# The Autonomic Nervous System and the Regulation of Body Functions

## Autonomic Adjustments of the Body and Behavior

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 the control of the central nervous system. The brain represents the extracorporeal space, the somatic body domains, the executive motor programs and programs for the diverse patterns of behavior initiated from higher centers. It generates complex motor commands on the basis of these central representations leading 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 state for their function. This enables the organism to adjust its performance to the varying internal and external demands placed on the organism. 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 and 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 flows and blood pressure by the cardiovascular regulation),
- excretion of substances (disposal of waste),
- body temperature (thermoregulation),
- reproductive behavior (mechanics of sexual organs),
- defensive behaviors,
- 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 system) and *hormonal* (by the neuroendocrine systems). The time scales of these controls may differ by orders of magnitude; changes in autonomic regulation are normally fast and occur 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, blood temperature, etc.).

The maintenance of physiological parameters such as concentrations 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 gas exchange (respiration). The concept of homeostasis was formulated by Walter Bradford Cannon (1929) based on the idea of the fixity of the internal milieu of the body (Claude Bernard 1957, 1974) (Note 1). However, this concept is too narrow and static to understand how the organism is able to maintain the parameters in the body stably and to temporarily adapt them during environmental changes. To understand how the internal milieu is maintained stably during changes in the body or in the environment, the concept of allostasis has been developed. This extends the concept of homeostasis and describes the temporary changes of set points of homeostatic regulation during large changes in the body or in the environment. It distinguishes between systems that are essential for life (e.g., the concentrations 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. 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, 2007; McEwen and Wingfield 2003; Schulkin 2003a, b; Schulkin and Sterling 2019).

## Autonomic Nervous System and Brain

The somatomotor system and the somatosensory system form "sensorimotor programs" for the control of movement of the organism in its environment. These somatic sensorimotor programs are represented in the spinal cord, brain stem and hypothalamus and are under the control of the telencephalon (Figure 0.1 right). By analogy, autonomic motor systems and neuroendocrine motor systems, together with interoceptive afferent neural, hormonal and humoral input systems that monitor the conditions of the inner milieu of the body, form autonomic and neuroendocrine "sensorimotor programs" for the regulation of the inner milieu of the body. Similarly, these autonomic and neuroendocrine sensorimotor programs are represented in the spinal cord, brain stem and hypothalamus and are under control of the telencephalon (Figure 0.1 left). Integration within the brain, between the centers that are involved with the autonomic, neuroendocrine and somatomotor as well as interoceptive sensory input systems, is essential for the coordination of the behavior of the organism within its environment.

The explanatory model in Figure 0.2 outlines the role of the autonomic nervous system in the generation of behavior. It is based on the "Four System Network Model" of Larry Swanson (Swanson 2012, 2013, Card and Swanson 2013). The four systems are the motor system, the sensory system, the cortical system and the state system. 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 the motor system we subsume

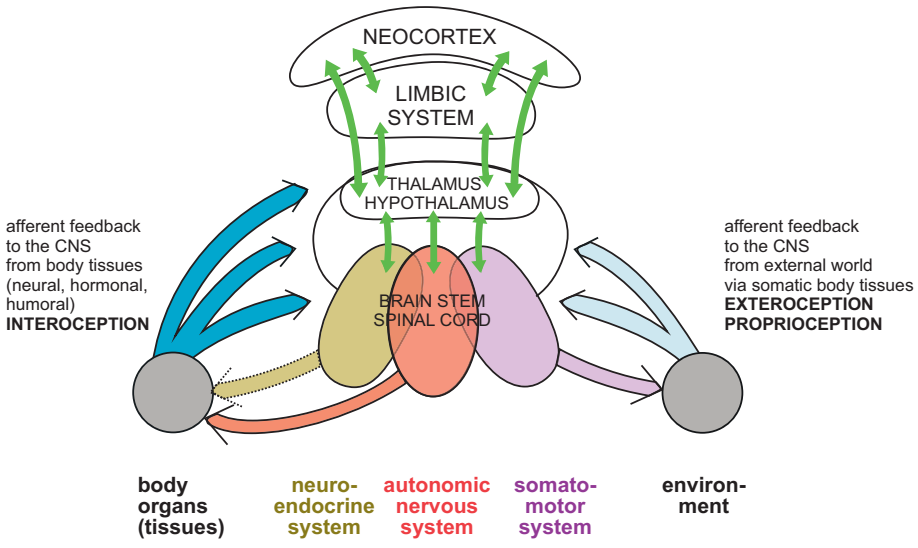


**Figure 0.1** Autonomic nervous system, brain and body. *Right*, somatic nervous system (somatomotor system and sensory systems to spinal cord and brain stem) and environment. *Left*, autonomic nervous system, neuroendocrine system and body organs. In the *middle*, spinal cord, brain stem, hypothalamus, limbic system and neocortex. The interoceptive afferent feedback from the body is neuronal, hormonal and humoral (physicochemical; e.g., glucose concentration, osmolality) and of other modalities (e.g., body temperature). *Solid-line arrows*, neuronal; *dotted-line arrow*, hormonal. 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 heterogeneous 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 green double arrows) indicating that the centers of the cerebral hemispheres control the autonomic regulation. Modified from Jänig and Häbler (1999) with permission.

