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Functional organization of autonomic neural pathways

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Abbreviations: ATP, adenosine 5'-triphosphate; CGRP, calcitonin gene-related peptide; CN, cranial nerve; SP, substance P; TRP, transient receptor potential (channels)

There is now abundant functional and anatomical evidence that autonomic motor pathways represent a highly organized output of the central nervous system. Simplistic notions of antagonistic all-or-none activation of sympathetic or parasympathetic pathways are clearly wrong. Sympathetic or parasympathetic pathways to specific target tissues generally can be activated tonically or phasically, depending on current physiological requirements. For example, at rest, many sympathetic pathways are tonically active, such as those limiting blood flow to the skin, inhibiting gastrointestinal tract motility and secretion, or allowing continence in the urinary bladder. Phasic parasympathetic activity can be seen in lacrimation, salivation or urination. Activity in autonomic motor pathways can be modulated by diverse sensory inputs, including the visual, auditory and vestibular systems, in addition to various functional populations of visceral afferents. Identifying the central pathways responsible for coordinated autonomic activity has made considerable progress, but much more needs to be done.

"Only One Nervous System" but Three Motor Outputs

In 1921, John Newport Langley[1] began his small but definitive treatise on the "The Autonomic Nervous System" with the following statement: "The autonomic nervous system consists of the nerve cells and nerve fibres, by means of which efferent impulses pass to tissues other than multi-nuclear striated muscle." This definition has served neuroscientists well since then and it is this definition I will use (albeit noting key exceptions) here. As such, autonomic pathways represent one of three general motor outputs of the central nervous system, along with somatic motor pathways controlling skeletal muscles (the "multi-nuclear striated muscle" of Langley) and the neuroendocrine output of the pituitary. A fundamental feature of peripheral autonomic neurons is that they lie within ganglia entirely outside the central nervous system.

Many discussions of autonomic neural function include the organization of visceral afferent pathways, as indeed they should. However, there is no special explanatory power to be gained by including visceral afferents as part of the autonomic "system." In his influential monograph, Blessing[2] has argued that we should not even use the term "autonomic nervous system" at all: indeed, in his words, there is "just one nervous system." Of course, this is true. Nevertheless, this critical observation is commonly overlooked and the "autonomic nervous system" all too often is somehow imbued with a life of its own. More than that, the insightful work of Walter Cannon[3] has been parodied relentlessly, so that autonomic pathways end up divided into two divisions, the sympathetic and parasympathetic, that struggle against each other to maintain homeostatic balance in the face of potentially fatal stress on one hand (sympathetic "flight or fight") or idle inactivity on the other (parasympathetic "rest and digest"). Despite the wide-spread prevalence of some version of this view in the popular and scientific literature alike, it is both over-simplistic and misleading (see also ref. 4).

Since the 1970s, considerable experimental evidence has accrued demonstrating the highly sophisticated ways in which autonomic motor pathways are organized to provide specific control of a diverse range of tissues throughout the body (for extended discussion, see ref. 5). With rare exceptions (see below), autonomic motor activity operates under subconscious control. Nevertheless, autonomic motor activity is routinely coordinated and integrated with other motor activity, either somatic or neuroendocrine or both, in response to some combination of external environmental cues, internal physiological conditions, or centrally generated emotional and cognitive states.[2,4,5]

The high level of target-related specificity in autonomic pathways presents a significant challenge to understanding their development. For example, what drives the phenotypic development of two distinct populations of autonomic neurons innervating the same target tissue? How are divergent phenotypic traits such as neuronal morphology, ion channel expression and neurotransmitter repertoire established in different neurons sharing very much the same local environment? The following discussion aims to provide a framework for considering questions such as these.

