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Sympathetic nervous system and inflammation: A conceptual view

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ABSTRACT

The peripheral sympathetic nervous system is organized into function-specific pathways that transmit the activity from the central nervous system to its target tissues. The transmission of the impulse activity in the sympathetic ganglia and to the effector tissues is target cell specific and guarantees that the centrally generated command is faithfully transmitted. This is the neurobiological basis of autonomic regulations in which the sympathetic nervous system is involved. Each sympathetic pathway is connected to distinct central circuits in the spinal cord, lower and upper brain stem and hypothalamus. In addition to its conventional functions, the sympathetic nervous system is involved in protection of body tissues against challenges arising from the environment as well as from within the body. This function includes the modulation of inflammation, nociceptors and above all the immune system. Primary and secondary lymphoid organs are innervated by sympathetic postganglionic neurons and processes in the immune tissue are modulated by activity in these sympathetic neurons via adrenoceptors in the membranes of the immune cells (see Bellinger and Lorton, 2014). Are the primary and secondary lymphoid organs innervated by a functionally specific sympathetic pathway that is responsible for the modulation of the functioning of the immune tissue by the brain? Or is this modulation of immune functions a general function of the sympathetic nervous system independent of its specific functions? Which central circuits are involved in the neural regulation of the immune system in the context of neural regulation of body protection? What is the function of the sympatho-adrenal system, involving epinephrine, in the modulation of immune functions?

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1. Introduction

Living organisms continuously receive multiple signals from the environment via their sensory systems and respond by way of their somato-motor systems. Sensory processing and motor actions are entirely under the control of the central nervous system (CNS). On the basis of the central representations of the deep and superficial body domains and the afferent feedback from the body and from the environment, complex motor commands are generated by the brain and implemented using the effector machines as tools, the skeletal muscles, and their controlling somato-motoneurons. This motor activity is only possible when the internal milieu of the body is controlled to keep the tissues and organs (including the brain and skeletal muscles) maintained in an optimal state for their functioning. The control of the internal milieu of the body is also exerted by the brain acting on many peripheral target tissues (smooth muscle cells of various organs, cardiac muscle cells, exocrine glands, endocrine cells, metabolic tissues, primary or secondary immune tissues, etc.). The *efferent signals* from the brain to the periphery of the body by which this control is achieved are *neural* by the autonomic nervous systems and *hormonal* by the neuroendocrine systems. The *afferent signals* from the periphery of the body to the

brain are neural, hormonal (e.g., hormones from the endocrine organs including those in the gastrointestinal tract, cytokines from the immune system, leptin from the adipose tissue) and physicochemical (e.g., blood glucose level and body core temperature).

Regulation of body functions by the autonomic nervous system is based on specific neuronal final autonomic pathways in the periphery and a specific organization of neural circuits connected to these pathways in the CNS. The principle of this organization of the autonomic nervous system and the priority of the brain in autonomic regulation is already visible early in evolution of vertebrates going back up to 500 million years (e.g., of the heart, the gastrointestinal tract, and the evacuative organs; see Holmgren and Olsson, 2011; Jänig, 2013b).

The sympathetic nervous system and neuroendocrine systems have, in addition to their conventional functions, functions that are conceptually best described as regulation of protection of body tissues during challenges arising internally or externally to the body. These systems serve to adapt organ functions to behavior responses in threatening environments. The coordinated responses of the organism, which are represented in the brain (brain stem, hypothalamus, limbic system and neocortex), prepare the organism to generate the appropriate responses to the threatening events. The central representations receive neural afferent, hormonal and humoral signals that monitor continuously the mechanical, thermal, metabolic and chemical states of the tissues (Fig. 1). Control of inflammation and hyperalgesia by the CNS are integral components in this scenario and require sympathetic systems

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SENSATION, AFFECTION, COGNITION

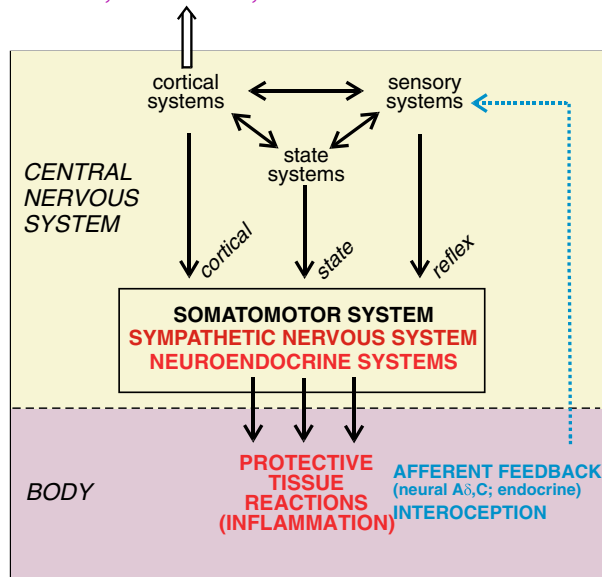


Fig. 1. Functional organization of the nervous system to generate protective behavior. The motor system consists of the somatomotor, the autonomic (visceromotor) and the neuro-endocrine systems and controls behavior. The motor systems are hierarchically organized in the spinal cord, brain stem and hypothalamus and receive three global types of synaptic input: (a) Sensory neural, endocrine and humoral systems signal the mechanical, metabolic, thermal and inflammatory states of the body tissues and the state of the immune system (blue) generating reflex behavior (*reflex*). (b) The cerebral hemispheres are responsible for cortical control of the behavior (*cortical*) based on neural processes related to cognitive and affective–emotional processes. (c) The behavioral state system controls attention, arousal, sleep/wakefulness, and circadian timing (*state*). The three general input systems to the motor systems communicate bidirectionally with each other (upper part of the figure). Integral components of behavior are sensations, affective–motivational processes and cognitive processes which are dependent on cortical activity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Designed after Swanson (2000, 2008).

which function in a differentiated way. An important component of this protective neural system, promoting tissue repair and recuperation, is the bidirectional communication between the brain and the immune system.

Here I will summarize two groups of experimental data that are important to understand the hypothetical mechanisms being involved in the control of inflammation and therefore also the immune system by the brain via the sympathetic nervous system:

1. The autonomic nervous system is organized in the periphery in many functionally and anatomically separate pathways that transmit the centrally generated impulses faithfully to the effector cells. These autonomic pathways are connected to distinct neural circuits in the spinal cord, brain stem and hypothalamus (Fig. 2; Jänig, 2006, 2013a; Jänig and McLachlan, 2013).
2. The sympatho-neural and sympatho-adrenal systems are important in the regulation of protection of the body against injury from outside as well as from inside of the body. Thus they are involved in the regulation of the immune system, inflammation and nociceptor functions, i.e. pain and hyperalgesia. Here I will concentrate on general aspects of neural control of inflammation and of the immune system. Details of this control are presented and discussed in this issue of Autonomic Neuroscience (see particularly Bellinger and Lorton, 2014; Birder, 2014; Cervi et al., 2014; Jänig and Green, 2014; Martelli et al., 2014; McGovern and Mazzone, 2014; McLachlan and Hu, 2014; Schaible and Straub, 2014; Sharkey and Savidge, 2014; Schlereth et al., 2014 in this issue of Autonomic Neuroscience).

