CHAPTER 25

Specificity in the organization of the autonomic nervous system: a basis for precise neural regulation of homeostatic and protective body functions

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Introduction

Regulations of cardiovascular system, body temperature, energy balance (gastrointestinal tract), evacuative organs, sexual organs and some other special body functions during different behaviors of the organism require precisely working autonomic nervous systems. These regulations and their coordination with the different motor behaviors are represented in the brain, notably spinal cord, brain stem and hypothalamus. The brain contains ‘sensorimotor programs’ for these coordinated regulations and sends efferent commands to the peripheral target tissues through the autonomic and endocrine routes. There is considerable overlap within the brain, not only between the neuron ensembles which are involved with the outputs of autonomic and endocrine signals, but also with the somatomotor system. This overlap is essential for the coordination of behavior and regulation of body functions during a continuously changing environment.

The role of the autonomic nervous system in these integrative programs for maintaining the body’s internal environment is primarily to distribute specific signals to the various target organs. In order to achieve the overall coordination, the signals need to be precisely patterned to implement reactions in each target tissue or organ. There is always interaction between the multiple afferent signals in determining the autonomic outflows, and between the autonomic and endocrine systems in modifying function in the periphery. Some of the autonomic signals pass continuously to the periphery in the resting state, others are recruited during particular body behaviors.

The precision and biological importance of the control of peripheral target organs by the autonomic nervous system is normally taken for granted, but the mechanisms by which it comes about are not generally appreciated. Both of these aspects become quite obvious, however, when the autonomic nervous system fails to function. This may occur during severe infectious diseases, when the peripheral (efferent) autonomic neurons are damaged (e.g. as a consequence of a metabolic disease such as long-term diabetes mellitus), when certain types of peripheral autonomic neurons are damaged (e.g. Hirschsprung’s disease) when the spinal cord is traumatically lesioned (leading to interruption of the connections from supraspinal centers to a large part of the autonomic outflow), or quite commonly in old age.

Autonomic regulation of all the different body functions requires the existence of anatomically
and functionally specific neuronal pathways in the periphery and a specific organization in the central nervous system. Otherwise it would not be possible to have the precision and flexibility of control and the rapid adjustments during diverse behaviors. This implies that the various autonomic systems must be centrally integrated and have multiple but distinct peripheral pathways. These pathways are defined according to the function they effect in the target cells they innervate. From this point of view, it is clear that the autonomic nervous system is the major efferent component of the peripheral nervous system. In its diversity of function and size, it by far outweighs the somatic efferent pathways. Finally, neurons in the autonomic pathways transmit centrally generated patterns of signals to their target cells via neuroeffector junctions.

Here we will discuss the neuronal basis for the precise autonomic control of the peripheral target organs. In the first part we will summarize our ideas of how autonomic neurons in the periphery and in the central nervous system are organized and how these neurons integrate and transmit centrally derived signals to their peripheral targets. For details we refer the reader to various reviews published by the authors (Jäning, 1985, 1996b; Jäning and McLachlan, 1987, 1992a, b, 1999; Habler et al., 1994b; Jäning and Häbler, 1995). In the second part we will discuss that the neural regulation of protective functions of the body by the autonomic nervous system at the cellular level (regulation of the immune system) and at the systemic/behavioral level (during defensive behaviors and expression of emotions) requires precisely working autonomic systems. In this sense, it will finally be argued that Cannon’s concept about functioning of the sympathetic nervous system is not correct and must be changed.

**Functional organization of autonomic (sympathetic and parasympathetic) pathways**

Langley (1921) originally proposed the generic term ‘autonomic nervous system’ to describe the innervation of virtually all tissues and organs except striated muscle fibers. Langley’s division of the autonomic nervous system into the sympathetic, parasympathetic and enteric nervous systems is now universally applied. The definition of the sympathetic and parasympathetic nervous systems is primarily anatomical (the craniosacral or parasympathetic system; the thoracolumbar system or sympathetic system). The enteric nervous system is intrinsic to the wall of the gastrointestinal tract and consists of interconnecting plexuses along its length (Furness and Costa, 1987).

In the definition of the terms sympathetic and parasympathetic, afferent neurons are not included. About 85% of the axons in the vagus nerves and up to 50% of those in the splanchnic nerves (greater, lesser, least, lumbar and pelvic) are afferent and are called spinal or vagal visceral afferents. They come from sensory receptors in the internal organs and have their cell bodies in the ganglia of the IXth and Xth nerves and in the dorsal root ganglia of the spinal segments corresponding to the autonomic outflow. Sometimes thoracolumbar and sacral afferents are labeled ‘sympathetic’ or ‘parasympathetic’; but this nomenclature is misleading. This somewhat strict separation does not preclude that visceral afferents are important in most distinct autonomic reflexes and regulations (Ritter et al., 1992; Jäning and Koltzenburg, 1993; Cervero, 1994; Jäning, 1996a).

The sympathetic and parasympathetic systems each consist of two populations of neurons in series which are connected synaptically. The cell bodies of the final sympathetic and parasympathetic neurons are grouped in autonomic ganglia. Their axons are unmyelinated and project from these ganglia to the target organs. These neurons are called ganglion cells or postganglionic neurons. The cell bodies of the preganglionic neurons lie in the spinal cord and brain stem. They send axons from the CNS into the ganglia and form synapses on the dendrites and somata of the postganglionic neurons. Their axons are myelinated as well as unmyelinated.