Divisions of Autonomic Pathways

At the outset, Langley[1] classified peripheral autonomic pathways into five ultimate divisions, based on a combination of their

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anatomical and functional properties. Langley's pentapartite schema still works well as an overall organizational principle and I will use it here, as I have done elsewhere.[6]

Sympathetic pathways leave the central nervous system via preganglionic neurons located in the intermediolateral columns of the spinal cord from thoracic to mid-lumbar levels. The final sympathetic motor neurons are aggregated into two main sets of ganglia: the paravertebral chains running from upper cervical levels to sacral levels either side of the vertebral columns; and the prevertebral ganglia associated with the major ventral branches of the aorta, including the celiac artery, the superior and inferior mesenteric arteries and the renal arteries. Neurons receiving sympathetic preganglionic inputs also occur in the pelvic plexuses where they are mixed with sacral parasympathetic neurons (more on this below). Sympathetic neurons project to all the organs and most tissues of the body. While most use noradrenaline (norepinephrine) as their primary neurotransmitter, there are well defined populations of non-noradrenergic sympathetic neurons, most notably the cholinergic sudomotor neurons responsible for sweating. Different populations of sympathetic neurons express neuropeptides, including neuropeptide Y, galanin, somatostatin and opioids, that vary with both pathway and species (for a comprehensive list in humans, see ref. 6). Furthermore, many sympathetic neurons use ATP as a fast co-transmitter.[7]

Parasympathetic pathways form three natural subdivisions that, as Langley recognized, have little in common other than that they are not sympathetic. Langley called the first subdivision ocular with preganglionic neurons in the tectum. These are the parasympathetic pathways of the oculomotor nerve that drive accommodation (i.e., close focus of the lens) and pupilloconstriction.[8] Accommodation is mediated by a small set of preganglionic neurons near the conventionally-defined Edinger-Westphal nucleus,[9] with cholinergic final motor neurons in the ciliary ganglion. Uniquely among autonomic motor pathways, accommodation can be controlled easily at will: we can choose where in the visual plane we wish to focus as easily as we can choose any other motor activity. Pupilloconstriction, which is largely under subconscious reflex control,[8,10] is mediated via an oculomotor parasympathetic pathway from the olivary pretectal nucleus that receives input from a recently described population of light-sensitive retinal ganglion cells.[11,12]

The second cranial parasympathetic division has its preganglionic neurons in the brainstem (Langley's bulbar subdivision). These preganglionic neurons project out branchiomeric cranial nerves (CN VII, facial; CN IX, glossopharyngeal; CN X, vagus) to small ganglia located in the head, neck, thorax and upper abdomen. The facial nerve and glossopharyngeal parasympathetic pathways arise from the superior and inferior salivatory nuclei of the pons, respectively, and are relatively simple, primarily with well defined secretomotor (e.g., lacrimation and salivation) or vasodilator functions.[6] In contrast, vagal pathways are complex, with a high degree of functional specificity both between and within target organs.[2,5] Vagal preganglionic neurons project from the dorsal motor nucleus and nuclues ambiguus to small ganglia usually closely associated with their target tissues, such as those in the heart, airways and pancreas as well as to the myenteric plexuses of the gastrointestinal tract.[2,5,6]

The third subdivision of parasympathetic pathways has its preganglionic neurons in the sacral spinal cord. From here they project to ganglia in the pelvic plexuses (such as the hypogastric ganglion and, in females, the paracervical ganglia) as well as numerous small microganglia in or near the walls of the pelvic viscera themselves.[6,13,14]

The final motor neurons in parasympathetic pathways generally use either acetylcholine or nitric oxide or both as their primary transmitters.[5,6] However, they can contain a wide range of co-existing neuropeptides, in some cases expressing four or more unrelated peptides.[15-17] As in sympathetic pathways, some parasympathetic neurons use ATP as a fast co-transmitter.[7]