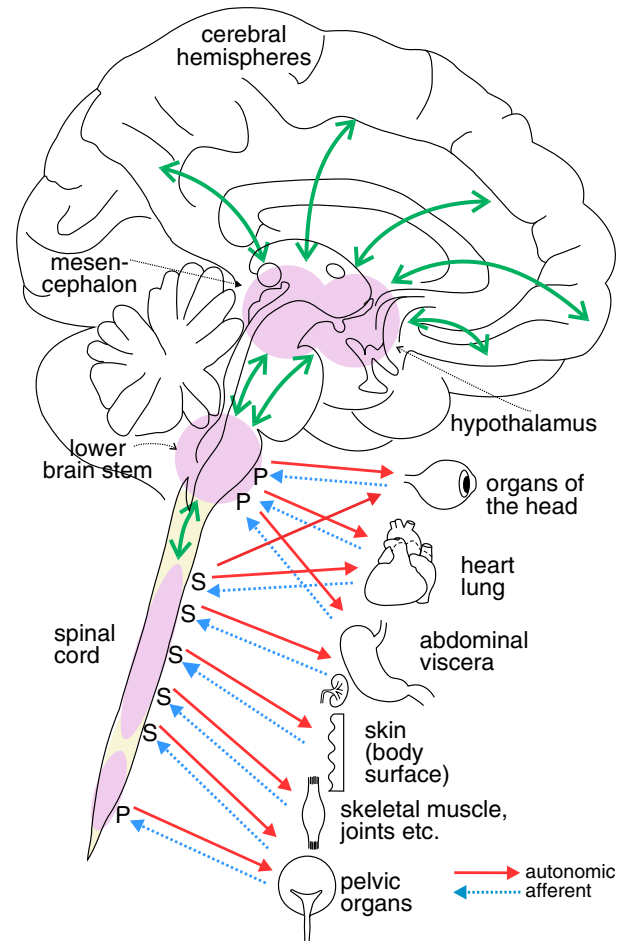


Fig. 2. Reciprocal communication between the brain and body tissues by efferent autonomic pathways and afferent pathways. The global autonomic centers in the spinal cord, lower and upper brain stem and hypothalamus are shaded in violet. These centers consist of the neural circuits that are the bases of the homeostatic autonomic regulation and their co-ordination with the neuroendocrine, the somatomotor and the sensory systems that establish behavior (see Fig. 1). The brain sends efferent commands to the peripheral target tissues through the peripheral autonomic pathways. The afferent pathways consist of groups of afferent neurons with unmyelinated or small diameter myelinated fibers. These afferent neurons monitor the mechanical, thermal, chemical and metabolic states of the body tissues. P, parasympathetic; S, sympathetic. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.) Modified from Jänig (2013b).

Involvement of the sympathetic nervous system in pain and hyperalgesia is discussed elsewhere (Jänig, 2009a, 2009b, 2013b).

2. Principles of organization of the sympathetic nervous system

Some principles of organization of the autonomic nervous system, in particular the sympathetic nervous system, will be described in order to emphasize the neurobiological background of this issue of Autonomic Neuroscience “Autonomic Nervous System and Inflammation”.

2.1. The functional differentiation of the sympathetic nervous system: Reflex patterns as functional markers of peripheral autonomic pathways

The division of the autonomic nervous system into sympathetic, parasympathetic and enteric nervous systems goes back to Langley (1921) and is now universally accepted. The definition of the peripheral sympathetic and parasympathetic nervous systems is primarily anatomical (the thoracolumbar system or sympathetic system; the craniosacral or parasympathetic system). The enteric nervous system is intrinsic to the wall of the gastrointestinal tract and consists of interconnecting

plexuses along its length (Furness, 2006; Jänig, 2006; Jänig and McLachlan, 2013). Primary afferent visceral (spinal and vagal) neurons are normally not labeled autonomic, parasympathetic or sympathetic although they form special reflex circuits with the final autonomic pathways (interrupted blue arrows in Fig. 2; for discussion see Jänig, 2006).

The sympathetic 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*. They have unmyelinated axons and project to the target organs. These neurons are therefore called *ganglion cells* or *postganglionic neurons*. The cell bodies of the *preganglionic* neurons lie in the spinal cord. They send axons from the CNS into the autonomic ganglia and form synapses on the dendrites and cell bodies of the postganglionic neurons. Their axons are myelinated or unmyelinated.

Individual sympathetic pre- and postganglionic neurons exhibit spontaneous activity in vivo or are silent. They can be activated or inhibited reflexly by appropriate physiological stimuli. This has been shown in anesthetized animals (mainly cats, rats) for neurons of the lumbar sympathetic outflow to the skeletal muscle, skin and pelvic viscera and for neurons of the thoracic sympathetic outflow to the head and neck (Jänig, 1985, 2006; Jänig and McLachlan, 1987, 2013). Using microneurographic recordings from bundles with few or single postganglionic axons in human skin or muscle nerves it has clearly been shown that muscle vasoconstrictor, cutaneous vasoconstrictor and sudomotor neurons have distinct reflex patterns. There is also evidence for the existence of sympathetic vasodilator neurons supplying the skin or skeletal muscle in humans. Direct recordings from autonomic preganglionic neurons and from autonomic neurons innervating the viscera and head cannot be made in humans (Jänig and Häbler, 2003; Wallin, 2013). The reflexes observed correspond to the effector responses which are induced by changes in activity of these neurons. The reflex patterns elicited by physiological stimulation of various afferent input systems are characteristic, and therefore represent the physiological “fingerprints”, for each sympathetic pathway.

Several functional groups of postganglionic and preganglionic sympathetic neurons have been identified in the lumbar sympathetic outflow to the skin, skeletal muscle and viscera and in the thoracic sympathetic outflow to the head and neck in anesthetized cats and rats under standardized experimental conditions. The *same types of reflex patterns* have been observed in both preganglionic as well as postganglionic neurons. Most neurons in several of these pathways (e.g., the vasoconstrictor, sudomotor, motility-regulating pathways, and other pathways) have ongoing activity whereas the neurons in other pathways are normally silent (e.g., pilomotor and vasodilator pathways, pathways to sexual organs). It is likely that other target cells are similarly innervated by functionally distinct groups of sympathetic neuron which have not been studied so far. These sympathetic neurons innervate, for example, the kidney (blood vessels, juxtaglomerular cells, tubules), the urogenital tract (e.g., urinary bladder, vas deferens, erectile tissue, and glandular tissue), the hindgut, the spleen (immune tissue, see below), the heart, and the brown adipose tissue (Morrison, 1999, 2001). Finally, the cells of the adrenal medulla that release epinephrine and are involved in glucose homeostasis (and other functions [see Jänig, 2006]) are innervated by a functionally special type of preganglionic neuron. Activity in these preganglionic neurons depends on distinct central circuits (Morrison and Cao, 2000; Verberne and Sartor, 2010).

