Autonomic Nervous System

14

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Abstract

The autonomic nervous system and the role it plays in governing the behavior of the cardiovascular system are significant in both its complexity and importance for one's quality of life. The hypothalamus is the brain center which governs all essential "homeostatic" functions of the human body; these integrative functions include control over the autonomic nervous system, various somatic pathways, and the body's hormonal systems. The autonomic nervous system can be considered to have two subdivisions that are considered somewhat antagonistic but also function in a complementary nature; simultaneous changes within the parasympathetic and sympathetic branches of this system allow for rapid and essential changes in cardiac parameters such as heart rate, contractility, and/or stroke volume. Increased sympathetic outflow relative to normal resting conditions most often causes an excitatory response in physiologic parameters (such as increases in heart rate and/or smooth muscle contraction), whereas parasympathetic stimulation usually results in calming adjustments (lower heart rates, decreased contractility, and/or vasodilatation). Alterations of the cardiac and aortic baroreceptors, as well as the autonomic nerves that innervate the heart, are important to consider in many disease states.

Keywords

Sympathetic anatomy • Parasympathetic anatomy • Baroreceptors • Homeostasis • Hypothalamic control • Effector pathways • Heart rate • Stroke volume • Contractility • Arteriolar pressure • Cardiac denervation

14.1 Introduction

The autonomic nervous system coordinates the involuntary control of the viscera and other tissues throughout the body, with the primary exception of skeletal muscle. The hypothalamus is the brain center which governs all essential *homeostatic* functions of the human body; these integrative functions include control over the autonomic nervous system, various somatic pathways, and the body's hormonal systems. Briefly, h*omeostasis* can be defined as the control of the internal milieu, which in general is kept nearly constant within quite narrow limits, despite potential severe perturbations that human bodies can experience (e.g., extreme hot and cold temperatures). The hypothalamus is a small part of the brain considered as a neuronal continuum extending from the midbrain through to the basal regions of the telencephalon. Further, the lateral hypothalamus can be thought to be reciprocally connected with the upper brainstem and the limbic system (these are the brain centers which control emotions, learning, etc.). As such, it receives primary sensory inputs from afferents near the body surface and from internal structures via the ascending spinobulboreticular pathways.

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P.A. Iaizzo (ed.), *Handbook of Cardiac Anatomy, Physiology, and Devices*, DOI 10.1007/978-3-319-19464-6_14

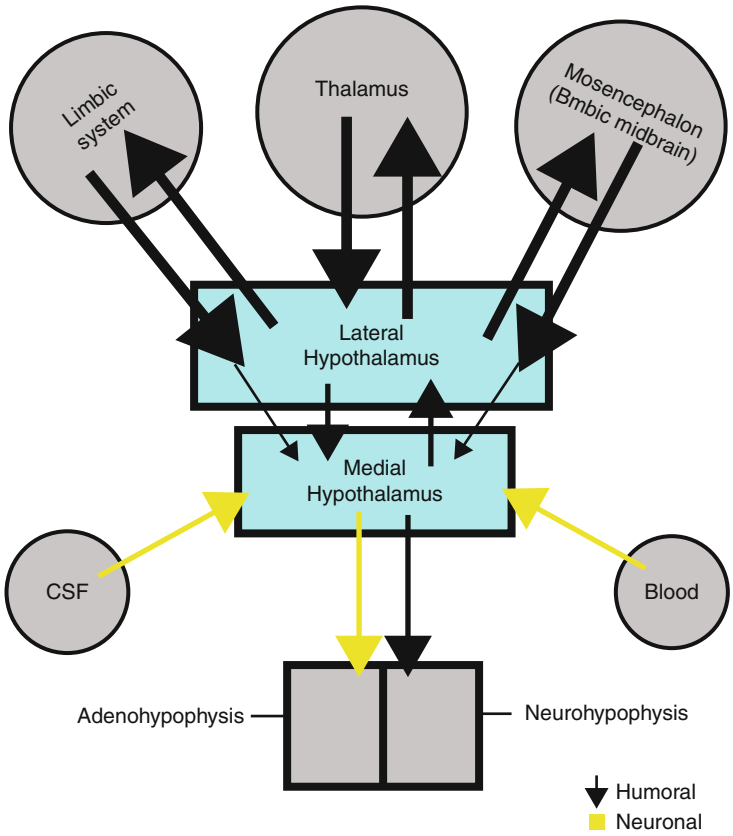

Fig. 14.1 General afferent and efferent pathways/ connections of the hypothalamus (medial and lateral), the pituitary gland (adeno- and neurohypophysis), the limbic system, the thalamus, and the mesencephalon. Note the medial hypothalamus, via the neuroendocrine interface, controls the primary functions of the pituitary gland

