Introduction

The autonomic nervous system and the regulation of body functions

Somatomotor activity and adjustments of the body

All living organisms interact continuously with their environment. They receive multiple signals from the environment via their sensory systems and respond by way of their somatomotor system. Both sensory processing and motor actions are entirely under control of the central nervous system. Within the brain are representations of both extracorporeal space and somatic body domains, the executive motor programs and programs for the diverse patterns of behavior which are initiated from higher levels. The brain generates complex motor commands on the basis of these central representations; these lead to movements of the body in its environment against different internal and external forces. The tools for performing these actions are the effector machines, the skeletal muscles and their controlling somatomotoneurons.

The body's motor activity and behavior are only possible when its internal milieu is controlled to keep the component cells, tissues and organs (including the brain and skeletal muscles) maintained in an optimal environment for their function. This enables the organism to adjust its performance to the varying internal and external demands placed on the organism. In the *short term* the mechanisms involved include the control of:

- fluid matrix of the body (fluid volume regulation, osmoregulation),
- gas exchange with the environment (regulation of airway resistance and the pulmonary circulation),
- ingestion and digestion of nutrients (regulation of the gastrointestinal tract, control of energy balance),
- transport of gases, nutrients and other substances throughout the body to supply organs, including the brain to maintain consciousness (regulation of blood flow and blood pressure by the cardiovascular regulation),
- excretion of substances (disposal of waste),
- body temperature (thermoregulation),
- reproductive behavior (mechanics of sexual organs),
- defensive behaviors,

and in the *long term* the control of:

- body recovery (control of circadian rhythms, of sleep and wakefulness),
- development and maintenance of body organs and tissues,

- body protection at the cellular and systems level (regulation of inflammatory processes, control of the immune system).

These body functions responsible for maintaining the internal milieu are controlled by the brain. The control is exerted by the autonomic nervous system and the endocrine system. Specifically, the brain acts on many peripheral target tissues (smooth muscle cells of various organs, cardiac muscle cells, exocrine glands, endocrine cells, metabolic tissues, immune cells, 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 time scales of these controls differ by orders of magnitude: autonomic regulation is normally fast and occurs within seconds, and neuroendocrine regulation is relatively slow (over tens of minutes, hours or even days). The *afferent signals* from the periphery of the body to the brain are neural, hormonal (e.g., hormones from both endocrine organs and the gastrointestinal tract, cytokines from the immune system, leptin from adipocytes) and physicochemical (e.g., blood glucose level, temperature, etc.).

The maintenance of physiological parameters such as concentration of ions, blood glucose, arterial blood gases, body core temperature in a narrow range (but around predetermined "set points") is called *homeostasis*. Homeostatic regulation involves autonomic systems, endocrine systems and the respiratory system. The concept of homeostasis has been formulated by Walter B. Cannon (1929a) based on the idea of the fixity of the internal milieu of the body (Bernard 1957, 1974).[1] However, this concept is too narrow and static to understand how the organism is able to maintain the parameters in the body stable and to temporarily adapt them during environmental changes. To understand how the internal milieu is maintained stable during changes in the body and in the environment the concept of allostasis has been developed. This concept extends the concept of homeostasis. It distinguishes between systems that are essential for life (e.g., the concentration of ions and pH in the extracellular and intracellular fluid compartments; homeostasis in the narrow sense) and systems that maintain these systems in balance ("allostasis") as the environment changes (McEwen and Wingfield 2003). This is achieved by the autonomic nervous systems and the endocrine systems and is fully dependent on a functioning central nervous system, notably the hypothalamus and the cerebral hemispheres (Sterling and Eyer 1988; McEwen 2001b; McEwen and Wingfield 2003; Schulkin 2003a, b).

Autonomic nervous system, behavior and brain

By analogy with the organization of the somatomotor system and the sensory systems in the brain, it is natural to accept the concept that the regulation of autonomic and endocrine homeostatic mechanisms is also represented in the brain (i.e., in the hypothalamus, brain stem and spinal cord) and that these systems are under the control of the forebrain and integrated there with the somatomotor and sensory