Several systematic studies have been made on the functional properties of parasympathetic pre- and postganglionic neurons (Jänig, 2006). 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 main 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 the parasympathetic pathways are more restricted (Jänig, 2006; Jänig and McLachlan, 2013).

The conclusions to be drawn from these neurophysiological studies are important for the discussion of the regulation of inflammation and immune system by the sympathetic nervous system (Jänig, 2006; Jänig and McLachlan, 2013):

- (1) The peripheral autonomic (parasympathetic and sympathetic) systems consist of many separate neuronal channels transmitting the central messages to the autonomic target tissues. This conclusion is supported by morphological studies using tracers and by studies of neuropeptides co-localized in the postganglionic and preganglionic neurons with the classical transmitters acetylcholine or norepinephrine (Gibbins, 1995, 2004).
- (2) The distinct reflex patterns generated in autonomic neurons by physiological stimulation of afferents innervating the visceral, skin or deep somatic tissues indicate that each autonomic pathway is connected to specific neural circuits in the spinal cord, brain stem and hypothalamus that are involved in regulation of the activity.
- (3) The organization of the autonomic nervous system, in the periphery and in the CNS, is the basis for the precise regulation of body functions (cardiovascular regulation, thermoregulation, regulation of fluid balance, regulation of evacuative functions [pelvic organs], regulation of energy balance and nutrition [including the gastrointestinal tract], regulation of circadian timing of body functions, regulation of body protection [including the immune defense]).

We have some knowledge about the central circuits involved in cardiovascular regulation and thermoregulation. However, the central circuits, including the spinal ones, are largely unknown for most peripheral final autonomic pathways, and this applies also to the pathway potentially involved in regulation of the immune tissue and therefore inflammation (see Jänig, 2006; Llewellyn-Smith and Verbene, 2011; Mathias and Bannister, 2013; Robertson et al., 2012; see Bellinger and Lorton, 2014). The central circuits connected to the final autonomic pathways will not be discussed further in this article.

2.2. Transmission of signals in peripheral autonomic pathways

What is the evidence that the signals generated in the CNS are faithfully transmitted by the autonomic final pathways to the autonomic target tissues? (Fig. 3).

2.2.1. 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 as low as 1:4 in special pathways to small targets (e.g. in the ciliary ganglion) and 1:200 or more in pathways to extensive effectors (e.g., vasoconstrictor pathways to the skeletal muscle, skin or viscera) (McLachlan, 1995).

Within sympathetic paravertebral ganglia (in the sympathetic chains), ganglionic neurons have uniform properties. Each convergent cholinergic preganglionic axon produces excitatory postsynaptic potentials by activating nicotinic receptor channels. The amplitude of the potentials varies between inputs, ranging from a few millivolts (subthreshold weak synaptic inputs) to 10–40 mV (suprathreshold strong synaptic inputs). In most cases, one or two strong preganglionic synaptic inputs have, like the endplate potential at the skeletal neuromuscular junction, a high safety factor and always initiate an action potential. Thus, the ganglion cell relays the incoming CNS-derived signals in only a few of its preganglionic inputs (McLachlan et al., 1997, 1998; Bratton et al., 2010). The function of the weak preganglionic synaptic inputs generating small subthreshold potentials in paravertebral ganglia remains unclear.

In prevertebral (sympathetic) ganglia two groups of postganglionic neurons, like paravertebral neurons, have suprathreshold (strong)

FINAL AUTONOMIC MOTOR PATHWAYS

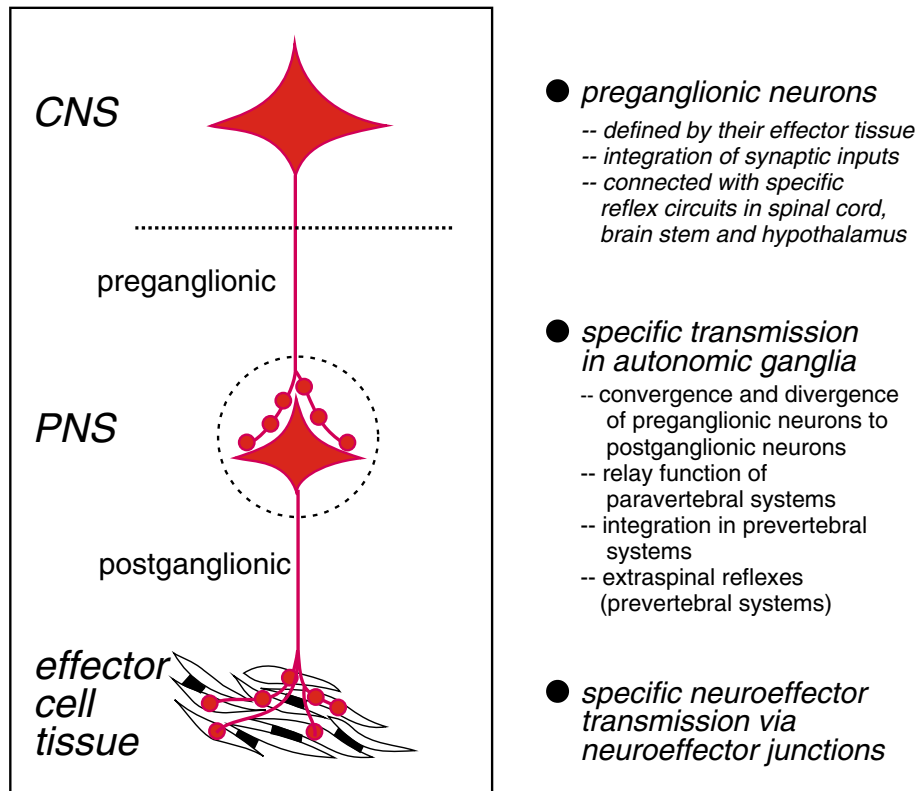


Fig. 3. Organization of the spinal autonomic systems in anatomically and functionally separate final autonomic pathways connecting the spinal cord with the autonomic effector tissues (vascular and non-vascular smooth muscle cells, secretory endothelia, cardiac muscle, metabolic tissues, etc.). Preganglionic neurons in the intermediate zones of the thoraco-lumbar and sacral spinal cord integrate the signals from the supraspinal autonomic premotor neurons, the spinal primary afferent neurons and the (segmental and propriospinal) interneurons. Parasympathetic systems in the brain stem have a similar organization. The preganglionic neurons project to the peripheral ganglia and converge and diverge on the postganglionic neurons. The main characteristics of signal transmission in the autonomic final pathways are listed on the right.

synaptic connections with one or two preganglionic axons which determine the firing pattern of these neurons. These neurons have vasoconstrictor or secretomotor functions (e.g., in the gastrointestinal tract). Postganglionic neurons of the third group receive only weak preganglionic synaptic inputs and also many cholinergic nicotinic inputs from intestinofugal neurons of the enteric nervous system which can be activated by mechanical stimulation of the gastrointestinal tract. Summation of synaptic potentials from peripheral and preganglionic neurons seems to be necessary to initiate their discharge. These postganglionic neurons also receive synaptic input from collaterals of visceral primary afferent neurons (that have their cell bodies in the dorsal root ganglia) and depolarize slowly when these inputs are activated. The slow responses are generated by the neuropeptide substance P released from the afferent collaterals. These prevertebral neurons therefore depend on temporal and spatial integration of incoming synaptic signals and may establish peripheral (extraspinal) reflexes. They are involved in regulating motility (e.g., of the gastrointestinal tract).