**Reflex patterns as functional markers**

Most individual sympathetic pre- and postganglionic neurons are spontaneously active and/or can be activated or inhibited by appropriate physiological stimuli. This has been shown in anesthetized cats (and for some systems in rats) for neurons of the lumbar sympathetic outflow to
skeletal muscles, skin and pelvic viscera (Jänig, 1985, 1996b; Jänig and McLachlan, 1987; Jänig et al., 1991; Hábler et al., 1993, 1994a, 1999) and for neurons of the thoracic sympathetic outflow to the head and neck (Boczek-Funcke et al., 1992), as well as in unanesthetized humans for the sympathetic outflow to skeletal muscles and skin (Wallin and Fagius, 1988; Wallin, 1999). The reflexes observed correspond to the effector responses which are induced by changes in activity in these neurons. The reflex patterns elicited by stimulation of various afferent input systems are characteristic for each functional sympathetic pathway and therefore represent physiological ‘fingerprints’ for each pathway. Some major classes of sympathetic neurons are characterized as follows:

- Reflex patterns in muscle and visceral vasoconstrictor neurons consist of inhibition by arterial baroreceptors, but excitation by arterial chemoreceptors, cutaneous nociceptors and spinal visceral nociceptors (Fig. 1A).
- Most cutaneous vasoconstrictor neurons are inhibited by stimulation of cutaneous nociceptors of the distal extremities, spinal visceral afferents, arterial chemoreceptors and central warm-sensitive neurons in the spinal cord and hypothalamus (Fig. 1B).
- Sudomotor neurons are activated by stimulation of Pacinian corpuscles in skin and by some other afferent stimuli.
- Motility-regulating neurons innervating pelvic organs are excited or inhibited by stimulation of sacral afferents from the urinary bladder, hindgut or anal canal, but are not affected by arterial baroreceptor activation. Functionally different types of motility-regulating neurons can be discriminated by way of their reflex pattern.

So far 12 different functional groups of postganglionic and preganglionic sympathetic neurons have been identified. The same types of reflex patterns have been observed in both preganglionic as well as postganglionic neurons. The neurons in eight of these pathways (e.g. the vasoconstrictor pathways) have ongoing activity whereas in four pathways (e.g. the pilomotor and vasodilator pathways) the neurons are normally silent. It is likely that other target cells are innervated by other functionally distinct groups of sympathetic neurons which have not been studied so far. These sympathetic neurons innervate, for example, the kidney (blood vessels, juxtaglomerular cells), the spleen (immune tissue), the heart, the fat tissue, etc. To emphasize, most of the data have been obtained under standardized experimental conditions in anesthetized cats. In humans this type of standardized experimentation is not possible. Furthermore, no direct recording from autonomic preganglionic neurons and from autonomic neurons innervating viscera and head can be made. However, using microneurographic recordings from bundles with few or single postganglionic axons in human skin and muscle nerves it has clearly been shown that muscle vasoconstrictor, cutaneous vasoconstrictor and sudomotor neurons have distinct reflex patterns (Wallin and Fagius, 1988; Wallin, 1999) and that there is also evidence for the existence of sympathetic vasodilator neurons supplying skin and skeletal muscle in humans.

Relatively few systematic studies have been made on the functional properties of parasympathetic pre- and postganglionic neurons. However, there are good reasons to assume that the principle of organization into functionally discrete pathways is the same as in the sympathetic nervous system, the only difference being that some targets of the sympathetic system are widely distributed throughout the body (e.g. blood vessels, sweat glands, erector pili muscles, fat tissue) whereas the targets of most parasympathetic pathways are more restricted (Jänig and McLachlan, 1992a, b).

**Autonomic ganglia**

A major function of the peripheral ganglia is to distribute the centrally integrated signals by connecting each preganglionic axon with several postganglionic neurons. The extent of divergence varies significantly, the ratio of pre- to postganglionic axons being, in pathways such as in the ciliary ganglion to the iris and ciliary body, as low as 1:4 and in others, such as in the superior cervical ganglion with many vasoconstrictor neurons, as high as 1:150. However it is clear that limited divergence and much divergence, respec-
Fig. 1. Responses of muscle (A) and cutaneous (B) vasoconstrictor-type neurons to stimulation of cutaneous nociceptors, arterial baroreceptors and arterial chemoreceptors. Recordings from single thoracic preganglionic neurons projecting in the cervical sympathetic trunk of the anesthetized cat. A1-B1. Responses to mechanical noxious stimulation of the ear. Note excitation in A and inhibition in B. A2-B2. Changes of the activity with respect to phasic stimulation of arterial baroreceptors by the pulsatile blood pressure ('cardiac rhythmicity', 500 sweeps superimposed). Note strong cardiac rhythmicity in A and weak rhythmicity in B. A3-B3. Responses to stimulation of arterial chemoreceptors by retrograde bolus injection of 0.2 ml CO2-enriched Ringer solution into the lingual artery. Note excitation in A and inhibition in B. Upper trace in A1-B1 blood pressure (BP); third trace in A3-B3 excitation of chemoreceptor afferents in the carotid sinus nerve (CSN). Modified from Boczek-Funcke et al (1992).
tively, are not characteristics of the parasympathetic and sympathetic systems (see Wang et al., 1995). Probably, by analogy with somatic motor units, limited divergence is common in pathways to small targets with discrete functions (e.g. autonomic pathways to the inner muscles of the eye) whereas widespread divergence is a feature of pathways to anatomically extensive effectors that act more or less simultaneously (e.g. vasoconstrictor pathways).