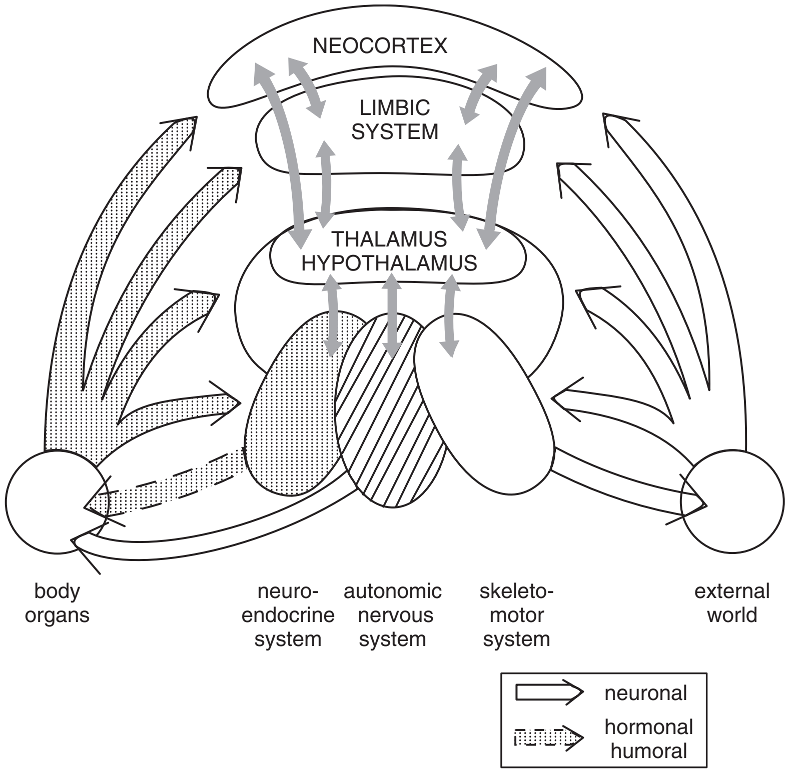

Figure 1 Autonomic nervous system, brain and body. *Right*, somatic nervous system (motor system and sensory systems) and environment. *Left*, autonomic nervous system, neuroendocrine system and body organs. In the *middle*, spinal cord, brain stem, hypothalamus' limbic system and neocortex. The afferent feedback from the body is neuronal, hormonal and humoral (physicochemical; e.g., glucose concentration, osmolality) and of other types (e.g., body temperature). *Solid line arrows*, neuronal; *dashed line arrow*, hormonal; *dotted*, neuroendocrine system, hormonal and humoral feedback. Limbic system is anatomically descriptive and a collective term denoting brain structures common to all mammals that include hippocampus, dentate gyrus with archicortex, cingulate gyrus, septal nuclei and amygdala. These forebrain structures are functionally heterogenous and not a unitary system (as the term "limbic system" may imply). They are involved in the generation of emotional and motivational aspects of behavior (see LeDoux [1996]). Note the reciprocal communication between hypothalamus, limbic system and neocortex (symbolized by the shaded arrows) indicating that the centers of the cerebral hemispheres have powerful influence on all autonomic regulations. Modified from Jänig and Häbler (1999) with permission.

representations. Thus the brain contains autonomic "sensorimotor programs" for coordinated regulation of the internal environment of the body's tissues and organs and sends efferent commands to the peripheral target tissues through the autonomic and endocrine routes (see Figure 1). Integration, within the brain, between the areas that are involved with the outputs of the autonomic, endocrine, somatomotor, and sensory systems is essential for the coordination of behavior of the organism within its environment, for the expression and development of normal feelings and emotions, and for the perception of the body and self as a unified being.

The essential role of the autonomic nervous system in these integrative homeostatic and allostatic programs is primarily to