The preganglionic input to parasympathetic ganglion cells is correspondingly simple, often consisting of a single suprathreshold input. Some parasympathetic ganglia in the body trunk contain, in addition to postganglionic neurons, neurons which behave as local primary afferent neurons, interneurons or autonomic motoneurons without preganglionic synaptic input. Thus these ganglia have the potential for reflex activity independent of the CNS, like the enteric nervous system (e.g., intracardiac parasympathetic ganglia, Edwards et al., 1995; Jänig, 2011).

2.2.2. Transmission of signals at the autonomic neuroeffector junctions

Anatomical investigations of neuroeffector junctions at arterioles, veins, pacemaker cells of the heart, iris dilator myoepithelium, iris dilator melanophores, longitudinal muscle of the gastrointestinal tract or some other effector cells, using electron microscopical serial sections, have demonstrated that varicosities of autonomic nerve fibers which are not surrounded by Schwann cells form close neuroeffector junctions with the effector cells. At the junctions the basal lamina covering the effector cell syncytium and the varicosities fuse. The neuroeffector gap is 20 to 80 nm wide and covers about 0.1 to 1% of the effector cell surface. Small vesicles containing the transmitter(s) accumulate at the junctional cleft. These structures are the morphological substrate for the precise transmission of the centrally generated signals in the postganglionic neurons to excitable effector cells (Hirst et al., 1992, 1996; see Jänig, 2006).

Non-excitable effector cells, such as epithelial cells, endothelial cells or immune cells are also innervated by autonomic nerves. Whether the varicosities of the terminals of the autonomic axons form close neuroeffector junctions, as they do with smooth muscle cells and muscle cells of the heart, is unknown for most endothelial and epithelial cell syncytia. For immune cells close neuroeffector junctions have been shown to exist (Felten et al., 1987). Quantitative data about the frequencies of these close junctions are not available. However, it is not far-fetched to assume that the transmitter released by the autonomic postganglionic neurons innervating the non-excitable effector cells reaches these cells at high concentration which may be in the 0.1 mM range leading to specific effector responses.

Classically, chemical transmission at these neuroeffector junctions is based on the release of one of the “conventional” transmitters, acetylcholine or norepinephrine. However, several chemical substances, 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 potentially involved are nitric oxide (NO), ATP 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 norepinephrine, but sympathetic sudomotor and muscle vasodilator axons (in some species) are cholinergic. Most but not all nerve-mediated effects can be antagonized by blockade of adrenoceptors or muscarinic acetylcholine receptors. All postganglionic parasympathetic neurons are cholinergic, i.e. release acetylcholine on excitation (Keast et al., 1995). However, not all effects of stimulating parasympathetic nerves are blocked by muscarinic antagonists implying that other transmitters and/or other receptors are 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, 2013). 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 analog is applied exogenously. The endogenously released transmitter acts primarily or exclusively on the subjunctional receptors (which cover <1% of the surface of the effector cells) whereas the exogenously applied transmitter acts on the extrasynaptically located receptors (Hirst et al., 1996).

In conclusion, the centrally generated signals are faithfully transmitted from the preganglionic neurons to the postganglionic neurons and from the postganglionic neurons to the effector tissues at the neuroeffector junctions or at the contact sites where the varicosities of the postganglionic axons are in close proximity with the tissue (e.g., non-excitable tissues). This signal transmission is function-specific and the basis for the precise regulation of autonomic effector tissues, probably including primary and secondary lymphoid organs, by the brain. Integration of central (preganglionic) synaptic inputs and synaptic inputs from the periphery occurs in some parasympathetic and sympathetic ganglia (e.g., in parasympathetic cardiac ganglia, in prevertebral sympathetic ganglia, in the stellate ganglion). However the functions of these peripheral integrative processes, including extracenteral reflexes, are poorly understood. At the level of the target tissues neural and non-neural signals may be integrated (e.g., by the syncytial nature of the smooth musculature of blood vessels). Also these integrative processes are not well understood at the cellular and subcellular levels in the context of the organ regulations by the autonomic nervous system.

3. Sympathetic nervous system and body 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. These integrated responses displayed by the organism are states of the organism which are represented in the brain (brain stem, hypothalamus, limbic system and telencephalon). Somato-motor responses, autonomic responses, endocrine responses, perception of sensations, and experience of emotions, occur principally in parallel and are therefore parallel read-outs of these representations in the brain (see Fig. 1).

These central representations receive continuously afferent neuronal, hormonal and humoral signals monitoring the state of the different tissues (Fig. 4). The adaptation of the immune system, control of inflammation and control of the nociceptive system (related to pain and hyperalgesia) by the CNS are integral components in this scenario and require sympathetic systems which function in a differentiated way (see above). During real or impending tissue damage, this integrated protective system organized by the brain is strongly activated leading to protective illness responses including pain and hyperalgesia and other aversive sensations (Dantzer et al., 2007). An important part of this protective system, that promotes tissue repair and overall recuperation, is the bidirectional interaction between the functioning immune system and brain in which the brain receives continuously signals from the immune system (cytokines) and modulates the reactivity of the immune system, via the sympatho-neural system, probably the sympatho-adrenal system and the hypothalamo-pituitary-adrenal (HPA) system. This bidirectional brain-immune system is relatively slow and fosters tissue healing and recovery.

Regulation of pain and hyperalgesia are integral components of the fast defense system (fight and flight) and the slow (recuperative) defense system. During *fast defense*, organized by the hypothalamo-mesencephalic system, fast analgesia, mobilization of energy, activation of various sympathetic channels (including the sympatho-adrenal system) and activation of the HPA system occur. This fast defense is preferentially activated from the periphery by stimulation of nociceptors of the body surface and is accompanied by an increase of arterial blood pressure and heart rate and an increased vigilance and alertness. During *slow defense*, the organism switches to recuperation and healing of tissues. It is characterized by pain and hyperalgesia in the deep body domains, which keep the organism in a state of quiescence and rest. This slow defense system is activated by peripheral signals mainly in afferent nociceptive neurons from deep body tissues (deep somatic tissues, viscera) and from the immune system by cytokines via the circumventricular organs or via afferent vagal neurons. It is accompanied by decreased arterial blood pressure and heart rate. The involvement of cytokines in sensitization of nociceptors during inflammation, possibly via the terminals of sympathetic fibers (see Jänig, 2009a; Jänig and Levine, 2013) and/or the activity of the sympatho-adrenal system (Khasar et al., 1998a, 1998b; Jänig et al., 2000), may be a component of the slow defense system (Fig. 4) (Maier and Watkins, 1998; for literature see Jänig and Levine, 2013).