Enteric neurons form vast interconnecting ganglionic plexuses within the walls of the gastrointestinal tract[18,19] and comprise the final major autonomic division of Langley's classification. The enteric plexuses are considerably more complex than any other component of the peripheral nervous system, employing a wide range of transmitters in a highly organized, pathway-specific manner.[18-21] Most regions of the gastrointestinal tract contain two main sets of interconnected ganglia: the myenteric plexus lying between the longitudinal and circular smooth muscle layers; and the submucosal plexus lying in the connective tissue layer between the mucosal epithelium and the circular smooth muscle layer. The myenteric plexus primarily regulates motility, while the submucosal plexus mainly regulates secretion and local blood flow. The myenteric plexus, in particular, contains not only multiple classes of excitatory and inhibitory motor neurons regulating smooth muscle activity, but also several populations of interneurons, and, probably uniquely for the viscera, primary sensory neurons that do not project to the central nervous system.[18,19] Consequently, the enteric plexuses can detect local mechanical and chemical stimuli and then generate or modulate patterned gastrointestinal activity independently of any central control.

Nevertheless, vagal and sacral preganglionic neurons project to enteric neurons in the myenteric plexuses of the foregut and distal hindgut respectively,[2,18] providing avenues for direct central input to the enteric plexuses. In addition, prevertebral sympathetic neurons inhibit the activity of excitatory motor neurons in the myenteric plexus and secretomotor neurons in the submucosal plexuses.[22] In turn, a population of myenteric neurons, the intestinofugal neurons, project from the intestinal myenteric plexuses back to these same prevertebral sympathetic neurons.[23] Thus, they create a long-range peripheral sympathetic-enteric neural control circuit.

The Basic Organization of Autonomic Ganglia

Sympathetic and parasympathetic final motor neurons lie in ganglia completely outside the central nervous system, and receive excitatory synaptic inputs from preganglionic neurons in the brainstem or spinal cord. In common with somatic final motor neurons, sympathetic and parasympathetic final motor neurons normally do not display any spontaneous activity in the absence of synaptic inputs.[5]

Most sympathetic and parasympathetic final motor neurons receive convergent input from several preganglionic neurons. The number of inputs per neuron varies with pathway and is generally more for sympathetic neurons compared with parasympathetic neurons. Overall, there is a good correlation between the dendritic complexity of the target motor neuron and the number of convergent inputs it receives.[24] However, the total number of synaptic contacts per neuron is low, with less than 2% of the neuronal surface covered with synapses.[25,26]

Although the final motor neurons may receive several preganglionic inputs, in general, one of the inputs is much stronger than the rest. This input is suprathreshold for generating action potential and provides the dominant drive to the target neuron.[5,27] The remaining inputs are usually subthreshold for action potential generation. Their main function seems to be to set the gain of ganglionic transmission.[28] Alternatively they may represent inputs from a secondary central pathway that is effective only at high levels of convergent activity[28] or under pathological conditions where their influence is magnified.[27]

All fast ganglionic transmission is mediated by acetylcholine acting on nicotinic receptors. However, many populations of preganglionic neurons express co-existing neuropeptides, including calcitonin gene-related peptide (CGRP), substance P (SP), or opioid peptides. In mammals, it has been surprisingly difficult to identify a definitive function of these peptides. Some, such as SP, enhance post-ganglionic neuronal excitability, others such as the opioid peptides, reduce preganglionic transmitter release, while others, such as CGRP have relatively little effect on neuronal excitability or ganglionic transmission. In some cases, the receptors expressed by sympathetic neurons for peptides are unconventional in that they do not desensitize, allowing for sustained regulation of excitability.[29,30] Indeed, some slow components of ganglionic transmission are clearly non-cholinergic[5] and may result in long-term enhancement of excitability in final motor neurons, sometimes significantly outlasting the initial synaptic activation.[31]

Neurochemical and Functional Specificity of Autonomic Pathways

Convergent evidence supporting the highly specific connectivity of peripheral autonomic pathways arose from extensive neuroanatomical and functional studies done mostly during the 1980s and 1990s.[5,6] Immunohistochemical analyses combined with pathway tracing techniques reveal that, in many cases, autonomic neurons projecting to particular targets can be identified by their expression of characteristic combinations of neuropeptides that coexist with non-peptide transmitters,[6,24] such as noradrenaline (norepinephrine), acetylcholine, nitric oxide or ATP. This concept has become known as "chemical coding."[32,33] In some cases, the final motor neurons projecting to specific targets can be further distinguished by their morphological features, such as cell body size or the extents of their dendritic field arborization.[24]