Sympathetic paravertebral ganglia. Within sympathetic paravertebral ganglia (in the sympathetic chains), ganglionic neurons have uniform properties. Each convergent cholinergic preganglionic axon produces an excitatory postsynaptic potential by activating nicotinic receptor channels. The amplitude of the potential varies between inputs, ranging from a few mV to suprathreshold. In most cases, one or a few inputs have, like the endplate potential at the skeletal neuromuscular junction, a high safety factor and always initiates an action potential. Thus the ganglion cell relays the incoming CNS-derived signals of only a few of its preganglionic inputs (McLachlan et al., 1997, 1998). The function of the subthreshold synapses in ganglia is not clear.

Sympathetic prevertebral ganglia. In prevertebral (sympathetic) ganglia postganglionic neurons, at least in experimental animals, do not have uniform properties. Three broad groups differ electrophysiologically (by the K⁺ channels that control excitability), morphologically (by their size and dendritic branching) and neurochemically (by their neuropeptide content) (see Boyd et al., 1996). Two groups, like paravertebral neurons, have suprathreshold synaptic connections with one or two preganglionic axons which determine the firing pattern of these neurons. The mode of synaptic transmission in the third group is different. These neurons receive preganglionic inputs that do not necessarily activate them. However, they also receive many nicotinic inputs from mechanosensitive afferents in the intestine. Summation of synaptic potentials from peripheral and preganglionic inputs is necessary to initiate their discharge. These neurons also depolarize slowly when their inputs are activated at high frequency. The slow responses arise from the release of neuropeptides such as vasoactive intestinal polypeptide (VIP) from the enteric afferent projections or substance P (SP) released from primary afferent neuron collaterals. These prevertebral neurons therefore depend on temporal and spatial integration of incoming signals, much like neurons within the CNS, and may establish peripheral (extra-central) reflexes.

Parasympathetic ganglia. The structure of many parasympathetic ganglion cells, with few dendrites, is simpler than that of sympathetic neurons. The preganglionic input is correspondingly simple, often consisting of a single suprathreshold input. However, some parasympathetic ganglia in the body trunk contain, in addition to postganglionic neurons, neurons which behave as primary afferent and interneurons, i.e. they have the potential for reflex activity independent of the CNS, like the enteric system (intracardiac ganglia (Edwards et al., 1995); see also Mawe, 1995).

The pelvic or hypogastric plexuses contain the neurons that innervate the pelvic organs. Some of these ganglion cells are noradrenergic and are innervated by lumbar sympathetic preganglionic axons, others are cholinergic and receive sacral parasympathetic inputs (Keast, 1995). A proportion of pelvic neurons receive synaptic connections from both hypogastric and pelvic nerves. In bladder ganglia, noradrenaline from stimulated sympathetic postganglionic terminals can inhibit acetylcholine release from preganglionic parasympathetic axons and so depress transmission of sacral signals. Norepinephrine does not affect the parasympathetic neurons directly.

Transmission of signals at the autonomic neuroeffector junctions

In peripheral tissues, the effects of activity in autonomic nerve terminals on autonomic effector cells are complex and may depend on the release of several different compounds and on the presence and distribution of the receptors in the effector membranes for these compounds. Anatomical investigations of neuroeffector junctions at arterioles, veins, pacemaker cells of the heart and longitudinal muscle of the gastrointestinal tract
have demonstrated that varicosities of autonomic nerve fibers which are not surrounded by Schwann's cells form close synaptic contacts with the effector cells (Hirst et al., 1992, 1996). These structures are the morphological substrate for the precise transmission of the centrally generated signals in the postganglionic neurons to the effector cells.

Classically, chemical transmission at these neuroeffector junctions is based on the release of the 'conventional' transmitters, acetylcholine and noradrenaline. However, it is now clear that several chemical substances are often contained within individual autonomic neurons, can be released by action potentials and can have multiple actions on effector tissues (Furness et al., 1989; Morris and Gibbins, 1992). The compounds which may be involved are nitric oxide (NO), ATP and/or a neuropeptide (e.g. vasoactive intestinal peptide [VIP], neuropeptide Y [NPY], galanin [GAL] and others). Immunohistochemistry has revealed the presence of many peptides although only a few of these have been demonstrated to modify function after release from nerve terminals in vivo (e.g. NPY or VIP).

Most sympathetic postganglionic axons release noradrenaline, but sympathetic sudomotor and muscle vasodilator axons are cholinergic. Cholinergic sympathetic muscle vasodilator neurons have been shown to exist in cat, dog and some other mammal species (for review see Uvnäs 1960) yet not in rat, hare and monkey (Bolme et al., 1970). Whether they exist in humans is a controversial issue (Dietz et al., 1994). Most but not all nerve-mediated effects can be antagonized by blockade of adrenoceptors or muscarinic acetylcholine receptors. All parasympathetic neurons are cholinergic, i.e. release acetylcholine on stimulation (Keast, 1995). However, not all effects of stimulating parasympathetic nerves are blocked by muscarinic antagonists. This clearly implies that other transmitters and/or other receptors are involved.