the three divisions, the somatic, the autonomic and the neuroendocrine motor systems (Swanson 2000; Watts and Swanson 2002; Card and Swanson 2013):

- The three divisions of the motor system are closely integrated in the 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) exteroceptive and interoceptive sensory systems, (2) cortical systems and (3) behavioral state systems (Figures 0.1 and 0.2).
- The sensory systems monitor events in the body (*interoceptive* in Figure 0.2) or in the environment (*exteroceptive* in Figure 0.2). They are closely welded to the motor hierarchy and generate on all levels of this hierarchy reflex behavior (*reflex* in Figure 0.2).
- The cerebral hemispheres initiate and maintain behavior based on cognition and affective-emotional processes (*cortical* in Figure 0.2).
- The behavioral state system consists of intrinsic neural systems that control circadian timing of all body functions, sleep and wakefulness, arousal, attention, vigilance (*state* in Figure 0.2). This system modulates the somatic, autonomic and neuroendocrine motor systems.
- 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

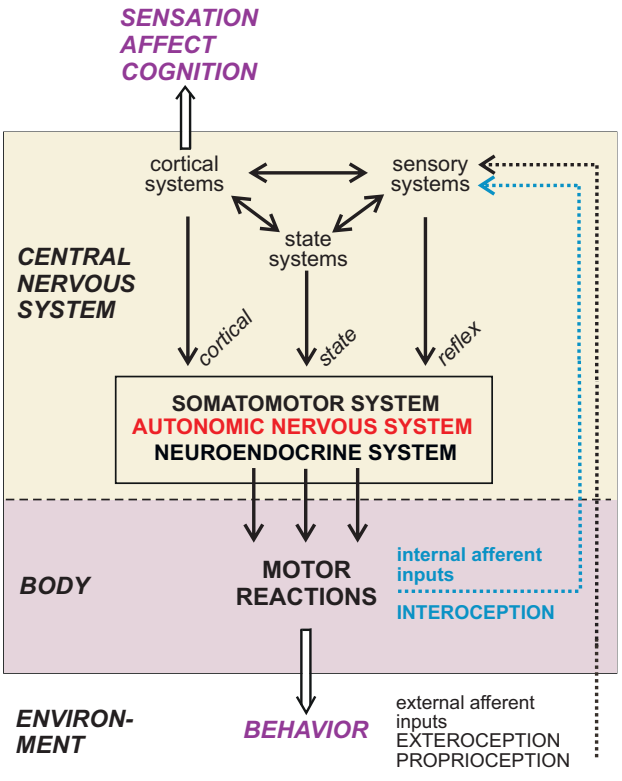


**Figure 0.2** Functional organization of the nervous system to generate behavior. The motor system, consisting of the somatomotor, the autonomic (visceromotor) and the neuroendocrine systems, controls behavior. It is hierarchically organized in the spinal cord, brain stem and hypothalamus. The motor system receives three general types of synaptic input: (1) from the sensory systems monitoring processes in the body or the environment to all levels of the motor system generating reflex behavior (*reflex*); (2) from the cerebral hemispheres responsible for cortical control of the behavior based on neural processes related to cognitive and affective-emotional processes (*cortical*); (3) from the behavioral state system controlling attention, arousal, sleep/wakefulness, circadian timing (*state*). The three general input systems communicate bidirectionally with each other (upper part of the figure). Modified from Swanson (2012, 2013) and Card and Swanson (2013).

neurons is dependent on the intrinsic structure of the sensorimotor programs of the motor hierarchy and on its three global input systems. Any change in these input systems should be reflected in the activity of the neurons of the final autonomic pathways and therefore in autonomic regulation of different organ systems.

## Precision of Autonomic Regulation 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. Failure of autonomic control may occur at a time when the somatomotor and the sensory systems are functioning normally (Low 1993; Appenzeller 2000; Robertson et al. 2012; Buijs and Swaab 2013; Mathias and Bannister 2013). It 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 the 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 2013); or in *Hirschsprung's disease* in which some of the inhibitory motor neurons of the enteric nervous system of the gut are missing (Christensen 1994);
- when the *spinal cord* is *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 complex regional pain syndrome type I or type II (Stanton-Hicks et al. 1995; Jänig and Stanton-Hicks 1996; Harden et al. 2001; Jänig and Baron 2002, 2003; Jänig 2020);
- when hypothalamic functions are impaired (e.g., in anorexia nervosa or as a consequence of a tumor or trauma);

- during severe infectious diseases, when central regulation of the cardiovascular system or gastrointestinal tract fails;
- quite commonly in *old age* when peripheral autonomic neurons may die and autonomic regulation may be reduced in effectiveness.