If the final autonomic final motor neurons form target-specific populations, as identified by their neurochemical codes, it might be expected that these populations are in turn specifically targeted by different populations of preganglionic neurons. Indeed, there are many examples in which preganglionic neurons, all of which are functionally cholinergic, express different neuropeptides or other neurochemical markers, and then form specific associations with neurochemically defined populations of final motor neurons.[34,35] These observations provide a strong neuroanatomical basis for considering the sympathetic and parasympathetic motor outflows as highly discrete channels projecting to well-defined target tissues.

A large amount of work in experimental animals and in humans, derived mainly from microneurographic recordings of action potential traffic, supports this concept:[5,36] sympathetic and parasympathetic motor outflows do indeed display pathway-specific patterns of activity consistent with the chemically-coded neuroanatomy. Furthermore, there is abundant evidence that target-specific sympathetic and parasympathetic pathways are activated or inhibited with a high degree of precision under diverse physiological and pathophysiological conditions. These observations in turn predict that there must be multiple central pathways feeding into a highly organized set of autonomic motor outputs.[2,4,5] While not surprising, this simple conclusion is often overlooked.

Activity Levels in Autonomic Motor Pathways

Embedded within the popular misconception of autonomic function is the notion that sympathetic activity is primarily phasic (i.e., active only for a short time, such as when faced with a sudden stressor), whereas parasympathetic activity is more on-going and regular. A misleading corollary of this view is that any signs of tonic sympathetic activity must then be a sign of pathology. However, there is abundant evidence that this whole concept is simply wrong, as illustrated by the following examples, summarized in **Table 1**.

At rest, tonic sympathetic activity maintains a regulated level of vasoconstriction in most vascular beds, including those of the skin, skeletal muscles, kidneys and gastrointestinal tract.[2,5,37] Indeed, this on-going sympathetic vasoconstrictor activity is the major factor maintaining central blood pressure. Tonic sympathetic activity through prevertebral ganglia acts as a brake on gastrointestinal motility and secretion.[22] Sustained sympathetic input to the urinary bladder, potentially over several hours, simultaneously relaxes the detrusor smooth muscle and contracts the internal urethral sphincter while the bladder distends and fills with urine. Sympathetic input to the bladder is coordinated with somatic motor neuronal activity which simultaneously contracts the external urethral sphincter.[38,39] In each of these examples, the level of sympathetic activity is set centrally, biased, at least in part, by sensory inputs from relevant peripheral receptors, such as baroreceptors for central blood pressure,[2,5,37,40] cutaneous thermoceptors for skin blood flow,[5,41,42] and stretch receptors in the urinary bladder.[38,43]

In response to specific physiological demands, activity in particular sympathetic outflows can be selectively altered. For example, a sudden loss in blood pressure, such as when standing up quickly, will lead to vasoconstriction in the skeletal muscle

Table 1. Tonic and phasic activity in autonomic pathways

Tonic activity	Phasic Activity
Sympathetic pathways	
Skin vasoconstriction	Sweating (thermal or emotional)
Muscle vasoconstriction	Piloerection
Gut vasoconstriction	Increased cardiac output
Inhibition of gut motility	Mucous saliva production
Inhibition of gut secretions	Pupil dilation
Detrusor relaxation	Sexual activity (ejaculation)
Internal urethral sphincter contraction	
Parasympathetic pathways	
Reduced cardiac output at rest	Accommodation
Pupil constriction	Tear production in crying
Basal tear production	Salivation (during speech, eating)
Basal saliva secretion	Receptive relaxation of stomach
	Stomach emptying
	Pancreatic secretion
	Urination
	Sexual activity (erection)

vasculature, but not, generally, in the cutaneous circulation.[5] Conversely, either cold or a sudden alerting stimulus selectively increases sympathetic vasoconstriction in the skin.[5,44] The duration of the increased sympathetic activity matches the stimulus: increased cutaneous vasoconstriction is likely to be long-lasting in response to a cold environment, but transient in response to a sudden noise. It is obvious in humans that sympathetic thermoregulatory responses are, for the most part, activated selectively.[5,45] Thus, we sweat via cholinergic sympathetic sudomotor neurons when hyperthermic. Alternatively, when hypothermic, we experience intense cutaneous vasoconstriction and, eventually, piloerection, each mediated by separate populations of sympathetic vasoconstrictor and pilomotor neurons.[46,47]