The fast defense behaviors (confrontational defense, flight) during pain and stress are integrated in the lateral and dorsolateral columns of the mesencephalic periaqueductal gray and the slow defense behavior (quiescence) is integrated in the ventromedial periaqueductal gray of the mesencephalon. Both are under cortical control and have been described elsewhere (Bandler et al., 1991; Bandler and Shipley, 1994; Bandler and Keay, 1996; Bandler et al., 2000; see Jänig, 2006).

4. Control of the immune system by the sympathetic nervous system

Anatomical, physiological, pharmacological and behavioral experiments on animals support the notion that the sympathetic nervous system can influence the immune system and therefore control the protective mechanisms of the body at the cellular level (see Besedovsky and del Rey, 1992, 1995; Hori et al., 1995; Madden and Felten, 1995; Madden et al., 1995). Control of the immune system by the sympathetic nervous system would mean that the telencephalon is principally able to influence, via the hypothalamus, immune responses. This is an attractive idea and, based on clinical and experimental observations, propagated by several groups (Besedovsky and del Rey, 1992, 1995; Schedlowski and Tewes, 1999; see Ader, 2007).

The anatomical evidence showing that the sympathetic nervous system, but not the parasympathetic nervous system, is involved in control of the immune system is overwhelming. This applies to the primary and

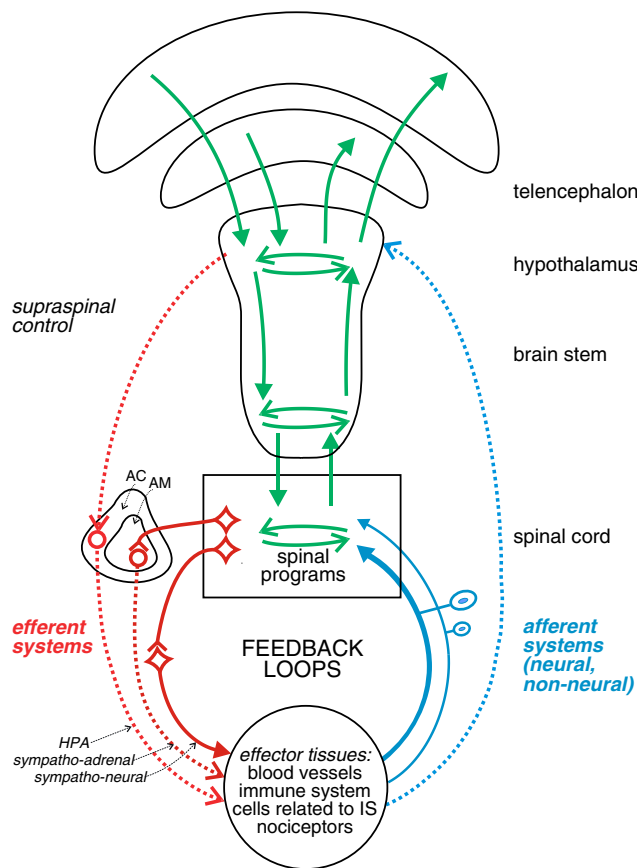


Fig. 4. Scheme for the feedback loops between the spinal cord and brain stem on one side and the effector tissues involved in protective body reactions on the other side. Effector tissues (blood vessels, immune tissue, cells related to the immune system [IS], nociceptors) are modulated by the sympatho-neural, the sympatho-adrenal and the hypothalamo-pituitary-adrenal (HPA) systems. Function of the effector tissues are signaled by afferent neurons with unmyelinated (C-) or small-diameter myelinated (A δ -) fibers, by signals from the immune system, and by endocrine/humoral signals to the spinal cord, brain stem and hypothalamus. The spinal neuronal circuits ("spinal programs") are under supraspinal control (brain stem, hypothalamus). AC, adrenal cortex; AM, adrenal medulla. Modified from Jänig (2011).

secondary lymphoid organs. Whether it also applies to the tertiary lymphoid organs (Grogan and Ouyang, 2012; Neyt et al., 2012) and the so-called "skin immune system" or SIS (Arck and Paus, 2006; Arck et al., 2006; Bos and Luiten, 2009) is discussed elsewhere (Fig. 5) (Nance and Sanders, 2007; Bellinger et al., 2013; Bellinger and Lorton, 2014).

Furthermore, pharmacological and molecular biological investigations show that most immune cells express adrenoceptors (particularly β_2 -, but also α_1 -adrenoceptors) and that most functional processes in the immune system can be influenced (enhanced or attenuated) by adrenoceptor agonists or antagonists (Bellinger et al., 2013; Bellinger and Lorton, 2014). However, the mechanisms by which the brain modulates the immune system via the sympathetic outflow remain largely unsolved (Ader, 2007; Ader and Cohen, 1993; Saphier, 1993; see Bellinger and Lorton, 2014). In view of the functional specificity of the peripheral sympathetic pathways to other targets as outlined above (Fig. 3) the key question to be asked is: *Are the primary and secondary lymphoid organs supplied by a sympathetic pathway which is functionally distinct from other sympathetic pathways and specifically mediates an immune-modulatory effect?* Several observations reported in the literature support the idea that the neural communication from the brain to the immune system occurs via a sympathetic final pathway that is *functionally distinct from all other peripheral sympathetic pathways* (such as

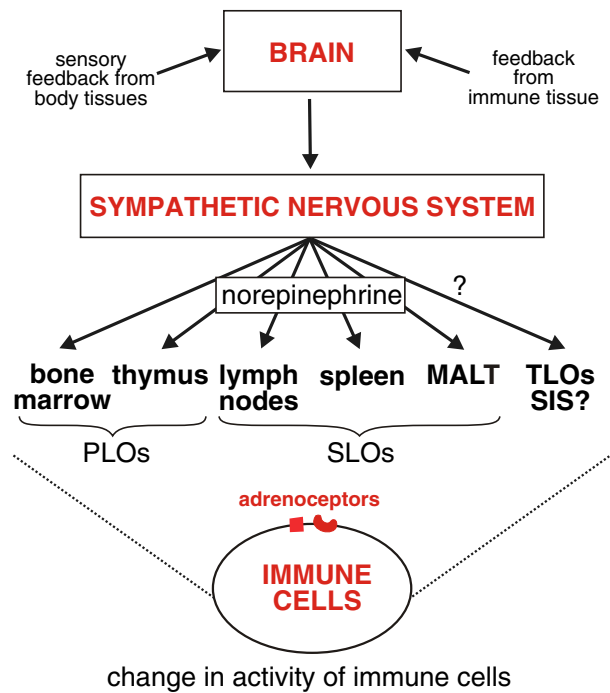


Fig. 5. Modulation of the immune organs by the brain via the sympatho-neural system. The immune organs consist of the primary lymphoid organs (PLOs), secondary lymphoid organs (SLOs which include the Peyer's patches and tonsils) and tertiary lymphoid organs (TLOs and possibly the skin immune system [SIS]). PLO and SLO are innervated by noradrenergic sympathetic postganglionic neurons (for details see Bellinger and Lorton, 2014) that act on the immune cells via adrenoceptors (mainly β_2 , but also α_1 [see Bellinger and Lorton, 2014]). Whether this also applies to the TLO is still debatable. The centers in the brain that are involved in the regulation of the immune organs (and therefore in the regulation of body protection during inflammation) receive afferent neural inputs from the affected body tissues and humoral/endocrine inputs from the immune tissues (e.g., via cytokines). MALT, mucosa-associated lymphoid tissue (includes the bronchial-associated lymphoid tissue [BALT; see McGovern and Mazzone, 2014], the gut-associated lymphoid tissue [GALT; see Cervi et al., 2014; Sharkey and Savidge, 2014], the nasal-associated lymphoid tissue [NALT, Bienenstock and McDermott, 2005] and the lymphoid tissue associated with the vulvo-vaginal tissues [see Birder, 2014]). Modified from Nance and Sanders (2007).

