 1985). There was no obvious topography of retrograde labeling within any brain structure that contained labeled presympathetic cells. In double-labeling studies, using two distinguishable retrograde tracers to identify inputs to two spinal levels simultaneously, mixed collections of cells were seen with every pair of injections, with only occasional doubly labeled cells. These observations suggested that there is a fair degree of specificity of projection (i.e., that most presympathetic neurons do not project diffusely to every level of the spinal cord). At the same time, the studies failed to find any organizational principles that could explain how the projections were ordered or any mechanism for generating patterns of response.

VIRAL TRANSNEURONAL TRACER STUDIES The introduction of viral transneuronal tracers has allowed the extension of this strategy to looking for topographic organization of the inputs to sympathetic preganglionic neurons regulating different organ systems. A key issue in considering these findings is the extent to which the virus crosses between neurons only at synapses (transsynaptically) vs. crossing between nearby neurons that may not establish synaptic contacts. When pseudorabies virus of the Bartha strain is applied at peripheral tissues, the retrograde labeling in the sympathetic ganglia corresponds closely to the pattern of conventional retrograde tracers (i.e., the virus does not leak out of ganglion cells and infect neighboring cell bodies that innervate other tissues) (Strack & Loewy 1990). Furthermore, the pattern of transneuronal labeling in the spinal sympathetic preganglionic column is highly characteristic for each peripheral tissue but often different from other tissues served by the same ganglion. For example, the sympathetic preganglionic neurons labeled from the eye are in the T1–T3 segments, but those labeled from the pinna are in the T2–T5 segments (Strack & Loewy 1990). Because the two tissues are targets of independent but intermixed populations of sympathetic neurons in the superior cervical ganglion, the transfer of virus appears to be highly selective (i.e., to the presynaptic preganglionic population for each cell type). Thus, the transneuronal labeling at the level of the sympathetic preganglionic neurons is likely to be transsynaptic.

However, the specificity of the transynaptic transfer after successive waves of transport, replication, and release within the CNS is less well established. Card and colleagues (1993) carefully documented the passage of pseudorabies virus at an ultrastructural level through infected neurons in the dorsal motor vagal nucleus. They found that viral particles were packaged into bilaminar membranous particles in the Golgi apparatus and that the viral particles were preferentially released near the sites of afferent synaptic content. Nonsynaptic transfer was limited by astrocytic processes. Even after a severely infected cell died, local astrocytes and macrophages tended to limit the spread of infective particles. However, such studies are not capable of proving that viral transfer within the CNS occurs only at synapses.

This issue becomes important because injections of pseudorabies virus into a wide variety of tissues produce retrograde labeling in a very similar set of CNS structures. Careful studies of the transneuronal labeling after injections of pseudorabies virus have included, for example, skeletal muscle (Rotto-Percelay et al. 1992), kidney (Schramm et al. 1993, Huang & Weiss 1999), stellate ganglion (Jansen et al. 1995), pancreas (Jansen et al. 1997), tail artery (Smith et al. 1998), and spleen (Cano et al. 2001). These experiments virtually all demonstrated retrograde labeling of neurons in four structures: the C1 adrenergic neurons in the ventrolateral medulla, the medullary raphe nuclei and adjacent ventromedial medulla, the A5 noradrenergic neurons in the ventrolateral pons, and the paraventricular nucleus and adjacent lateral hypothalamus. Furthermore, the pattern was similar regardless of whether the labeling was restricted to parasympathetic or sympathetic afferents to the target tissue. Interestingly, large numbers of cells in those structures were often labeled from quite restricted injections into target tissues, suggesting a substantial amount of divergence of output from individual cells in these structures to multiple tissue types. Another interpretation, however, might be that virus is transferred nonsynaptically in the advanced stages of the infection, when several CNS synapses have been crossed.

Evidence for somatotopic ordering of transneuronal labeling within specific hypothalamic nuclei argues against this interpretation. For example, Strack and colleagues (Strack et al. 1989) demonstrated that injections into different sympathetic ganglia produced slightly different patterns of retrograde labeling in the paraventricular nucleus of the hypothalamus and that only injections of the stellate ganglion demonstrated retrograde labeling in the lateral hypothalamic area. Sved and coworkers (Sved et al. 2001) also noted some organotopic organization in the paraventricular nucleus, with cells retrogradely labeled from brown fat clustering mainly in the anterior and dorsal parvicellular subnuclei, whereas neurons in the lateral parvicellular subnucleus were most prominently retrogradely labeled from spleen and pineal gland injections. However, within the dorsal and ventral parvicellular subnuclei, no topography was apparent.