Similarly, parasympathetic activity, even in the same nominal outflow tract can be phasic or tonic. Indeed, at rest, there may be relatively little parasympathetic activity. Vagal pathways to the heart mediate a tonic reduction in heart rate and force of beat (negative chronotropic and inotropic actions, respectively), especially in physically fit individuals. Even so, they may operate concomitantly with sympathetic pathways to the heart.[48] Eating activates a sequence of phasic parasympathetic pathways, including salivation, inhibition of gastric contractility (receptive relaxation), and stimulation of pancreatic secretion of bicarbonate and digestive enzymes once stomach contents enter the duodenum, among many other events.[49-51] Between meals, most of these pathways will be quiescent or show only low levels of activity, such as that regulating the basal secretion of saliva.[52]

Parasympathetic activity in sacral pathways is characteristically phasic in nature and is generally coordinated with somatic motor activity, as seen, for example, in the initiation and maintenance of bladder voiding during micturition.[39] Phasic parasympathetic activity is coordinated with sympathetic activity and somatic motor activity during sexual behavior in both males and females.[39,53] In males, for example, erection is maintained by sacral parasympathetic and somatic pathways, while ejaculation requires sympathetic and somatic activation.[6]

Multiple Afferent Inputs, Coordinated Motor Outputs: "Autonomic Afferents" Confuse the Issue…

As far as we know, in addition to their sympathetic innervation, all thoracic, abdominal and pelvic viscera are innervated by spinal afferent (sensory) neurons with cell bodies located in the dorsal root ganglia. Furthermore, many viscera, such as the heart, airways and upper gastrointestinal tract, receive additional sensory innervation via the vagus.[54] Consequently, it is sometimes argued that these neurons should be included as part of the "autonomic" nervous system (for more discussion, see refs. 2, 4, 5 and 55). Many, but by no means all, of these visceral afferents are peptidergic, most commonly expressing SP and CGRP. Both SP and CGRP can be released from the peripheral endings of visceral afferents via axon reflex mechanisms, usually in response to some kind of noxious stimulus, such as tissue damage or inflammation. Furthermore, both SP and CGRP can affect the behavior of tissues within which the visceral afferent fibers terminate. CGRP, for example, is a potent vasodilator,[56] while SP generally contracts smooth muscle.[57,58] Thus, activation of these peptidergic visceral afferents can simulate "motor" innervation.

The argument for considering visceral afferents as part of the autonomic "system" runs that since they share common target tissues and anatomical pathways with autonomic motor pathways, and since they can have direct effects on the behavior of those same tissues, they should be linked as a functional network. However, there is little compelling evidence to support this concept: visceral afferents can regulate somatic motor activity as much as autonomic pathways, while, conversely, almost any kind of sensory input can alter autonomic motor activity (see also refs. 4, 51 and 55). In this context, perhaps the only "true" autonomic afferents are the intrinsic sensory neurons of the enteric plexuses that project only to other enteric neurons.[23] The following examples illustrate the range of afferent inputs and motor outputs that can generate or influence autonomic activity.

Visceral afferent input to somatic motor response. Activation of visceral afferents can stimulate a range of somatic motor outputs. For example, sudden abdominal pain produces contraction of abdominal wall muscles, generally regarded to be some kind of "protection" reflex;[59] stimulation of low threshold mechanoceptors in the upper airways results in coughing due to strong rapid contractions of the abdominal muscles, among many others;[60-62] stimulation of gastric chemoceptors may result in vomiting, also involving the abdominal musculature.[63] Each of these motor patterns has autonomic motor components (e.g., in the case of vomiting, relaxation of the lower esophageal sphincter, salivation[64]) but they maybe considered secondary to the primary somatic motor response.