Responses of tissues to nerve-released noradrenaline and acetylcholine usually only follow repetitive activation of many axons. High frequency stimuli, particularly in bursts, may produce effector responses due to the concomitant release of a neuropeptide. Alternatively, when the effects of nerve activity are not blocked completely by an adrenoceptor or muscarinic antagonist at a concentration that entirely abolishes the response to exogenous transmitter, it may not necessarily be the case that a transmitter other than acetylcholine or noradrenaline is involved. Although the effects of exogenously applied substances which have putative transmitter function on cellular functions are known for many tissues, the consequences of activation of postjunctional receptors by neurally-released transmitters have rarely been investigated. When they have, the mechanisms of neuroeffector transmission have been found to be diverse involving a range of cellular events (Jänig and McLachlan, 1999). One important concept that has emerged is that the cellular mechanisms utilized by an endogenously released transmitter are often not the same as when this transmitter substance or its analogue is applied exogenously (Hirst et al., 1996).

**Conclusion**

The experimental studies on the autonomic systems show that (Fig. 2):

1. The reflex patterns observed in each group of sympathetic neurons are the result of integrative processes in spinal cord, brain stem and hypothalamus. With the possible exception of some groups of postganglionic neurons in prevertebral and cardiac ganglia, which have functions other than vasoconstriction, postganglionic neurons do not generate spontaneous activity and do not have reflex activity independent of the synaptic activity from preganglionic neurons which is generated in the neuraxis.

2. Functionally similar preganglionic and postganglionic neurons are synaptically connected in the autonomic ganglia, probably with little or no 'cross-talk' between different peripheral pathways. The centrally generated reflex patterns are faithfully transmitted through the autonomic ganglia without distortion. In prevertebral sympathetic ganglia, the central messages may be modulated by extraspinal
synaptic inputs in pathways being involved in regulation of motility and secretion of the gastrointestinal tract.

The messages in these functional pathways are transmitted to the autonomic effector cells by distinct neuroeffector mechanisms. This has clearly been shown for arterioles and the heart.

This anatomically and physiologically distinct organization of autonomic pathways in the neuraxis and in the periphery is the basis for the precise regulation of body functions during internal and external challenges.

**Autonomic nervous system and protection**

Responses of the organism during pain and stress, whether elicited by external or internal stimuli, are integral components of an adaptive biological system and important for the organism to function in the confines of a dynamic and frequently challenging and dangerous environment (see Brown et al., 1991). These responses consist of autonomic, neuroendocrine and somato-motor responses which include the appropriate sensory perceptions and emotions. They serve to adapt organ functions to the changing behavior and the behavior to changing environments. The integrated responses displayed by the organism are states of the organism which are represented in the brain (brain stem, hypothalamus, limbic system and neocortex). Perception of sensations, experience of emotions, autonomic responses, endocrine responses and somato-motor responses occur principally in parallel and are therefore parallel read-outs of these central representations. They obtain continuous afferent, hormonal and humoral signals monitoring the state of the different tissues (Fig. 3). Here we argue that adaptive and protective reactions of the body during defensive behaviors, adaptation of the immune system and basic emotions require autonomic nervous systems which function in a differentiated way.

**Defense behavior during pain and stress integrated in the mesencephalon**

Reactions of the autonomic (in particular sympathetic) nervous system to peripheral noxious stimuli are expressions of the state of the organism in pain. These reactions are well-orchestrated and the functional specificity resides in the individual responses which are associated with the functionally discrete autonomic pathways. They enable the organism to cope with dangerous situations and are presumably protective and adaptive under normal biological conditions and associated with the activation of the hypothalamo-pituitary adrenal axis and the somato-motor system.
The general pattern of reaction when the organism is in pain and stress can best be exemplified by the different types of defense behavior which are integrated responses consisting of autonomic, endocrine and motor components and sensory (antinociceptive) adjustments. They are triggered by stimuli which challenge the integrity of the organism, such as by noxious stimuli as well as by stimuli and situations which are perceived by the brain as being threatening. These stereotyped defense behaviors are labeled confrontational defense, flight and quiescence and are integrated in the midbrain periaqueductal gray (PAG) (Bandler et al., 1991; Bandler and Shipley, 1994; Bandler and Keay, 1996; Bandler et al., Chapter 24, this volume). Confrontational defense is characterized by hypertension, tachycardia, decrease of blood flow through the limb muscles and viscera and increase of blood flow through the face; it is represented in the rostral part of the lateral PAG. Flight is characterized by hypertension, tachycardia, increase of blood flow through the limb muscles and decrease of blood flow through the face; it is represented in the caudal part of the lateral PAG. Both types of defensive behaviors are accompanied by endogenous non-opioid analgesia. Quiescence (hyporeactivity) is characterized by hypotension, bradycardia and endogenous opioid analgesia; it is represented in the ventrolateral PAG. The systemic cardiovascular changes (and probably other autonomic changes, such as blood flow through skin, piloerection, sweating, change of motility of the gastrointestinal tract, activation of the adrenal medulla, change of pupil size etc.) are generated by activation or inhibition of specific sympathetic and parasympathetic pathways (Fig. 4).