An alternative approach to determining whether the projections to the different tissues actually emerge from the same central neurons was provided by the use of two different strains of pseudorabies virus to label simultaneously the inputs to the superior cervical ganglion and adrenal medulla (Jansen et al. 1995). Antibodies were used to distinguish the two viral strains and demonstrated that a large percentage of infected CNS cells, particularly in the brainstem catecholaminergic fields and in the paraventricular nucleus of the hypothalamus, contained both viruses. This overlap could still be interpreted as nonspecific transfer of virus (i.e., the proof of specificity would be in the maintenance of distinct channels of communication rather than the presence of double labeling). However, Loewy and coworkers interpreted the convergence of these different pathways at the same central cells as evidence for "command neurons" in the central autonomic control system, with wide-ranging outputs that could produce patterns of autonomic response in different tissues. They therefore interpreted their findings as providing a possible basis

for Cannon's predictions of a diencephalic pattern generator for sympathetic response in fight-or-flight situations (i.e., single hypothalamic neurons could contact a wide range of sympathetic preganglionic neurons concerned with producing an integrated response involving multiple tissues). However, these studies do not provide insight into how the very different patterns of sympathetic response required by varying physiological conditions may be generated, nor do they pinpoint which neurons are critically involved in generating the fight-or-flight response, which is just one of a large array of hypothalamic response patterns.

Evidence for Functional Organization of Neuronal Pools that Generate Patterned Autonomic Responses

A different perspective on the organization of sympathetic pattern generation has come from recent studies of the functional neuroanatomy of presympathetic neurons at several levels of the central autonomic control system outlined by the viral tracer studies. Evidence now is available for the generation of specific patterned autonomic responses by identified populations of neurons in the ventrolateral medulla, the rostral medullary raphe, the periaqueductal gray matter, and the hypothalamus.

VENTROLATERAL MEDULLA Neurons in the ventrolateral medullary reticular formation are thought to play a key role in producing the pattern of autonomic and endocrine response necessary to maintain adequate arterial perfusion of the body's tissues (Morrison 2001). Information from baroreceptors that monitor vascular wall stretch in the aortic arch and the carotid sinus converges in the nucleus of the solitary tract and is conveyed from there to the ventrolateral medulla. A fall in arterial pressure causes reduced excitatory drive from the nucleus of the solitary tract to cardiovagal motor neurons in the compact formation of the nucleus ambiguus, which slows vagal firing, thus increasing heart rate (Beiger & Hopkins 1987, Ross et al. 1985). There is also reduced excitation of inhibitory interneurons in the caudal part of the ventrolateral medulla that project to a population of neurons in the rostral ventrolateral medulla that regulate vasoconstrictor sympathetic tone. The disinhibition of these rostral ventrolateral medullary neurons increases their excitation of vasoconstrictor sympathetic preganglionic neurons, resulting in elevated arterial blood pressure (Elliott et al. 1985). Other neurons in the caudal ventrolateral medulla project to the forebrain, where they regulate release of vasopressin. A fall in baroreceptor input results in the release of vasopressin, thus increasing fluid retention and causing vasoconstriction (Blessing & Willoughby 1985). The net effect of these three limbs of the baroreceptor response is to increase cardiac output, blood pressure, and heart rate in the short term and to increase blood volume in the longer term. This pattern of response appears to be intrinsic to the connections of the baroresponsive neurons of the ventrolateral medulla.

There is some evidence for topographic ordering of the sympathetic vasoconstrictor responses elicited from the rostral ventrolateral medulla in cats (see

Morrison 2001). Interestingly, the topographic arrangement is more along the lines of functional groupings than body map. Hence, neurons controlling vasocontrictor tone to muscles were more caudolateral, those regulating cutaneous vasoconstriction were more medial, and those involved with increasing sympathetic tone to renal, cardiac, and splanchnic beds were rostromedial. Other classes of sympathetic response such as pupillomotor responses, cutaneous vasoconstriction, and brown fat activation apparently were not represented, lending further support to the functional specificity of this region.