In contrast, the medial hypothalamus receives main inputs from the lateral hypothalamic regions. This brain region of the hypothalamus contains specialized neurons important for sensing the conditions of the blood and cerebrospinal fluid. In turn the medial hypothalamus makes numerous connections to the pituitary (hypophysis) and there are two main types: (1) neuronal connections to the neurohypophysis (axonal) and (2) hormonal releases affecting the adenohypophysis (anterior region). Thus, these multimodal connections are referred to as a *neuroendocrine interface* (Fig. 14.1). Also known as the hypothalamo-pituitary system, the activity of most endocrine glands is regulated by hormones from the adenohypophysis (anterior pituitary). The hypothalamus releases both stimulating and inhibitory-releasing hormones. It should be noted that there is a built-in, multilevel, negative feedback system (via blood concentrations).

The tight control of homeostatic functions that are modulated via the hormone system is accomplished by a multilevel, multi-hormone feedback mechanism. For example, the blood levels of releasing hormones and the released hormones can both be sensed within the medial hypothalamus (Fig. 14.2). Interestingly, electrical stimulation of nearly any region in the hypothalamus is likely to cause a cardiovascular response (change in activity). The hypothalamic effects on this system are mediated through both synergistic parasympathetic and sympathetic pathways. Additionally, afferent inputs for this control are many and include those from baro-, chemo-, and mechanoreceptors in the atria, ventricles, aorta, and elsewhere (see below).

In other words, the hypothalamus controls the autonomic nervous system which is organized into parasympathetic and sympathetic subdivisions and integrates efferent and afferent fibers that regulate the activities of the majority of organs (including the heart), glands, and smooth musculature found in the human body. The presynaptic cell bodies of these neurons originate in the gray matter of the spinal column but are classified by fundamental differences. Anatomically, the origin of the sympathetic (thoracolumbar) division of the central nervous system lies between the first thoracic (T1) and the second or third lumbar section (L2 or L3). In contrast, the exiting fibers of the parasympathetic division (craniosacral) originate from both the medulla oblongata and sacral portion of the spinal cord (S2–S4). The primary neurotransmitter released during depolarization is another means of characterizing these two subdivisions of the autonomic nervous system. In the sympathetic branch, norepinephrine is the principal postsynaptic neurotransmitter, whereas acetylcholine is the chief neurotransmitter found throughout the parasympathetic fibers. The primary physiological response induced by each respective neurotransmitter is also a useful way to categorize the divisions of the autonomic nervous system. Such