These defensive behaviors represented in the lateral and ventrolateral columns of the PAG are basic neuronal substrates of the body to meet threatening demands from the environment and from the deep body domains. The following points support this idea:

- Neurons in the lateral and ventrolateral PAG columns project to various autonomic centers in
the medulla oblongata which contain the parasympathetic and ‘presympathetic’ neurons, which are involved in regulating different types of autonomic target organs related to the cardiovascular system and gastrointestinal tract, neurons which are involved in control of respiration and neurons which control transmission of nociceptive impulses in the dorsal horn and caudal trigeminal nuclei (see Fields, Chapter 18, this volume).

- Lateral and ventrolateral PAG columns receive afferent inputs from the superficial and deep body domains via spinal cord and trigeminal nuclei. The afferent input to the lateral PAG is somatotopically organized and derives preferentially from the body surface. The afferent input to the ventrolateral PAG derives preferentially from the deep somatic body structures and from viscer.

- Cortical structures and subcortical forebrain structures (e.g. the central nucleus of the amygdala and the medial preoptic area) have powerful projections to the PAG. These afferent projections from the forebrain also have a columnar organization, those from the neocortex probably being spatially more discrete than those from subcortical structures. Furthermore, many projections from subcortical structures are more dense than those from the cortex (An et al., 1998).

The attraction of the idea of Bandler and others is that the PAG contains the neural networks which enable the forebrain structures to coordinate, on a moment-to-moment basis, the integrated somatic, autonomic and antinociceptive mechanisms and other sensory mechanisms during stress and pain. These fast neuronal adjustments are critical for the survival of the organism. Primitive strategies for coping with threatening events seem to be represented in the longitudinal columns of the PAG: noxious events occurring at the body surface and deriving from the environment are associated with active coping strategies (e.g. confrontational defense and flight) whereas noxious events in the deep body domains are associated with passive coping strategies (quiescence). These fast neuronal protective mechanisms are coordinated with hypothalamic mechanisms controlling homeostatic body functions which includes the associated behaviors and neuroendocrine processes (e.g. thermoregula-
tion, regulation of energy balance, regulation of sexual behavior).

The fast neuronally directed protective adjustments of body functions require precisely working sympathetic and parasympathetic systems which are functionally specific as described in the first part of this article.

**Control of the immune system by the sympathetic nervous system**

A large body of evidence from anatomical, physiological, pharmacological and behavioral experiments on animals supports the notion that the sympathetic nervous system can influence the immune system and therefore control protective mechanisms of the body at the cellular level (see Ader et al., 1991; Besedovsky and del Rey 1992, 1995; Hori et al., 1995; Madden and Felten, 1995; Madden et al., 1995). However, the mechanisms of this influence remain largely unsolved (Besedovsky and del Rey, 1992; Ader and Cohen, 1993; Saphier, 1993). This has conceptional and methodical reasons. In view of the functional specificity of the sympathetic pathways, as described in the first part of this article, the key question which has to be addressed is:

Does a specific sympathetic subsystem exist which communicates signals from the brain to the immune system or is this efferent communication a general function of the sympathetic system? In other words, is the immune system supplied by a sympathetic pathway which is distinct from other (classical) sympathetic pathways and mediates only an immunomodulatory effect?

Several observations support the idea that an important channel of efferent communication from the brain to the immune system occurs via the sympathetic nervous system:

- Primary and secondary lymphoid tissues are innervated by noradrenergic sympathetic neurons. Varicosities of the sympathetic terminals can be found in close proximity with T lymphocytes and macrophages (see Ader et al., 1991; Madden et al., 1995; Felten et al. (Chapter 27, this volume) for review) as described for other neuroeffector junctions of the sympathetic nervous system (see above).
- The spleen of the cat is innervated by approximately 12 000 sympathetic postganglionic neurons. This innervation is numerically, relative to the weight of the organs, three times the number of neurons innervating the kidneys (Baron and Jänic, 1988). Functional neurophysiological studies have shown that the sympathetic innervation of the spleen is different from that of the kidney: sympathetic neurons innervating the kidney behave like 'classical' vasoconstrictor neurons (Dorward et al., 1987; Jänic, 1988; Kopp and DiBona, 1992). Many sympathetic neurons innervating the spleen are not under control of the arterial baroreceptors and show distinct (spinal) reflexes to stimulation of afferents from the spleen and the gastrointestinal tract which are different from those in vasoconstrictor neurons (Meckler and Weaver, 1988; Stein and Weaver, 1988). These results suggest that many sympathetic neurons innervating the spleen have a function other than to elicit vasoconstriction or capsular contraction. This function may be related to the immune system.
- Functional studies performed on the spleen of rodents have shown that:
  - Surgical and chemical sympathectomy alters the splenic immune responses (e.g., increase of natural killer cell cytotoxicity, lymphocyte proliferation responses to mitogen stimulation and production of IL-1β).
  - Stimulation of the splenic nerve reduces the splenic immune responses.
  - Lesions or stimulation as well as microinjection of cytokines (IFN-α, IL-1β, IL-2) at distinct hypothalamic sites activate some splenic immune responses. These changes are not any longer present after denervation of the spleen.
  - Activity in the splenic nerve is affected by these central manipulations and changes in neural activity are correlated with the changes of the splenic immune responses. For example, activity in sympathetic neurons to the spleen elicited by interventions at the hypothalamus (in particular the ventromedial nucleus of the hypothalamus) is highly
correlated with suppression of natural killer cell cytotoxicity in the spleen. This suppression is mediated by β-adrenoceptors (Katafuchi et al., 1993; Okamoto et al., 1996). It has been postulated that there is a hypothalamo-sympathetic neural system which controls the immune system (for review see Hori et al., 1995 and references therein).