ROSTRAL MEDULLARY RAPHE Recent evidence has identified a different patterned sympathetic response generated by the rostral part of the raphe pallidus formation in the rostral ventromedial medulla. Neurons in this parapyramidal region (between the pyramidal tracts at the level of the caudal part of the facial nucleus) show Fos expression and increased firing rates in response to external cooling (Morrison et al. 1999, Rathner et al. 2001). Injection of GABA agonists into the parapyramidal region inhibits cooling-induced sympathetic outflow to brown adipose tissue (Morrison et al. 1999), and injection of excitatory amino acids at the same site causes increased sympathetic outflow to the tail artery in rats. Because sympathetic stimulation of brown adipose tissue results in thermogenesis, and vasoconstriction of the tail artery limits passive heat loss, the rostral medullary raphe region has been considered a pattern generator for thermogenic responses (Morrison 2001). These responses are important not only for allowing small animals to survive in a harsh climate but also are involved in energy balance and metabolism, as thermogenesis is metabolically expensive (Lowell & Flier 1997).

PERIAQUEDUCTAL GRAY MATTER Stimulation in discrete regions of the periaqueductal gray matter may produce quite distinct and highly stereotyped patterns of both somatic and autonomic response in cats (Zhang et al. 1990, Bandler & Shipley 1994). For example, excitatory amino acid stimulation in the ventrolateral periaqueductal gray matter caused motor quiescence and a fall in blood pressure, whereas stimulation in the lateral periaqueductal region produced a flight reaction with an accompanying increase in blood pressure. The fall in blood pressure with stimulation of the rostral part of the ventrolateral column was associated with a fall in heart rate as well as a reduction in vasoconstrictor tone to the hindlimbs, but not the kidneys; stimulation of the caudal part of the ventrolateral column resulted in bradycardia plus renal, but not hindlimb, vasodilation (Carrive & Bandler 1991). Interestingly, there was a topographically ordered projection from these sites to the ventrolateral medulla, with the rostral part of the ventrolateral periaqueductal gray matter projecting to the caudal part of the rostral ventrolateral medulla, which controls blood flow to muscles, and the caudal part of the ventrolateral periaqueductal gray matter sending efferents to the part of the rostral ventrolateral medulla, which regulates blood flow in renal and other visceral vascular beds (Carrive & Bandler 1991, Morrison 2001). This functional organization suggests that higher

levels of the neuraxis may produce progressively more complex and highly integrated response patterns by means of their activation of multiple, more elemental response generators.

HYPOTHALAMUS The hypothalamus contains several distinct sets of neuronal populations that innervate the parasympathetic and sympathetic preganglionic populations: the paraventricular nucleus, the lateral hypothalamic area, and the arcuate nucleus and adjacent retrochiasmatic area (Saper et al. 1976, Swanson & Sawchenko 1983, Cechetto & Saper 1988). Within the paraventricular nucleus, neurons that project to the spinal cord are found in the dorsal, ventral, and lateroposterior parvicellular subnuclei. The dominant neurotransmitters appear to be oxytocin and vasopressin (Cechetto & Saper 1988, Hallbeck & Blomqvist 1999, Hallbeck et al. 2001), although many neurons also contain either dynorphin or enkephalin, and many of these same cells may employ excitatory neurotransmitters as well. In the lateral hypothalamic area, neurons that project to the spinal cord are found at levels roughly coextensive with the ventromedial nucleus. They are most dense in the perifornical region but spill over medially into the lateral edge of the dorsomedial nucleus and dorsally into the zona incerta and reach laterally to the edge of the cerebral peduncle. The lateral hypothalamic presympathetic neurons include cells containing orexin/hypocretin and melanin-concentrating hormone (van den Pol 1999, Bittencourt & Elias 1993) but also encompass many other neurons whose neurotransmitter specificity is not known. The arcuate neurons are also located at the level of the ventromedial nucleus, and they spill out laterally into the region ventral to the ventromedial nucleus (the retrochiasmatic area). They include many neurons that express the pro-opiomelanocortin gene, and hence make α-melanocyte-stimulating hormone (α-MSH) (Cechetto & Saper 1988), as well as cocaine and amphetamine-regulated transcript (CART) (Elias et al. 1998).