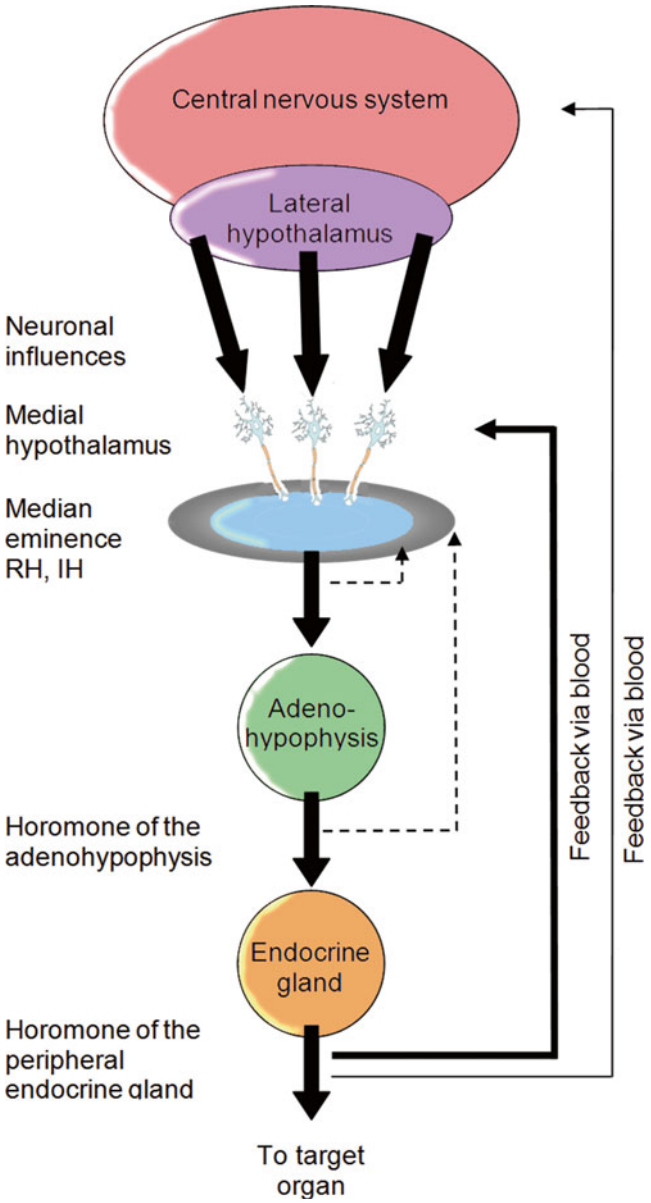

Fig. 14.2 Multilevel feedback loops are employed to regulate both hormone levels and neural responses. For example, the medial hypothalamus can sense blood levels of releasing hormones, the hormone levels released by the pituitary gland, and also those released by target endocrine glands

classifications are important considerations when investigating the autonomic nervous system regulation of the heart.

14.2 Sympathetic Anatomy

Cell bodies of presynaptic sympathetic efferent neurons are found in the paired lateral horns of the spinal cord, an area identifiable between the T1 and L2 or L3 vertebrae. The axons of these cells exit the interior of the spinal cord through ventral rootlets, which coalesce to form the larger ventral roots and eventually become ventral rami. Sympathetic fibers almost immediately divert into white rami communicantes (Fig. 14.3) branching from these spinal nerves, which connect them to paired columns of sympathetic ganglia located on either side of the spinal cord called the *sympathetic trunks*. Vertebrae from T1 to S5 have corresponding pairs of ganglia, each of which are interconnected with both ascending and descending nerve fibers, forming the complex column-like structures; these structures allow for rapid, coordinated, multi-segmental control of the cardiovascular system.

Preganglionic sympathetic neurons synapse within the ganglia of the sympathetic trunk. The 10–20 nm separation distance [1] between presynaptic and postsynaptic cells is called the synaptic cleft, where neurotransmitter is released from synaptic vesicles. Note that acetylcholine is the neurotransmitter released from preganglionic neurons in both the sympathetic and parasympathetic branches of the autonomic nervous system (Fig. 14.4). This compound binds to receptors on postsynaptic cell bodies, causing localized depolarization of cell membranes, which may subsequently initiate action potentials that propagate down the axons of postsynaptic cells. In the sympathetic nervous system, norepinephrine is the primary postsynaptic neurotransmitter released. Such junctions can also be activated by epinephrine, and both can often be found with cotransmitters such as dopamine [2] and/or histamine [3]. Both norepinephrine and epinephrine play important roles during sympathetic stimulation of the heart, as will be discussed in later portions of this chapter.

Three primary paths of travel are commonly identified for presynaptic (also referred to as *preganglionic*) nerve fibers upon reaching the sympathetic trunk. A preganglionic fiber can immediately synapse on the cell body of a postganglionic fiber at the level of the trunk upon which the fiber entered. Preganglionic fibers can also follow a route that traverses through the sympathetic trunk, either ascending or descending to synapse within a higher- or lower-level ganglion. A third but less common path of travel for presynaptic neurons involves passing through the sympathetic trunk completely, then synapsing within a prevertebral ganglion in close proximity to the viscera innervated. In general, presynaptic fibers traveling to the head, neck, thoracic cavity, and limbs will follow one of the first two courses. Innervation of organs and glands located in the abdominopelvic cavity follow the third path through prevertebral ganglia (Fig. 14.3).

A variation of the second path discussed above occurs primarily with innervation of sweat glands, hair follicles, and peripheral arteries. Presynaptic nerves that arrive at the paired sympathetic ganglion, as discussed previously, traverse through the white rami communicantes. Rather than immediately continuing to peripheral regions of the body after synapsing, the postsynaptic neurons next travel through gray (unmyelinated) rami (Fig. 14.3) and exit along large bundles of nerve fibers called *primary rami*. From the pri-