- The skin is innervated by sympathetic vasoconstrictor, sudomotor, pilomotor and vasodilator neurons. These neurons can functionally be recognized (Jänig, 1985, 1996b). It is however obvious from neurophysiological studies that there are many sympathetic neurons projecting in skin nerves which do not exhibit spontaneous and reflex activity and the function of which is unknown. Is it possible that these postganglionic neurons do not innervate the ‘classical’ sympathetic target organs but are associated with the skin immune system (Edelson and Fink, 1985; Bos et al., 1986; Bos, 1989; Williams and Kupper, 1996).

These observations argue that the lymphoid tissue is innervated by a specific sympathetic system which is functionally distinct from all other sympathetic systems (such as the vasoconstrictor systems etc.) and under control of the hypothalamus.

This hypothesis is testable in vivo using classical neurophysiological recordings of sympathetic neurons innervating spleen, kidney, skin and skeletal muscle. If the electrical signals to the lymphoid tissue are distinct it should be possible to decipher this neural code and to discriminate it from that of other functional types of sympathetic neurons (e.g. vasoconstrictor neurons to skin, skeletal muscle, kidney or spleen). This is exemplified in Table 1 showing the target cells in particular organs which are innervated and possibly controlled by sympathetic neurons and the functions of these neurons. One sympathetic channel in three of these organs projects to the immune tissue (IC, immune cells) and possibly regulates the immune response (IR).

The different types of vasoconstrictor neurons are functionally characterized by their reflex patterns and their discharge pattern with respect to respiration and blood pressure changes which are their functional markers (Jänig, 1985, 1996b; Häbler et al., 1993, 1994a, b). In analogy it should theoretically be possible to characterize the sympathetic neurons innervating lymphoid tissues by using stimuli which are adequate to elicit immune responses (as done by Hori et al., Katafuchi et al. and others; for review and references see Hori et al., 1995). This idea leads to the formulation of two alternative hypotheses:

(1) Neurons of sympathetic pathways which are functionally specific for the immune tissues should be characterized by distinct reflex patterns elicited in these neurons by adequate stimuli which are related to the immune system and therefore related to defense and protection of the organism. If the hypothesis is correct one should find reflex-firing patterns which are characteristic for neurons innervating lymphoid tissues in neurons innervating the spleen and possibly the skin but not in neurons innervating kidney and skeletal muscle. These reflex patterns should be different from those innervating ‘classical’ target organs.

(2) The alternative hypothesis would be that reflex responses in sympathetic neurons which elicit immune responses are found indiscriminately in all sympathetic neurons; these responses would therefore not be functionally specific for the lymphoid tissue. This could mean that more or less all sympathetic pathways have, in

**TABLE 1**

Examples of function-specific sympathetic pathways to different targets within some organs

<table>
<thead>
<tr>
<th>Organ</th>
<th>Target cells</th>
<th>Function</th>
</tr>
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<tbody>
<tr>
<td>Spleen</td>
<td>BV, IC</td>
<td>VC, IR</td>
</tr>
<tr>
<td>Hairy skin</td>
<td>BV, IC</td>
<td>VC (VD?), IR</td>
</tr>
<tr>
<td>Hairless skin</td>
<td>BV, SG, IC</td>
<td>VC (VD?), SM, IR</td>
</tr>
<tr>
<td>Kidney</td>
<td>BV, JGA</td>
<td>VC, renin release</td>
</tr>
<tr>
<td>Skel. muscle</td>
<td>BV, muscle</td>
<td>VC (VD?)</td>
</tr>
</tbody>
</table>

Abbreviations: BV, blood vessel; VC, vasoconstriction; VD, vasodilation; IC, immune cells; IR, immune response; SG, sweat gland; SM, sudomotor response; JGA, juxtaglomerular cells.

addition to their specific target-organ related functions, a general function which is related to defense and protection of the tissues. Also this result could be interesting because it would render an argument which unifies both, Cannon's concept about the general function of the sympathetic nervous system and the concept of the specificity of the sympathetic nervous system.

Basic emotions and autonomic systems

Emotional feelings and the corresponding emotional expressions generated by the somato-motor system are highly integrated components of behavior in humans and animals which are important (externally and internally) for the regulation of the social behavior and for survival (Darwin, 1872, 1998). The most influential theory of emotions which has been first propagated by James (James and Lange, 1920; see Meyers, 1986) at the end of the last and at the beginning of this century states that the experience of the basic emotions is closely associated with the afferent feedback from the deep body domains. According to this theory, the brain triggers bodily changes by the activity in the autonomic systems (innervating cardiovascular target organs and visceral organs) and the conscious experience of these changes, which is generated by the afferent feedback from the visceral organs, leads to the felt emotions. It was assumed that without this afferent feedback the emotional expressions are not accompanied by the internally experienced emotions and that the expressed emotions are so-to-speak 'cold'.