Evidence has accumulated within the past few years that specific subsets of neurons within the hypothalamo-spinal system may be engaged by distinct physiological processes. For example, expression of Fos protein is often used to determine whether neurons are engaged by a particular physiological stimulus. Administration of lipopolysaccharide, a bacterial cell wall component, produces a vigorous CNS response that augments the immune response to this stimulus (see Elmquist et al. 1996). The CNS components include fever, secretion of corticosteroids, and sickness behavior (Figure 4). Fever, in turn, is mainly due to engaging a series of sympathetic responses, including increased activity of brown adipose tissue (thus generating heat), shunting of blood flow to deep from cutaneous vascular beds (particularly the tail, which radiates heat in rats), and increased cardiac output and heart rate, as well as increased adrenalin secretion (see Zhang et al. 2000 for review). After lipopolysaccharide treatment, Fos immunoreactive neurons are found in a range of central autonomic structures including the ventrolateral medulla, the nucleus of the solitary tract, the ventromedial preoptic nucleus, and the paraventricular nucleus and lateral hypothalamic area (Elmquist et al. 1996). By combining retrograde tracing from the sympathetic preganglionic column with Fos

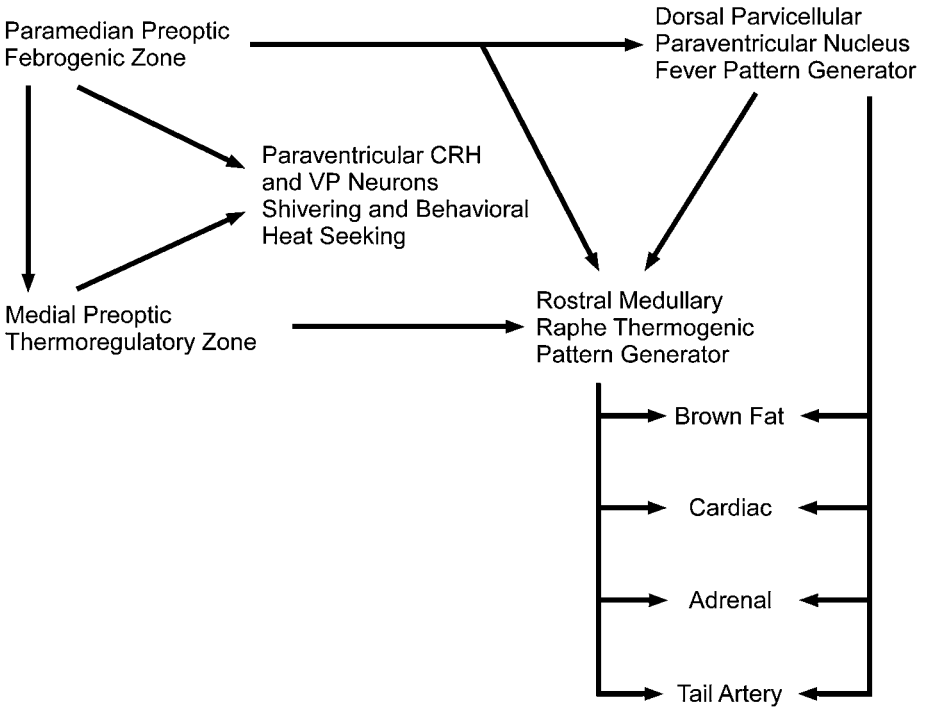

Figure 4 A schematic outline of the possible interactions among pattern generators for thermogenesis, thermoregulation, and fever in rats. Under normal circumstances, the medial preoptic area contains thermosensitive neurons that regulate body temperature around a set point. The medial preoptic area can elicit appropriate endocrine and behavioral patterns of response necessary to increase or decrease body temperature. It also controls a rostral medullary thermogenic pattern generator. This region, in the rostral medullary raphe, controls the sympathetic input to both brown adipose tissue (which results in thermogenesis in small animals) and the tail artery (which regulates heat radiation in rats). Sympathetic cardiac outflow and adrenal outflow may also be elevated during thermogenesis. The paramedian preoptic region, surrounding the anterior tip of the third ventricle, contains neurons that respond to prostaglandins elaborated during an immune stimuli, by producing a fever. Prostaglandin E2 activates the fever response, which includes the thermogenic pathways that are engaged during thermoregulation in the cold. In addition, the paraventricular nucleus is also engaged, including neurons in its medial part that secrete corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone and neurons in the dorsal parvicellular subnucleus, which contains vasopressin (VP) and contributes to thermogenesis by means of their pattern of projections to sympathetic preganglionic neurons, as well as to the rostral medullary raphe.

immunostaining, it has been possible to identify the hypothalamo-spinal neurons that demonstrate Fos activation after lipopolysaccharide administration.