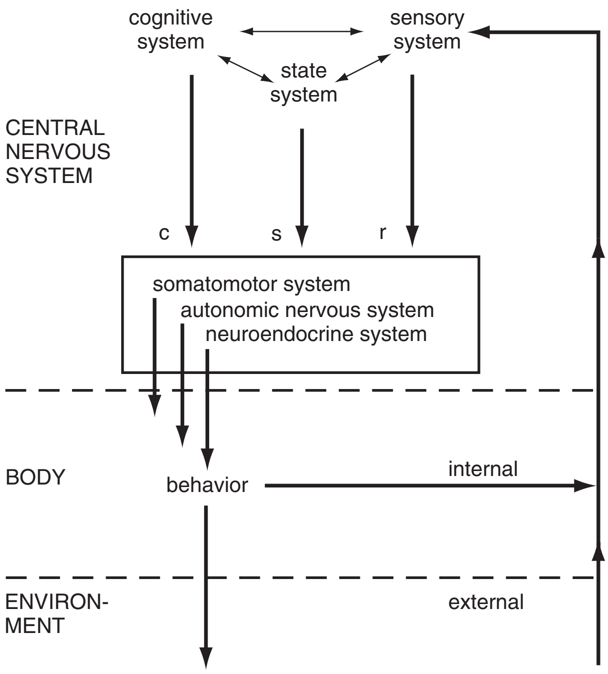

Figure 2 Functional organization of the nervous system to generate behavior. The motor system, consisting of the somatomotor, the autonomic (visceromotor) and the neuroendocrine systems, controls behavior. It is hierarchically organized in spinal cord, brain stem and hypothalamus. The motor system receives three general types of synaptic input: (a) from the sensory systems monitoring processes in the body or the environment to all levels of the motor system generating reflex behavior (*r*); (b) from the cerebral hemispheres responsible for voluntary control of the behavior (*c*), cognitive based on neural processes related to cognitive and affective-emotional processes; (c) from the behavioral system controlling attention, arousal, sleep/wakefulness, circadian timing (*s*). The three general input systems communicate bidirectionally with each other (upper part of the figure). Modified from Swanson (2000, 2003).

distribute specific signals generated in the central nervous system to the various target organs. In order to achieve overall coordination, the signals need to be precisely patterned to implement appropriate reactions in each target tissue or organ. Some of these signals pass continuously to the periphery in the resting state; others are recruited (or switched off) during particular body behaviors and states of the internal milieu.

The model in Figure 2 outlines the role of the autonomic nervous system in the generation of behavior. Behavior is defined as the purposeful motor action of the body in the environment. It is generated by coordinated activation (1) of somatomotor neurons to move the body in the environment and (2) of autonomic and neuroendocrine motor neurons to prepare and adjust the internal milieu and body organs enabling the body to move. Thus, under motor system we subsume the three divisions, the somatic, the autonomic and the neuroendocrine motor systems (Swanson 2000, 2003; Watts and Swanson 2002):

- The divisions of the motor system are closely integrated in spinal cord, brain stem and hypothalamus. Both somatomotor and autonomic motor systems are hierarchically organized, their integration occurs at each level of the hierarchy. The neuroendocrine motor system is represented at the top of this hierarchy (in the hypothalamus).
- The motoneuron pools (final motor pathways) extend from the midbrain to the caudal end of the spinal cord for the somatomotor system and the autonomic system (the latter with gaps in the

cervical and lower lumbar spinal cord). The neuroendocrine motor neurons are located in the periventricular zone of the hypothalamus.

- The activity of the motor system generating behavior is dependent on three major classes of input: (1) the sensory systems, (2) the cortical system that generates voluntary behavior and (3) the behavioral state system.
- The sensory systems monitor events in the body (*internal* in Figure 2) or in the environment. They are closely welded to the motor hierarchy and generate on all levels of this hierarchy reflex behavior (*r* in Figure 2).
- The cerebral hemispheres initiate and maintain behavior based on cognition and affective-emotional processes (*c* in Figure 2).
- The behavioral state system consists of intrinsic neural systems that determine the state of the brain in which it generates motor behavior. The behavioral state system controls sleep and wakefulness, arousal, attention, vigilance and circadian timing (*s* in Figure 2).
- The three global input systems to the motor system interact with each other too.

This way of looking at the autonomic nervous system shows that the activity in the autonomic neurons is dependent on the intrinsic structure of the sensorimotor programs of the motor hierarchy and on its three global input systems. Thus any change in these input systems should be reflected in the activity of the final autonomic pathways and therefore in the autonomic regulations.

Precision of autonomic regulations and its failure in disease

The precision and biological importance of the control of peripheral target organs by the autonomic nervous system are silently accepted, but the mechanisms by which they come about are not generally understood. Both of these aspects become quite obvious when the regulatory functions fail so that even the simplest actions of the body, such as standing up, may become a burden. Thus, as the blood collects in the venous system due to the effect of gravity, the control of the level of pressure perfusing the brain and other organs fails, leading to decreased cerebral perfusion and loss of consciousness. Such failure of autonomic control may occur at a time when the somatomotor and the sensory systems are functioning normally (Low 1993; Appenzeller 2000; Mathias and Bannister 2002). Failure may develop:

- when the peripheral (efferent) autonomic neurons are damaged (e.g., as a consequence of metabolic disease, such as long-term diabetes in which peripheral autonomic neurons are destroyed), resulting in failure of regulation of the cardiovascular system, the gastrointestinal tract, pelvic organs (sexual organs, urinary bladder, hindgut) or other organs;

- when certain types of peripheral autonomic neurons are inherently absent such as the rare cases of *pure autonomic failure* in which most neurons in the autonomic ganglia are absent or in which one enzyme for synthesis of the transmitter noradrenaline, dopamine-β-hydroxylase, is deficient or absent (Mathias and Bannister 2002); or in *Hirschsprung's disease* in which some of the inhibitory neurons of the enteric nervous system of the gut are missing (Christensen 1994);
- when the *spinal cord* is traumatically *lesioned* (leading to interruption of the control of these spinal autonomic circuits by supraspinal autonomic centers to the spinal autonomic circuits);
- when the efferent sympathetic and afferent pathways in the peripheral somatic tissues are disrupted after trauma (with or without nerve lesions), leading to abnormal relationships between sympathetic and afferent systems and consequently to pain syndromes such as reflex sympathetic dystrophy (complex regional pain syndrome type I) or causalgia (complex regional pain syndrome type II) (Stanton-Hicks *et al.* 1995; Jänig and Stanton-Hicks 1996; Harden *et al.* 2001; Jänig and Baron 2002, 2003);
- when hypothalamic functions are impaired (e.g., in anorexia nervosa or as a consequence of a tumor or trauma);
- during severe infectious diseases, probably since central regulation of the cardiovascular system or gastrointestinal tract fail;
- quite commonly in *old age* when many peripheral autonomic neurons may die and autonomic regulation may be reduced in effectiveness.

When the autonomic system fails for any of the reasons described above the potential range of an individual's behavior may be considerably reduced. In the extreme case, a patient with failure of blood pressure regulation may have to be confined permanently to bed in order to maintain adequate perfusion of the brain. Patients with distinct diabetic autonomic neuropathy may have problems with regulation of their pelvic organs, cardiovascular system or gastrointestinal tract. Finally, and quite commonly, life may become miserable in old age because autonomic systems decrease in their range of functioning without obvious disease triggered from within or without the body.

Functional diseases, involving the autonomic nervous system and neuroendocrine systems, may also develop when allostatic responses, which are physiologically rapidly mobilized during external and internal perturbations ("stress") and then turned off when no longer needed, remain active over a longer time. These maintained allostatic responses are called *allostatic load* or *overload* and are believed to contribute to various types of diseases, such as hypertension, myocardial infarction, obesity, diabetes type II, atherosclerosis, and metabolic syndrome (Folkow *et al.* 1997; McEwen 2001a; McEwen and Wingfield 2003).

Although we can principally live without the function of large parts of the autonomic nervous system, the life style of an individual in such a state becomes severely constrained so that many of the large range of activities for which our biology equips us, such as being sexually active, playing tennis, running a marathon, climbing mountains, diving in the sea, living in the tropics or in arctic climates or being involved in intellectual activities, are not possible without a normally functioning autonomic nervous system. Finally, all vertebrates are endowed with autonomic systems in order to meet extreme environmental challenges. Thus we can adapt, e.g., to very cold climates or very hot climates, to high altitudes, to extreme persistent exercise, to extreme states of starvation or to extreme dry climates. These examples illustrate the dynamic plasticity of autonomic regulations. This plasticity may have been essential for the evolution of mammals, humans probably being the most adaptable mammal. Development, anatomical differentiation and functional differentiation of the autonomic nervous system evolved in association with the behavioral repertoire of the different vertebrate species. Thus the complexity of autonomic regulation increased with the complexity of the behavioral repertoire (Nilsson 1983; Nilsson and Holmgren 1994). This is fully in line with the concept of functioning of the hierarchically organized motor system that includes the somatomotor, the autonomic and neuroendocrine systems as outlined above (Figure 2).

Autonomic regulation of body functions requires the existence of specific neuronal pathways in the periphery and specific organization in the central nervous system; otherwise it would not be possible to have the precision and flexibility of control that higher vertebrates possess for rapid adjustments during diverse behaviors. This implies that the various autonomic systems must be centrally integrated and have multiple, but distinct, peripheral motor pathways. These pathways are defined according to the function they mediate in the target cells they innervate. The effector cells of the autonomic nervous system are very diverse while those of the somatic efferent system are not. From this point of view, it is clear that the autonomic nervous system is the major efferent component of the peripheral nervous system and outweighs the somatic efferent pathways in the diversity of its functions and its size.