Interestingly, the James-Lange theory of emotions strictly requires that the autonomic efferent pathways are functionally specific. If this were not the case it would barely be possible to generate the distinct basic emotions by functionally distinct patterns of afferent discharge from internal organs. Also Cannon was intrigued by the general idea of this theory that the various emotional states are brought about by afferent signals from these organs and that different emotions are generated by different patterns of activity in afferent neurons from the internal organs. However, Cannon argued that the discharges of sympathetic neurons to various target organs were "...too uniform to offer a satisfactory means of distinguishing emotional states which in man, at least, are subjectively very different. For this reason I am inclined to urge that the visceral changes merely contribute to an emotional complex more or less indefinite, but still pertinent, feelings of disturbance, in organs of which we are not usually conscious". Instead he proposed (Cannon, 1914) that the different emotional states are represented in the brain rather than being peripheral in origin, and are expressed by general changes of activity in sympathetic and parasympathetic neurons.

In its original form the James-Lange theory is not any longer tenable because experimentally it cannot be refuted. It appears to be impossible to design an experimental situation in which the perception of emotions can be investigated without afferent feedback from the body (viscera and deep somatic structures). However, it is generally accepted that the activity in afferents from the deep somatic and visceral body domains shapes the emotions. This afferent activity may be generated by activation of the efferent autonomic systems. From this point of view the James-Lange theory of emotions is of course in principle not at variance with the idea that different basic emotions (or groups of related affected states [see below]) can be characterized by specific autonomic motor patterns (see below).

There is some, although not generally accepted, consensus that there exist universally six basic emotions that are the product of evolution: Anger, fear, disgust, sadness, surprise, happiness. This idea goes back to Charles Darwin's famous book 'The expression of emotions in man and animals' (1872/1998). The term 'basic emotion' should not be taken too literally. Each emotion is, according to Ekman and Panksepp, not a single discrete affective state but a group of related affected states. These states are universal and the result of evolution. They unfold and develop in specific environments. They are represented in central circuits, are not the result of associative learning and cannot completely be changed or modified (for extensive discussion see Ekman and Davidson, 1994). The relatively invariant expression of these basic emotions by the motor system (above all by the facial muscles in
humans and primates) are represented in the central programs of the limbic system and neocortex (notably the amygdaloid complex and the orbitofrontal cortex; see Aggleton, 1993). These central programs are also responsible for the internal experience of the emotions (see Ekman and Davidson, 1994).

Psychologists are traditionally interested in as to whether the basic emotions are also expressed in and can be characterized by distinct autonomic reaction patterns, i.e. patterned activation of autonomic final pathways and their effector organs. Ekman and his coworkers have measured on American actors, American college students, Americans in old age and inhabitant people from West Sumatra, whose cultural background is entirely different from that of the Americans, the subjective experience which was reported by the experimental subjects and the patterns of autonomic responses (changes in heart rate, skin temperature (dependent on cutaneous vasoconstrictor activity), skin conductance (dependent on sudomotor activity)) when subjects followed muscle-by-muscle instructions and coaching to produce facial configurations which resemble the different types of basic emotions during instruction of the expression of the different types of basic emotions (Ekman et al., 1983; Levenson et al., 1990, 1991, 1992; Levenson, 1993). In their study of elderly Americans they also measured autonomic activity in another task in which subjects attempted to relive past emotion experiences. They found that the patterns of autonomic reactions are principally specific for each basic emotion, that this specificity is independent of cultural background, age and profession and that the three parameters (expression of emotions, relived emotions and autonomic patterns) correlate significantly with each other (Fig. 5). All three, the emotional feelings, the somatomotor expression of the emotions and the autonomic expression of the emotions, are parallel (not sequential) 'read-outs' of the same brain centers in which the emotions are represented (Fig. 3).

The authors came to the conclusion that the autonomic patterns which are specific for the different groups of affective states are functionally distinct adaptive autonomic motor responses which have developed during evolution. The authors express their view in stating that "there is an innate affect program for each emotion that once activated

![Graph of autonomic parameters during basic emotions](image)

Fig. 5. Changes of autonomic parameters during the six basic emotions. The facial motor expression of the basic emotions were generated experimentally under visual control. The experimental persons did not know the type of emotion expressed. Changes of heart frequency (dependent on changes in activity of parasympathetic cardiomotor neurons), of skin temperature of the finger tips (dependent on skin blood flow and therefore on activity in cutaneous vasoconstrictor neurons) and of skin conductance (dependent on activity of sweat glands and therefore on activity in sudomotor neurons) were measured simultaneously. The relived emotions experienced by the experimental subjects were reported afterwards. The patterns of the autonomic reactions and the type of relived emotions are highly correlated with each other. Data from 12 experimental subjects. Mean + SEM. Modified from Levenson et al. (1992).
directs for each emotion changes in the organism’s biological state by providing instructions to multiple response systems including facial muscles, skeletal muscles and the autonomic nervous system” (Levenson et al., 1990, 1991; Ekman, 1992). Finally they come to the conclusion that a general arousal model of the sympathetic nervous system, as originally propagated by Cannon (1928, 1939), cannot account for differentiated autonomic responses seen during the basic emotions. This conclusion is fully compatible with the findings that the autonomic, and in particular also sympathetic, pathways are functionally specific (see above).