Surprisingly, although Fos-immunoreactive neurons are found throughout the range of the hypothalamo-spinal cell groups, the only population that shows doubly labeled neurons is the dorsal parvicellular part of the paraventricular nucleus (Zhang et al. 2000). Fos-immunoreactive neurons in this one cluster project to every level of the intermediolateral cell column, and few other hypothalamo-spinal neurons are doubly labeled. Interestingly, retrograde transneuronal tracing from the rat tail artery using pseudorabies virus results in intensive labeling in the dorsal parvicellular part of the paraventricular nucleus (Smith et al. 1998). Lesions of the paraventricular nucleus attenuate fever responses to lipopolysaccharide but do not affect circadian cycles of body temperature or the thermoregulatory response to cooling (Horn et al. 1994, Zhang et al. 2000). Thus, the dorsal parvicellular part of the paraventricular nucleus may be a pattern generator for fever responses during immune stimulation, and it may work at least in part by its projections to the spinal cord. However, it may also activate the rostral medullary raphe region that generates sympathetic patterns resulting in thermogenesis. The rostral medullary raphe, on the other hand, may play a broader role in thermogenesis related to cooling or energy metabolism, responses regulated by the medial preoptic area (Chen et al. 1998, Zhang et al. 1997) and in which the dorsal parvicellular paraventricular nucleus may have little role.

Similarly, after intravenous administration of leptin, a hormone made by white fat cells during times of high levels of substrate availability, there is a restricted pattern of Fos expression in the hypothalamus, including neurons in the paraventricular nucleus, lateral hypothalamus, and arcuate/retrochiasmatic groups (Elmquist et al. 1997, Elias et al. 2000). After retrograde labeling from the sympathetic preganglionic column (to identify leptin-activated sources of sympathetic activation), doubly labeled neurons were found in the arcuate/retrochiasmatic area but not in the other sources of hypothalamo-spinal projections, regardless of which spinal levels were injected (Elias et al. 1998). A high percentage of the doubly labeled neurons also contained the neuropeptides a-MSH (a derivative of pro-opiomelanocortin) and CART.

These observations suggest that specific patterns of sympathetic response, associated with discrete stimuli, may differentially activate small populations of neurons within the hypothalamo-autonomic projection system. These neurons, which may be marked by chemical (neurotransmitter phenotype) as well as functional and anatomical specificity, appear as a group to project to the entire length of the sympathetic preganglionic cell column. It is not yet clear whether individual hypothalamic neurons may contact sympathetic preganglionic cells at multiple spinal levels. Double-label retrograde tracer studies suggest that there is relatively little collateralization of axons from individual hypothalamic neurons to different spinal levels (Tucker & Saper 1985), with only 1–2% of cells being doubly labeled after injections of different colored fluorescent tracers at two distinct spinal levels. However, such studies may understate the degree of collateralization, if each axon

contacts a small subset of (e.g., two or three) spinal levels rather than branching diffusely over the entire column. (For example, a single combination of injections at the T2 and T10 levels of the intermediolateral column would identify only about 8% (one twelfth) of the neurons projecting to either the T2 or T10 level that also innervate a second level of the sympathetic preganglionic column). Superficially, it might seem that the command neurons, described by Loewy and colleagues (Jansen et al. 1995), would demand a much higher degree of collateralization. However, the preganglionic neurons projecting to any ganglion or peripheral tissue are generally scattered across at least four to five spinal levels, so that a high degree of double-labeling is possible in their double-virus experiments, even if each neuron innervates only two or three spinal levels.

In this view, it would be possible for a population of neurons, each of which innervates only discrete portions of the preganglionic column, as a whole to undertake the entire range of sympathetic preganglionic projections necessary to produce a patterned response. The pattern of sympathetic (as well as parasympathetic and endocrine) response that is generated would be intrinsic to the specificity of the connections of this set of functionally defined neurons.