the vasoconstrictor systems, visceral secretomotor systems, and visceral motility-regulating systems):

- Primary and secondary lymphoid tissues are innervated by postganglionic noradrenergic sympathetic neurons. Varicosities of the sympathetic terminals can be found in close proximity to T lymphocytes and macrophages as described for other sympathetic target cells (Bellinger et al., 2013; Bellinger and Lorton, 2014).
- The spleen of the cat is innervated by sympathetic postganglionic neurons that are numerically, relative to the weight of the organs, three times as large as the sympathetic innervation of the kidneys (Baron and Jänig, 1988). The sympathetic innervation of the spleen is functionally different from that of the kidney: sympathetic neurons innervating the kidney behave like "classical" vasoconstrictor neurons (Meckler and Weaver, 1988; DiBona and Kopp, 1997; Kopp and DiBona, 2000). Many sympathetic neurons innervating the spleen are not under control of the arterial baroreceptors and show distinct 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, as incomplete as they are, suggest that many sympathetic neurons innervating the spleen have a function other than vasoconstriction function (or the function of those innervating the spleen capsule). This function may be related to the immune system.

- The activity in the sympathetic postganglionic neurons is transmitted to the cells of the primary or secondary lymphoid organs via release of norepinephrine that activates β_2 - and α_1 -adrenoceptors expressed on the immune cells. Bellinger and others show that most types of cells of the immune tissue express adrenoceptors (see Bellinger and Lorton, 2014). Are all adrenoceptor-expressing immune cells involved in the transmission of the central message to the immune tissue?
- Functional studies performed on the spleen of rodents have shown (for review see Hori et al., 1995, and references herein):
 - 1) Surgical or chemical sympathectomy alters the splenic immune responses (e.g., increased natural killer cell cytotoxicity and lymphocyte proliferation in responses to mitogen stimulation and production of interleukin-1 β).
 - 2) Electrical stimulation of the splenic nerve reduces the splenic immune responses.
 - 3) Lesions or stimulation of distinct hypothalamic sites or microinjection of cytokines at distinct hypothalamic sites activates some splenic immune responses. These changes are no longer present after denervation of the spleen.
 - 4) The interventions in the hypothalamus lead to changes of activity in the splenic nerve and changes in this 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 significantly correlated with suppression of natural killer cell cytotoxicity in the spleen. This suppression is mediated by β -adrenoceptors (Katafuchi et al., 1993a, 1993b; Okamoto et al., 1996). A hypothalamo-sympathetic neural system which controls the immune system has been postulated (Hori et al., 1995).

Using classical neurophysiological recordings *in vivo* from sympathetic neurons innervating the spleen, kidney, skin or skeletal muscle it should be possible to discriminate non-vasoconstrictor neurons innervating the primary or secondary lymphoid organs from other functional types of sympathetic neurons (e.g., cutaneous vasoconstrictor neurons, muscle vasoconstrictor neurons, vasoconstrictor neurons innervating the kidney, vasoconstrictor neurons innervating the spleen, motility-regulating neurons or secretomotor neurons innervating the gastrointestinal tract or pelvic organs). Table 1 shows examples of what might be the target cells in particular organs which are innervated by sympathetic neurons, the responses of the target tissue during activation of the sympathetic neurons, the functional types of sympathetic neurons involved and the physiological functions of these sympathetically induced responses. One sympathetic channel supplying the secondary immune organs possibly modulates the immune system by releasing norepinephrine and acting via adrenoceptors (mainly β_2 - and α_1 -adrenoceptors [see Bellinger and Lorton, 2014]).

By analogy to what has been described above (see Jänig, 2006), it should theoretically be possible to characterize the sympathetic neurons innervating the lymphoid tissues neurophysiologically by using peripheral adequate stimuli and central stimuli in eliciting immune

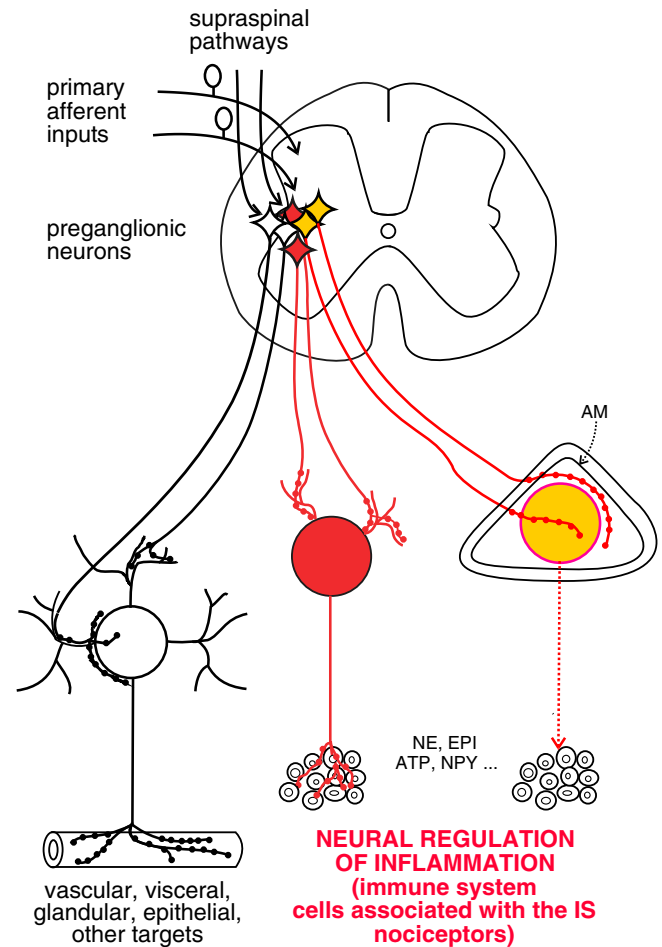


Fig. 6. Regulation of inflammation via the sympatho-neural system and the sympatho-adrenal system, involving as effectors the immune systems (IS), cells related to the IS and nociceptors. The hypothesis is that a functionally specific final sympathetic neural pathway and the sympatho-adrenal system releasing epinephrine are involved in this regulation. Spinal pathways are not indicated. AM, adrenal medulla; ATP, adenosine-tri-phosphate; NE, norepinephrine; EPI, epinephrine; NPY, neuropeptide Y.

responses and to assign in this way to the neurons of this channel *characteristic functional markers* which are dependent on the central circuits involved in the regulation of the activity of the sympathetic neurons innervating the primary and secondary lymphoid organs (Fig. 5; see Hori et al., 1995). This idea leads to the formulation of *two alternative testable hypotheses* (Fig. 6):

1. *Hypothesis 1:* Peripheral sympathetic neurons innervating the lymphoid organs (Fig. 5) are functionally specific for the immune tissues. These neurons show distinct reflex patterns generated by physiological (peripheral and central) stimuli which are related to the immune

Table 1

Examples of function-specific sympathetic pathways to different targets within some organs with emphasis on immune tissue.