"Special sensory" input to autonomic motor response. The most striking example here is visual input to autonomic

pathways projecting back to the eye. Accommodation (focus) and reduction of pupil diameter are both under precise parasympathetic control, using retinal inputs.[12] Elsewhere, auditory input can modulate sympathetic pathways controlling the cutaneous circulation and the heart, whereby a sudden loud noise leads to transient blanching of the skin and increased heart rate.[2,44] Mismatches between visual, vestibular and proprioceptive information can lead to motion sickness, which is accompanied by a range of vagal, enteric and sympathetic responses.[65,66]

Somatic afferent input to autonomic motor response. Sustained muscle activity is associated with increased sympathetic vasoconstrictor drive to skeletal muscle vascular beds. Some of this increased drive is generated centrally as part of an exercise-related motor pattern that preserves central blood pressure in the face of massively increased perfusion of the exercising muscle.[67] In addition, some of the increased sympathetic drive to skeletal muscle vasculature arises from so-called ergoreceptors in the muscles themselves, and probably involves a centrally-modulated spinal reflex.[40,68]

Cutaneous sensory input to autonomic motor response. The skin is not usually considered to be a "visceral" organ, yet sensory input from the skin can have profound effects on autonomic motor activity.[2,5] Most obvious is thermal sensation, mediated by different populations of unmyelinated afferents expressing various TRP channels,[69,70] leading to cutaneous vasoconstriction, eventually accompanied by piloerection, in sustained cold, and vasodilation accompanied by sweating under hyperthermic conditions.[41,47,71,72] Acute cutaneous pain causes sympathetic vasoconstriction not only in the skin but in skeletal muscle vasculature as well.[73] Equally important, low threshold mechanoceptor activation of the external genital skin is a primary input to autonomic pathways required for sexual activity.[53,74]

Coordinated Autonomic and Somatic Motor Activity

From the previous examples, it is clear that there is no single mode of sensory input that activates autonomic pathways. It is also clear that autonomic activity rarely occurs independently of somatic motor activity, or indeed, neuroendocrine regulation. A simple (partial) list emphasizes the point: (1) emotional crying includes characteristic facial musculature behavior, altered breathing patterns, possible vocalization, and parasympathetically-mediated lacrimation; (2) mastication and swallowing involves musculature of the tongue, lips, jaws, pharynx and esophagus together with parasympathetic control of salivation and integrated vagal-enteric control of lower esophageal motility with concomitant changes in local blood flow;[75,76] (3) exercise recruits multiple sympathetic pathways for blood redistribution to working muscle, cutaneous thermoregulation and increased cardiac output, while maintaining sphincter tone in the excretory organs, and contributing to the regulation of energy metabolism;[2,5,67] (4) thermogenesis activates sympathetic pathways to decrease cutaneous blood flow and increase brown fat metabolism, while specialized motor circuits produce thermogenic shivering;[45] (5) sexual activity in males requires parasympathetic and somatic activity for erection, parasympathetic activity for fluid secretion, but sympathetic and somatic activity for ejaculation.[53,77]

Over the last ten years, the central pathways that generate and coordinate autonomic activity have been increasingly well understood, although there is still much to learn.[2] While it remains self-evident that most autonomic pathways are not subject to direct conscious control, it is now apparent that multiple areas within the prefrontal cortex, anterior cingulate and insula cortex, as well as the amygdala, feed into autonomic control centers of the hypothalamus and brainstem.[4,55,78,79] Indeed, reciprocal connections from the brainstem and hypothalamus into these cortical areas almost certainly contribute significantly to the level of well-being we experience at any particular time. Ultimately, how well we feel depends to a large degree on how effectively our autonomic motor pathways have responded to whatever it is that is perturbing our external or internal environment.

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No potential conflicts of interest were disclosed.

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