Integration Across Multiple Levels of Autonomic Pattern Generators

The evidence reviewed here indicates that neurons at multiple levels of the CNS are capable of generating specific patterns of sympathetic response but that in each case the anatomical organization is along the lines of functionally related cell groups rather than somatotopic maps. The sympathetic response patterns organized at different brainstem levels may in turn be integrated at those sites with simple parasympathetic, endocrine, and behavioral components. For example, neurons in the ventrolateral medulla defend against low blood pressure with a sympathetic response (increased vasoconstrictor tone) that is tightly linked to parasympathetic activity (withdrawal of vagal cardiac inhibition resulting in tachycardia) and endocrine response (secretion of vasopressin). Neurons in the periaqueductal gray matter produce combinations of autonomic and behavioral patterns such as quiet coping (which is linked to withdrawal of vasoconstrictor tone, resulting in hypotension) or flight responses (which are accompanied by hindlimb vasodilation but splanchnic vasoconstriction, to provide maximal blood flow to the hindlimbs).

These specific functional patterns may, in turn, be incorporated into larger-scale response patterns. As in the examples of the fight-or-flight response or the thermoregulatory systems (Figures 4 and 5), the different pattern generators at different levels of the neuraxis are organized in a hierarchical manner that allows individual response patterns to become parts of larger responses. For example, fever responses engage sympathetic pattern generators at both the hypothalamic (paraventricular nucleus) and medullary (rostral medullary raphe) levels. Both of these sites engage the sympathetic preganglionic neurons directly, and the integrity of both sites is necessary to produce elevation of body temperature.

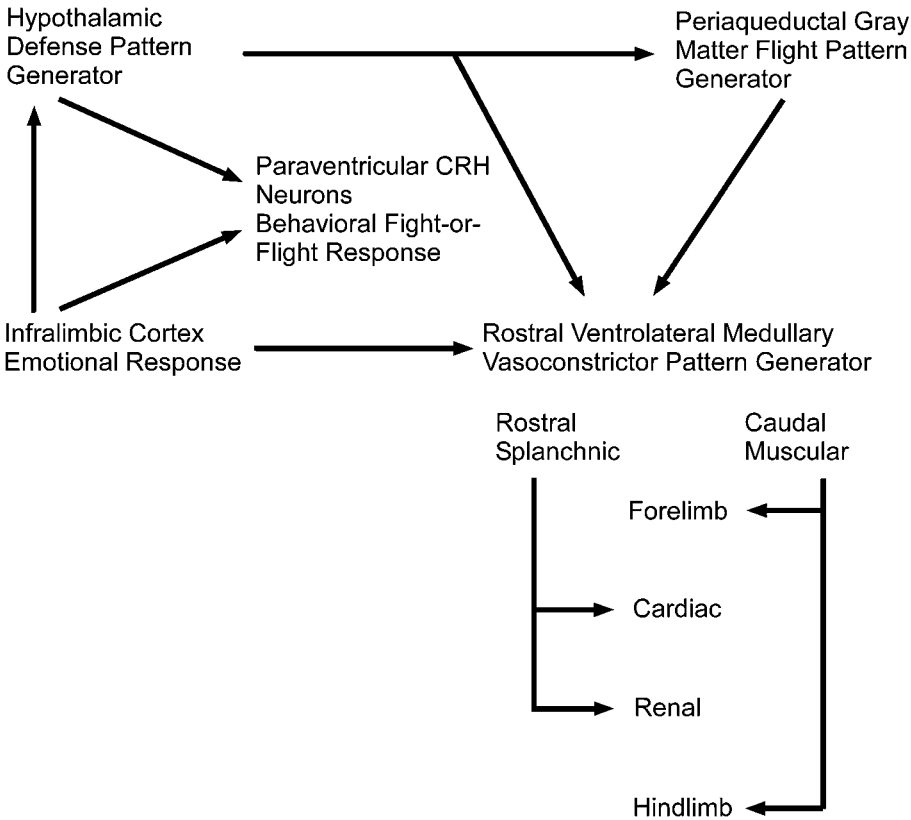

Figure 5 Schematic diagram of possible interactions among pattern generators for vascular responses to emotional stress and fight-or-flight reactions. The infralimbic cortex serves as an emotional motor cortex. It receives inputs from the prelimbic and cingulate areas and insures that the emotional reaction is linked to autonomic and endocrine responses by means of its projections both to the hypothalamus and to the ventrolateral medulla. The hypothalamic pattern generators for fight or flight can activate a coordinated pattern of autonomic, endocrine, and behavioral response associated with either fighting or fleeing. The flight response is due in part to hypothalamic activation of a region in the lateral part of the periaqueductal gray matter, which contains a pattern generator for flight behavior including associated autonomic responses. These responses include vasodilation of arterial supply to the hindlimb muscles but vasoconstriction of blood supply to the splanchnic vascular beds, along with increased cardiac output and adrenal secretion. This pattern of sympathetic response, in turn, is due to activation of distinct rostral and caudal components of the ventrolateral medullary pattern generator that differentially regulates tissue perfusion in splanchnic and muscular beds. CRH, corticotropin-releasing hormone.