**Cannon’s concept about the functioning of the sympathetic nervous system cannot work**

Cannon studied the role of the sympathetic nervous system in maintaining homeostasis during various disturbances of the body, such as hemorrhage, hypoglycemia, hypoxia, low and high body temperature, muscle exercise, emotional disturbances etc. On the basis of these studies, he formulated his concept of the fundamental role of the sympathetic nervous system in maintaining homeostasis and his generalizations in the following ways (Cannon, 1939):

The sympathetic nervous system acts promptly and directly to prevent serious changes of the internal environment. It serves to mobilize body energies. It exhibits a widespread discharge through the sympathetic channels and different sympathetic outflows act simultaneously in one direction. It is organized for diffuse effects.

Cannon obviously did not believe that individual sympathetic preganglionic neurons only make functional synaptic contacts with postganglionic neurons of the same function but, rather, that they diverge widely and form contacts with postganglionic neurons of many different functions. Generalized activation of the sympathetic nervous system included activation of the adrenal medulla causing the secretion of adrenaline and noradrenaline into the blood. It was assumed that the circulating adrenaline and noradrenaline reinforce the nervous effects on the target organs and mobilize glucose and free fatty acids from their stores, decrease the time for blood clotting, enhance gas exchange in the lung (by relaxation of the smooth muscles of the airways and subsequent reduction of airway resistance), and decrease fatigue of skeletal muscle etc. These broad functional effects are conceptualized under the term sympathico-adrenal system.

Cannon’s view of the autonomic nervous system was that of a system designed to preserve life during grave physical crises requiring extreme effort. The sympathetic division of the autonomic nervous system was considered to mobilize bodily forces during struggle, the cranial (parasympathetic) division to preserve body energies and the sacral (parasympathetic) division to serve emptying of the hollow organs and reproduction of the species (Cannon, 1914, 1929). Cannon was also aware that the autonomic nervous system is active during lesser disturbances. Cannon’s idea of synchronized sympathetic activity in the ‘Fright, Fight and Flight’ response (Cannon, 1929, 1939) is what we would call today the ‘defense reaction’ (see above); this idea was readily picked up by the scientific and clinical community. The coordinated response was taken to indicate that activity of all parts of the sympathetic system was linked so as to occur in an ‘all-or-none’ fashion without distinction between the different effector organs.

Cannon himself was surprised that the same unified action of the sympathetic nervous system could be useful in circumstances as diverse as hypoglycemia, hypotension, hypothermia etc. He was aware that the unified system apparently produced responses which, although physiologically meaningful in certain states of the body, were useless in others, e.g. sweating in hypoglycemia, rise of blood sugar in asphyxia (Cannon, 1939). But, as described in a review written in German (Cannon, 1928), he contended himself by assuming that the appearance of inappropriate features in the total complex of sympathico-adrenal function is made reasonable in the context of its emergency functions (‘Notfallfunktionen’) if one considers “first, that it is on the whole, a unitary system; second, that it is capable of producing effects in many different organs; and third, that among these
effects are different combinations which are of the utmost utility in correspondingly different conditions of need.” (Cannon, 1939).

This was an amazing way of arguing, given that the precise and distinct control of e.g. body temperature, cerebral perfusion, etc. by the autonomic nervous system was already known at that time. Such control systems could not work if Cannon’s concept about the sympathico-adrenal system were true! Cannon’s argument was the more surprising given the enormous amount of detailed experimental work described by Langley between 1890 and 1920, which supported the principle that each organ and tissue is innervated by distinct sympathetic and parasympathetic pathways (Langley, 1921).

Cannon had an enormous influence on our thinking as far as the functioning of the autonomic nervous system is concerned and this still lasts. However, it is quite clear from the experimental work on the neurobiology and the protective functions of the autonomic, in particular the sympathetic, nervous system that have been discussed in this article that the concept of functioning of the sympathetic nervous system is different from what Cannon has assumed. Its functioning in an ‘all-or-none’ fashion without distinction between the different effector organs is definitively not true for normal physiological conditions of body regulation and may only apply under extreme conditions.

Summary and conclusions

Experimental investigations of the lumbar sympathetic outflow to skin, skeletal muscle and viscera and the thoracic sympathetic outflow to the head and neck have shown that each target organ and tissue is supplied by one or two separate pathways which consists of sets of pre- and postganglionic neurons with distinct patterns of reflex activity. This probably applies to all sympathetic and parasympathetic systems. The specificity of the messages that these peripheral pathways transmit from the central nervous system arises from integration within precisely organized pathways in the neuraxis. The messages in these discrete functional pathways are transmitted to the target tissues often via organized neuroeffector junctions. Modulation in the periphery can occur within each pathway, both in ganglia and at the level of the effector organs.

This organization is the basis not only for precise neural regulations of all homeostatic body functions in which the autonomic nervous system is involved but also the basis of one main component in the regulation of protective body functions: (a) Elementary defense behaviors which are organized in the mesencephalon (confrontational defense, flight, quiescence), (b) regulation of the immune system by the sympathetic nervous system, and (c) adaptive autonomic motor responses during basic emotions require precisely working autonomic, in particular sympathetic, systems. In this sense, the concept of the functioning of the sympathetic nervous system in an “all-or-none” fashion, without distinction between different effector organs, and of simple functional antagonistic organization between sympathetic and parasympathetic nervous system is misleading, inadequate and untenable.

References

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