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 functional diseases, such as hypertension, myocardial infarction, obesity, type II diabetes, atherosclerosis and metabolic syndrome (Folkow et al. 1997; McEwen 2001a; McEwen and Wingfield 2003; Robertson et al. 2012).

Although we can in principle live without the function of large parts of the autonomic nervous system, the lifestyle of an individual in such a state becomes severely constrained so that many of the 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. All vertebrates are endowed with autonomic systems in order to meet extreme environmental challenges such as very cold or hot climates, high altitudes, extreme body motor activity, extreme states of starvation or extreme dry climates. These examples illustrate the dynamic plasticity of autonomic regulation. This plasticity may have been essential for the evolution of mammals, humans probably being one of the most adaptable mammals. 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; Holmgren and Olsson 2011; see Subchapter 1.5). 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 0.2).

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 anatomically and functionally very diverse while those of the somatic efferent system are not, i.e., it consists of skeletal muscle fibers. 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 principles of organization of the properties of autonomic circuits and of single autonomic neurons in the context of their biological functions in vivo. This description should help to explain why the brain is able to adapt and coordinate the different functions of the body so precisely during our daily activities, as well as during extreme exertion and physiological stress. The book is organized in five parts:

1. *The Autonomic Nervous System: Functional Anatomy and Interoceptive Visceral Afferents*. I describe the neuroanatomical basis for the precise regulation of the peripheral autonomic target organs in higher vertebrates. This provides definitions and lays the groundwork for this book. It also includes a general description of the anatomy and physiology of *interoceptive afferent neurons*, which are closely associated with the functioning of the autonomic nervous system, with interoceptive sensations and general feelings triggered from the body tissues 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 neuroeffector transmission.
4. *Representation of the Autonomic Nervous System in Spinal Cord and Lower 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 previous parts.
5. *The Centers of Homeostasis in the Mesencephalon and Hypothalamus and their Telencephalic Control*. I will discuss how the functions of autonomic systems that are represented in the spinal cord and lower brain stem are integrated in complex regulatory circuits involving somatomotor, autonomic and neuroendocrine systems (Figure 0.2) that are represented in the mesencephalon, the hypothalamus and the telencephalon. 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) (Note 2), *second*, to textbooks covering the autonomic nervous system or parts of it (Note 3) and, *third*, to selected review articles (Note 4). 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 (Note 5). This book is not intended to extensively describe special fields of the neurobiology of the autonomic nervous system, such as regulation of the cardiovascular system, body temperature, pelvic organs, gastrointestinal tract, etc. Furthermore, it is not intended to discuss the pathophysiology of the autonomic nervous system. However, it is of course the basis to understanding pathophysiological changes in autonomic functions.

## Suggested Reading

Cannon, W. B. (1939) *The Wisdom of the Body, 2nd Revised and Enlarged Edition*, Norton, New York.

Swanson, L. W. (2012) *Brain Architecture: Understanding the Basic Plan*, *2nd Edn*, Oxford University Press, Oxford.

Swanson, L. W. (2013) Basic plan of the nervous system. In *Fundamental Neuroscience*, *4th Edn* (Squire, L. R., Berg, D., Bloom, F. E., et al., eds.) pp. 15–38, Elsevier Academic Press, Amsterdam.

All references cited in the text are available online at www.cambridge.org/janig.

## 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 (1997); Morris and Gibbins (1997); Burnstock and Sillito (2000); Brookes and Costa (2002).
3. Randall (1984); Loewy and Spyer (1990); Ritter et al. (1992); Low (1993); Rowell (1993); Shepherd and Vatner (1996); Appenzeller and Oribe (1997); Blessing (1997); Appenzeller (1999); Undem and Weinreich (2005); Llewellyne-Smith and Verberne (2011); Mathias and Bannister (2013).
4. Jänig (1985, 1986, 1988a, 1995a, 1996a); Jänig and McLachlan (1987); Guyenet (1990, 2006, 2014); Dampney (1994, 2016); Häbler et al. (1994a); Spyer (1994); Kirchheim et al. (1998); Jänig and Häbler (1999, 2003); Folkow (2000); Schreihofer and Sved (2011); Guyenet and Bayliss (2015); reviews in Romanovsky (2018).
5. Low (1993); Robertson and Biaggioni (1995); Appenzeller and Oribe (1997); Appenzeller (2000); Robertson et al. (2012); Buijs and Swaab (2013); Mathias and Bannister (2013).