At the same time, an individual response pattern may be used for multiple different larger-scale responses. The rostral medullary raphe, for example, is a critical component of thermogenesis in defending body temperature against hypothermia, by increasing heat generation by brown adipose tissue and by shunting blood flow from cutaneous (tail artery) to deep vascular beds. At the same time, these responses are incorporated into fever responses, and brown adipose activity is used to balance energy metabolism (Lowell & Flier 1997, Hamann et al. 1998).

Highly integrated patterns of response, as first noted by Cannon (1929) and Bard (1928), are generally organized at a hypothalamic level. These integrated responses, which maintain energy metabolism, body temperature, and fluid and electrolyte balance, and allow for reproduction and defense against attack, involve autonomic, endocrine, and behavioral components that are played out on a temporal and spatial sequence as a combination of more limited patterned responses, organized at other levels of the basal forebrain, brainstem, and spinal cord. Thus, while the hypothalamus may determine the overall "composition" of the response (and how it will fit with other ongoing needs), subsidiary pattern generators may each produce a series of "chords," or more elementary response patterns, which are in turn composed of "keys" consisting of individual autonomic (and endocrine and motor) actions. When engaged in different combinations by different compositions, these pattern generators can produce the entire range of highly differentiated and complex patterned responses necessary to maintain homeostasis, defend against threat, and ultimately pass on genetic information to the next generation.

SUMMARY The highly interconnected nature of the central autonomic control system has for many years served as an impediment to assigning responsibility for specific autonomic patterns to identified neuronal populations. Although network properties of a system are a convenient explanation for complex responses, they tell us little about how they actually work, and the concept tends to stifle exploration for more parsimonious explanations. Recent data indicate that it is possible to correlate certain discrete patterns of autonomic response with identified neuronal sets, whose integrity may be necessary for that function. The challenge of identifying these pattern generators will lead in turn to determining their connections, neurotransmitters, and physiological activities. Such a prospect offers hope of controlling, or even reversing, maladaptive patterns of autonomic response such as occur during psychogenically elicited cardiac arrhythmias or gastrointestinal disease.

CONCLUSION

Although the two sections of this review may seem disparate in their intent, they both follow from the key issue of the specificity of organization of visceral control, a debate that dates back to the nineteenth century. The autonomic nervous system has often been viewed as lacking the finely regulated control that is inherent in somatic sensory and motor systems. While this view is undoubtedly correct in a temporal sense (i.e., somatomotor responses are generally much faster and contain

rapidly changing temporal patterns that autonomic responses lack), it has obscured the importance of fine discrimination within the visceral system, both at the level of conscious appreciation of visceral sensation, and in the recognition of fine gradations and differentiation of patterns of autonomic motor response.

Recent work makes it clear that the visceral sensory and motor systems contain elements of organization that have long been accepted in the somatomotor systems but have been neglected in central autonomic control. The ascending visceral sensory system, in addition to providing for short- and long-loop reflexes, also contributes a pathway that parallels the classical spinothalamic system, including a visceral sensory thalamic relay nucleus and visceral sensory cortex. This close relationship underscores the similarity in the way the brain handles visceral vs. cutaneous pain, and it suggests that pain itself may be thought of as a visceral modality, as it is concerned with maintenance of tissue integrity, rather than exploration of the external world (except in the sense that it threatens tissue integrity).

The emergence of evidence for pattern generators in the visceral motor system also parallels the somatomotor systems, where such pattern generators have long been accepted and studied. Recent evidence has pinpointed a number of sites that appear to serve this role for discrete autonomic patterns associated with specific physiological responses. The challenge over the next few years will be to test this hypothesis critically and to begin working out the relationships of these pattern generation modules with each other, and with forebrain endocrine and behavioral systems.

The "missing link" in autonomic research has long been the gap between understanding visceral sensory systems and their role in emotion on the one hand, and the ways in which emotional and cognitive responses impact autonomic function on the other. The advances described here narrow this gap and provide some anchor points for future investigators wishing to establish the links.

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CONTENTS