Organization and aims of the book

In this book, I will describe the properties of autonomic circuits and of single autonomic neurons or parts of autonomic neurons in the context of their biological functions in vivo so that the reader understands the principles of organization of the autonomic neurons and their interrelationships. This description should also help explain why the brain is able to adapt and coordinate the different functions of the body so precisely during our daily activities, during extreme exertion and physiological stress, as well as during various mental activities and while we experience emotions. The book is organized in five sections:

1. *The autonomic nervous system: functional anatomy and visceral afferents*. I describe the neuroanatomical basis for the precise regulation of the peripheral autonomic target organs in higher vertebrates. It provides definitions and lays the groundwork for this book. It includes a general description of the anatomy and physiology of *visceral afferent neurons*, which are closely associated with the functioning of the autonomic nervous system, with the sensations and general feelings triggered from the internal organs and, finally, also with emotions.
2. *Functional organization of the peripheral autonomic nervous system*. This section describes the functional organization of sympathetic and parasympathetic pathways in the periphery and the principles of the organization of the enteric nervous system.
3. *Transmission of signals in the peripheral autonomic nervous system*. I describe the "tools" by which the signals generated in the brain are transmitted by the autonomic pathways to the effector cells. This description includes the neurotransmitters and their receptors, ganglionic transmission and integration and neuroeffector transmission.
4. *Central representation of the autonomic nervous system in spinal cord and brain stem*. I describe some principles of organization of the autonomic control systems in the spinal cord and lower brain stem. This description will have its reference in the functional organization of the peripheral autonomic pathways that has been extensively described in the two sections before.
5. The last chapter is the *summary* and *synopsis* of the book. I will discuss how functions of autonomic systems that are represented in spinal cord and lower brain stem are integrated in complex regulatory circuits involving the somatomotor, the autonomic and the neuroendocrine systems (Figure 2) that are represented in the mesencephalon, the hypothalamus and the forebrain. I will reflect back on the concepts of how the autonomic nervous system works as those developed in the first half of the last century still direct our thinking. I will paraphrase Walter Bradford Cannon as expressed in his most influential book *The Wisdom of the Body* (Cannon 1939).

For the detailed physiology of the various autonomic control systems, as well as their specific organization in the spinal cord, brain stem and hypothalamus the reader is referred, *first*, to the series of volumes on the Autonomic Nervous System edited by Burnstock and by several volume editors (see under volume editors),[2] *second*, to Randall (1984), Loewy and Spyer (1990b), Ritter *et al.* (1992), Low (1993), Rowell (1993), Greger and Windhorst (1996), Shepherd and Vatner (1996), Appenzeller and Oribe (1997), Blessing (1997), Mathias and Bannister (2005), and Appenzeller (1999) and, *third*, to special review articles published recently (Jänig 1985a, 1986, 1988a, 1995a, 1996a; Dampney 1994; Häbler *et al.* 1994a; Spyer 1994; Kirchheim *et al.* 1998; Jänig and Häbler 1999, 2003; Folkow 2000). The approach used here should also lead to a better understanding of primary disorders of the autonomic nervous system and of autonomic disorders that are secondary to, rather than causative of, various diseases (Low 1993; Robertson and Biaggioni 1995; Appenzeller and Oribe 1997; Appenzeller 2000; Mathias and Bannister 2002). Thus, this book is not intended to discuss the pathophysiology of the autonomic nervous system; however, it is the basis to understand pathophysiological changes of autonomic functions.

Notes

1. Claude Bernard was the first to formulate the idea of the fixity of the internal milieu of the body. This formulation was not so much based on experimental observations, however, it related to the experiments he had conducted over tens of years (Bernard 1878). Physiologists became aware of the universal importance of this concept in the frame of experimental physiology and medicine when it was applied to regulation of acid–base balance in the first half of the last century.
2. Burnstock and Hoyle (1992); Hendry and Hill (1992); Maggi (1993); Nilsson and Holmgren (1994); McLachlan (1995); Bennett and Gardiner (1996); Shepherd and Vatner (1996); Unzicker (1996); Barnes (1997); Jordan (1997b); Morris and Gibbins (1997); Burnstock and Sillito (2000); Brookes and Costa (2002).

Part I

The autonomic nervous system: functional anatomy and visceral afferents