Organ innervated by sympath. neurons	Target cells of sympath. innervation	Responses to sympath. activation	Types of sympath. neuron	Functions
Spleen, lymph nodes	BV, IC (SLO)	VC, IR	VC, IC _{modul}	BFR, modulation of IR
Hairy or hairless skin	BV _{skin} , SG, APM	VC (VD?), SS, Pilo	CVC, CVD, SM, PM	BFR, thermoregulation
Kidney	BV _{renal} , JGA, tubules	VC, renin release, sodium excretion	RVC, R _{renin} , R _{tub}	BFR, regulation of fluid homeostasis
Skeletal muscle	BV _{muscle}	VC (VD?)	MVC, MVD	BFR, BP regulation

Abbreviations:

Target cells of sympath. innervation: APM arrector pili muscle (in cat and rat only the tail and back of the trunk), BV blood vessel, IC immune cells, JGA juxtaglomerular apparatus, SLO secondary lymphoid organs, SG sweat gland.

Responses to sympath. activation: IR immune response, Pilo piloerection, SS sweat secretion, VC vasoconstriction, VD active vasodilation.

Type of sympath. neuron: CVC cutaneous vasoconstrictor, CVD cutaneous vasodilator, IC_{modul} immune cell modulator, MVC muscle vasoconstrictor, MVD muscle vasodilator, PM pilomotor, RVC renal vasoconstrictor, R_{renin} renin-releasing, R_{tub} renal tubular sodium absorption, SM sudomotor, VC vasoconstrictor.

Functions: BFR blood flow regulation, BP blood pressure.

system and not to other functionally irrelevant afferent inputs. These sympathetic preganglionic and postganglionic neurons constitute distinct sympathetic pathways to the immune tissue that is connected to special central circuits. This neural immune-regulatory system is active during defense and protection of the body tissues.

2. **Hypothesis 2:** The alternative hypothesis is that reflex responses in sympathetic neurons which modulate immune responses are found indiscriminately in all populations of sympathetic neurons. These responses would therefore not be functionally specific for the lymphoid tissues. This could mean that more or less *all* sympathetic noradrenergic pathways have, in addition to their specific target-organ related functions (see above and Jänig, 2006), a general function which is related to defense and protection of the body tissues. This hypothesis does not collide with the idea that regulation of defense and protection of body tissues by the CNS is based on special circuits in the brain stem and hypothalamus (see Bellinger and Lorton, 2014).

These alternative hypotheses are testable using an *in vivo* approach and recording, extracellularly or intracellularly, from single postganglionic neurons innervating the immune tissue. The sympathetic innervation of the spleen or lymph nodes (Table 1) would consist of vasoconstrictor neurons and non-vasoconstrictor neurons hypothetically associated with the immune tissue. The vasoconstrictor neurons would exhibit their typical reflex patterns (e.g., inhibition to stimulation of arterial baroreceptors, excitation to stimulation of arterial chemoreceptors, correlation of their activity with the central respiration [monitored by recording from the phrenic nerve], correlation of their activity with the blood flow changes through the spleen or lymph node). Other known functionally different types of sympathetic neuron would exhibit other reflex pattern to physiological stimuli. The neurons hypothetically involved in immune-modulation would show a reflex pattern characteristic for this system (e.g., no control by arterial baroreceptors or arterial chemoreceptors, distinct responses to central or peripheral stimuli that are relevant for the immune target tissue) (Table 1). It would be extremely important to tailor the afferent stimuli precisely and to define the functional conditions of the animals under which the activity in the hypothetical immune-regulating sympathetic neurons is recorded.

5. Sympathetic nervous system and immune system:

Some comments

The topic “Sympathetic nervous system and inflammation” is controversial and raises several questions that are not easy to be answered:

1. The density of sympathetic terminals among the immune cells of the primary and secondary lymphoid organs is low when compared to the density of sympathetic terminals of some other sympathetic target tissues (e.g., small arteries, arterioles, cardiac pacemaker cells, heart muscle cells, and vas deferens). Some varicosities of the sympathetic terminals may form close contacts with T-lymphocytes in immune organs (Felten et al., 1987); however, it is debated whether these contacts are important for the signal transmission from the sympathetic terminals to the immune tissue. Furthermore Felten and co-workers claim that norepinephrine influences immune cells in a “paracrine fashion”. The mechanism of this communication is similar to “volume transmission” in the central nervous system. After all, the immune cells do not form functional syncytia in which the neurally evoked signals spread directly from cell to cell, as is the case with smooth muscle, cardiac muscle, and secretory epithelia. In the immune cell pool, the concentration of norepinephrine released by the varicosities may be in the millimolar range, but drops rapidly; this occurs as the 3rd power of the distance from the varicosities by diffusion, but is also dependent on neuronal uptake of norepinephrine. What is the gradient of norepinephrine concentration in the immune tissue down to the plasma concentration? In humans the plasma concentration of norepinephrine is in the range of

300 ng/l (1.7 nM). The great majority of plasma norepinephrine (92–98%) is released by the terminals of active sympathetic neurons in the body (overflow of norepinephrine in the skeletal muscle, kidney, gastrointestinal tract, heart, lung, skin; [Esler et al., 1990]), the remaining plasma norepinephrine being released by the adrenal medulla.

The concentration of norepinephrine in the primary and secondary lymphoid organs also will depend on the rate of ongoing and evoked activity of the sympathetic neurons innervating the immune tissues and on the reuptake of norepinephrine. This determines the accumulation of norepinephrine in these organs and therefore a standing concentration gradient may develop within the lymphoid organs. What are the discharge rates of these sympathetic neurons innervating the immune tissues under resting conditions and under conditions in which the immune system is challenged (e.g., during various types of stress)? This argumentation shows that the plasma concentration of norepinephrine is unlikely to be an important signal by which the immune tissue is modulated, except perhaps in extreme situations when most sympathetic systems are activated.

2. The plasma concentration of epinephrine in humans is in the range of 30–100 ng/l (0.16–0.54 nM) (Esler et al., 1990; Jänig, 2006). Epinephrine is released by cells of the adrenal medullae into the circulation following activation of the preganglionic neurons innervating them. The central circuits regulating the activity of these preganglionic neurons are different from those involved in the release of norepinephrine from the adrenal medulla and in the regulation of other sympathetic target organs (Morrison and Cao, 2000; Verberne and Sartor, 2010). What is the function of epinephrine in the regulation of the immune tissues?

