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Sympathetic nervous system and inflammation: A conceptual view

Wilfrid Jänig *

Physiologisches Institut, Christian-Albrechts-Universität zu Kiel, Olshausenstr. 40, D-24098 Kiel, Germany

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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?

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

* Tel.: +49 431 880 2036; fax: +49 431 880 4580.
E-mail address: w.janig@physiologie.uni-kiel.de.

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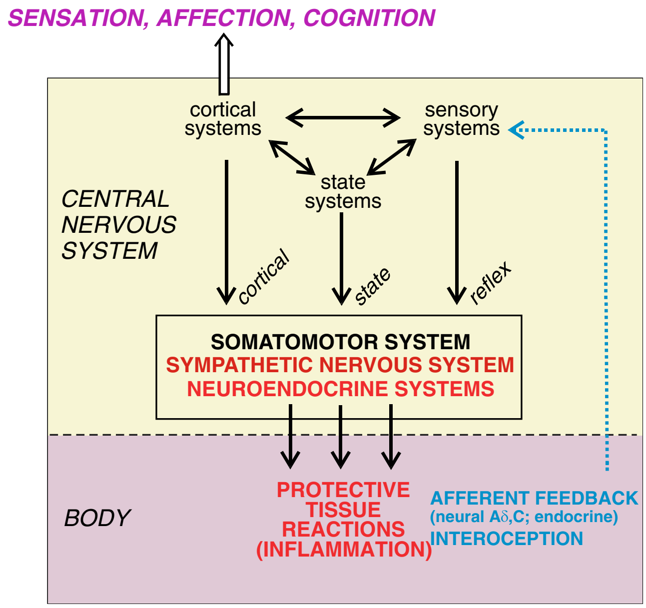

Fig. 1. Functional organization of the nervous system to generate protective behavior. The motor system consists of the somatomotor, the autonomic (visceromotor) and the neuroendocrine systems and controls behavior. The motor systems are hierarchically organized in the spinal cord, brain stem and hypothalamus 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. Designed after Swanson (2000, 2008).

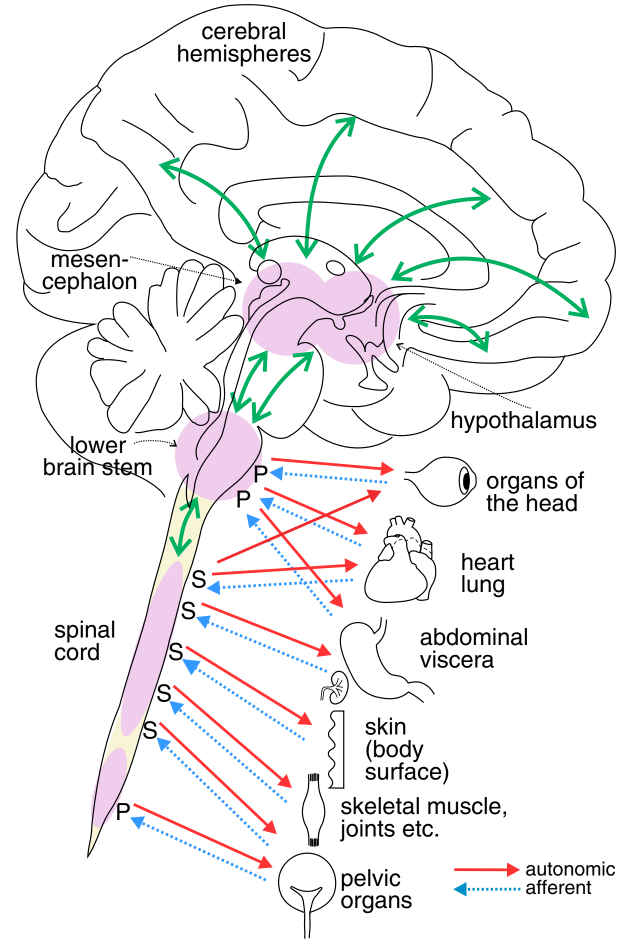

Fig. 2. Reciprocal communication between the brain and body tissues by efferent autonomic pathways and afferent pathways. The global autonomic centers in the spinal cord, lower and upper brain stem and hypothalamus are shaded in violet. These centers consist of the neural circuits that are the bases 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.
Modified from Jänig (2013b).

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). 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