Epinephrine has clear metabolic functions but no cardiovascular function (Vollmer et al., 1995). *In vivo* research on rats has shown that the sympatho-adrenal system leading to release of epinephrine into the circulation is also important in the modulation of ongoing and bradykinin-induced synovial plasma extravasation (an acute experimental inflammation; see Jänig and Green, 2014) and in the long-term regulation of the sensitivity of cutaneous nociceptors (Khasar et al., 1998a, 1998b, 2003). Both effects are mediated by β_2 -adrenoceptors. These functions are components of a protective system of the body tissues which is organized by the brain and under powerful inhibitory control of vagal afferents innervating the small intestine (Jänig et al., 2000; see Jänig and Green, 2014).

3. The skin is a powerful defense barrier of the body against invading microorganisms, toxins and injury and permanently exposed to exogenous and endogenous stressors. It contains various cell types which interact and are associated with cells of the immune system such as mast cells, keratinocytes, macrophages, and Langerhans cells. Furthermore, the number of T-cells in the skin is almost twice as high as the total number of T-cells in the circulation (Clark et al., 2006). It is believed that the immune cells and skin cells associated with them are very important in the normal (physiological) defense processes operating in the skin and, under pathophysiological conditions, in the development and maintenance of various skin diseases (e.g., atopic dermatitis, psoriasis, seborrheic eczema, prurigo nodularis, lichen planus, chronic urticaria, alopecia areata). Dermatologists have coined the term “skin immune system” (SIS) or “skin associated lymphoid tissue” (SALT) to describe the role of immune cells and their interaction with cellular defense mechanisms in the skin under physiological and pathophysiological conditions (Williams and Kupper, 1996; Kupper, 2000; Kupper and Fuhlbrigge, 2004; Arck and Paus, 2006; Arck et al., 2006; Bos and Luiten, 2009; Peters et al., 2012).

The skin is densely innervated by primary afferent neurons with unmyelinated axons, most of them being peptidergic and having nociceptive functions, and by sympathetic postganglionic neurons. These postganglionic neurons have – depending on the type of the skin – vasoconstrictor, sudomotor, pilomotor and possibly vasodilator

functions. They form separate, functionally distinct sympathetic pathways that can readily be recognized by their physiological discharge patterns and that are also differentiated by immuno-histochemical (peptide content) and electro-anatomical criteria (Jänig, 2006). The integrated cellular activity at the cutaneous defense line is under neuroendocrine control involving the hypothalamo-pituitary-adrenal (HPA) axis and possibly the sympathetic nervous system (Arck and Paus, 2006; Buske-Kirschbaum, 2007). Is the skin innervated by sympathetic neurons which are normally silent and the function of which is not to regulate the “classical” sympathetic target cells (such as blood vessels, sweat glands or arrector pili muscles) but to modulate defense processes in the skin involving the so-called SIS? Or is the sympatho-adrenal system releasing epinephrine primarily involved? Reviews on the SIS neither mention nor discuss this possibility but remain rather vague about the efferent sympathetic pathway(s) in the “brain–skin axis”, the reason probably being the erroneous belief that the sympathetic nervous system functions as a unitary neurohumoral system and not in a functionally differentiated way (see Section 2) (Williams and Kupper, 1996; Kupper, 2000; Kupper and Fuhlbrigge, 2004; Bos and Luiten, 2009).

4. The knee joint is densely innervated by sympathetic postganglionic neurons. This innervation is involved in regulation of blood flow and in regulation of synovial plasma extravasation, either directly or indirectly in association with leukocytes and other cells related to the immune system. In rats, acute experimental inflammation of the joint is enhanced by the sympathetic innervation but depressed in later stages of the inflammation (Schaible and Straub, 2014). About 60–70% of ongoing and bradykinin-induced synovial plasma extravasation is dependent in physiological conditions on the presence of the sympathetic innervation of the joint (but not on activity in these neurons and not on norepinephrine released by them). The extravasation is modulated in an inhibitory way by epinephrine released by the adrenal medullae (Jänig and Green, 2014). What are the cellular and subcellular mechanisms underlying the synovial plasma extravasation mediated by the sympathetic fibers? This plasma extravasation occurs at the venular site of the vascular bed and the sympathetic fibers do not appear to innervate the venules directly although this has to be investigated. Are the sympathetic postganglionic neurons innervating the precapillary arterioles and small arteries the same as those mediating the venular plasma extravasation? This could be studied using a morphological ultrastructural approach as has been done for the juxtaglomerular region of the kidney. These studies show that afferent and efferent arterioles, granular epitheloid (renin-secreting) cells and epithelial cells of the proximal tubules are differentially innervated by sympathetic noradrenergic nerve fibers (Luff et al., 1992; Denton et al., 2004).
5. Tertiary lymphoid organs often develop in tissues with chronic immune stimulation, i.e. during chronic inflammation induced by chronic infections, autoimmune reactions or graft rejections (lymphoid tissue neogenesis). These ectopic lymphoid organs are similar in their structure to secondary lymphoid organs allowing the organized interaction between recirculating T cells, B cells and antigen presenting cells (Neyt et al., 2012; Grogan and Ouyang, 2012; van de Pavert and Mebius, 2010). Are tertiary lymphoid organs innervated by postganglionic sympathetic noradrenergic neurons as has been shown for the primary and secondary lymphoid organs (Felten et al., 1985, 1987)? Are the interactions between immune cells in the tertiary lymphoid organs under control of the sympatho-neural and the sympatho-adrenal system?
6. Patients with pure autonomic failure (PAF) have very low circulating catecholamine levels (resting as well as evoked [e.g., by tilting or central stress]), due to loss of preganglionic and particular postganglionic neurons. In the rare patients with dopamine- β -hydroxylase deficiency, plasma levels of norepinephrine and epinephrine are below the detection level under all conditions. The plasma level of epinephrine does not increase during hypoglycemia, i.e. the cells of the adrenal

medullae are not activated and do not release epinephrine (Garland, 2012; Kaufmann and Schatz, 2012; Mathias et al., 2013). In both groups of patient, there appears to be no communication from the central nervous system to the primary and secondary lymphoid organs via the sympathetic nervous system. Are the immune responses during inflammatory challenges compromised in these patients?

These comments and the discussion whether the immune tissue is innervated by a sympathetic pathway that is anatomically and physiologically distinct from other sympathetic pathways clearly show that we are at the beginning in our studies of the relation between the sympathetic nervous system and immune system. The problem as to how the central nervous system is regulating inflammatory processes involving the immune system, sympathetic nervous system and small diameter afferent neurons innervating the body tissues requires a multidisciplinary experimental approach. Simple answers cannot be expected. Furthermore generalizations as far as the functioning of the sympathetic nervous system, adrenoceptors, central circuits, and immune system are concerned will not be very useful.

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