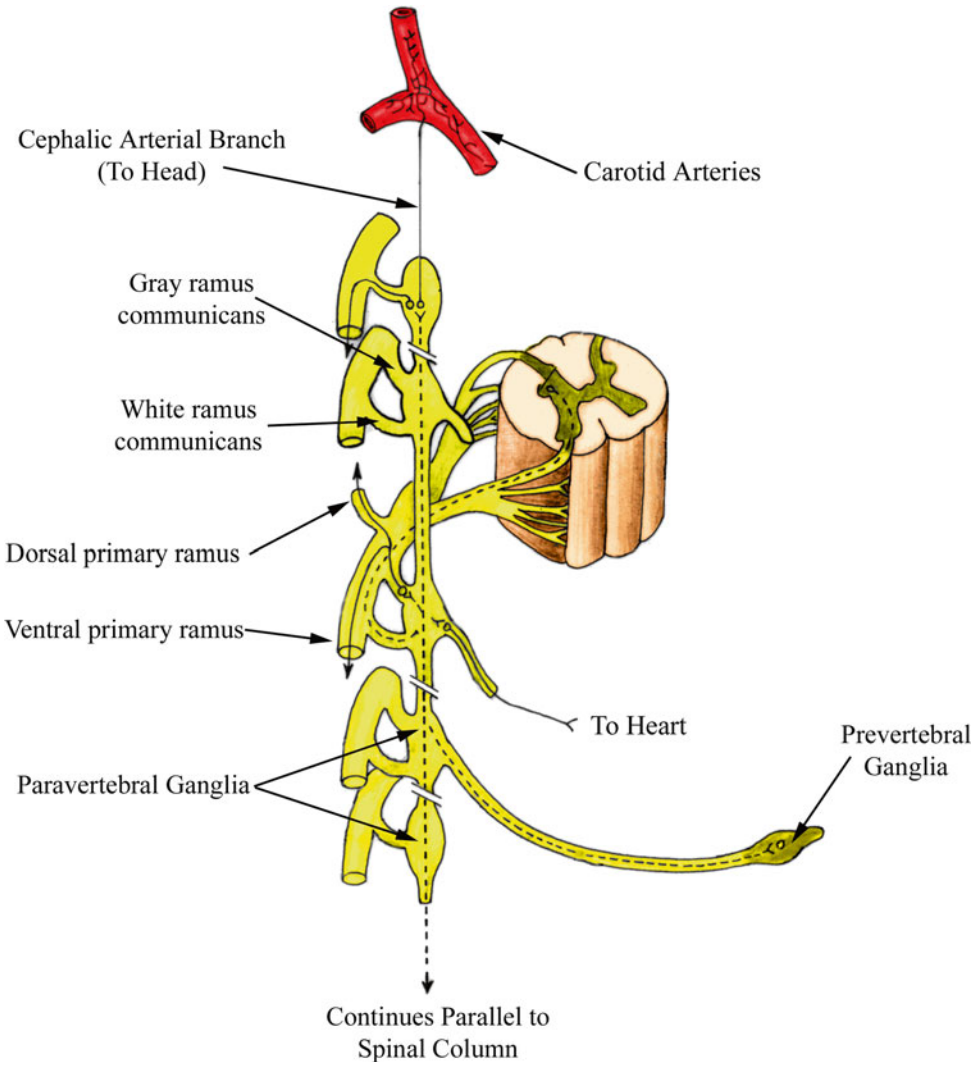

Fig. 14.3 Pathways of sympathetic motor fibers. The three potential paths of travel taken by presynaptic sympathetic motor fibers are shown. Preganglionic fibers traveling to the heart and other areas of the thoracic cavity synapse either immediately upon reaching the sympathetic trunk or traverse to other spinal levels to synapse. Complete passage through the paired trunks also occurs with prevertebral ganglia. Modified from Moore and Dalley [1]

mary rami, smaller nerve branches bifurcate and act to control the vasculature (either vasodilatation or vasoconstriction), hair follicle stimulation, and/or sweating. If the nerves are destined for the head, their cell bodies are located in the superior cervical ganglion and their axons follow the path of the carotid arteries to their respective destinations; the muscles of the eye are also innervated by this collection of sympathetic neurons.

Nerve fibers traveling from the central nervous system to a destination elsewhere in the body are termed *efferents*. In contrast, *afferents* carry sensory information from various locations in the body to the central nervous system. Frequently, these respective paths of travel occur in parallel but the flow of excitation is in the opposite direction; these fibers are typically bunched closely together to form larger nerve branches. The main nerve branches controlling the sympathetic behavior of the heart and lungs are the cardiopulmonary splanchnic nerves, which consist of both efferent and afferent fibers. Efferent nerves navigate a route originating from the ganglia in the upper cervical region (superior, middle, and inferior cervical ganglia) and the upper thoracic (T1–T5) levels of the sympathetic trunk. The inferior, middle, and superior cardiac nerves, in turn, originate from corresponding cervical ganglia and approach the base of the heart before splitting into smaller nerves and distributing themselves throughout much of the myocardium and vasculature. The cardiac plexus can be considered as groupings of the nerve bundles destined to and originating from the heart (Fig. 14.4); they are extremely difficult to visualize with the naked eye.

Incoming postsynaptic sympathetic neurons, which innervate the human heart, are highly concentrated around and near the aortic arch. Some of this innervation occurs throughout the aortic arch itself, as well as at the base of the ascending portion of this vessel. Many branches from these nerves continue down the aorta or under the arch to the pulmonary trunk, where they again diverge and track with the

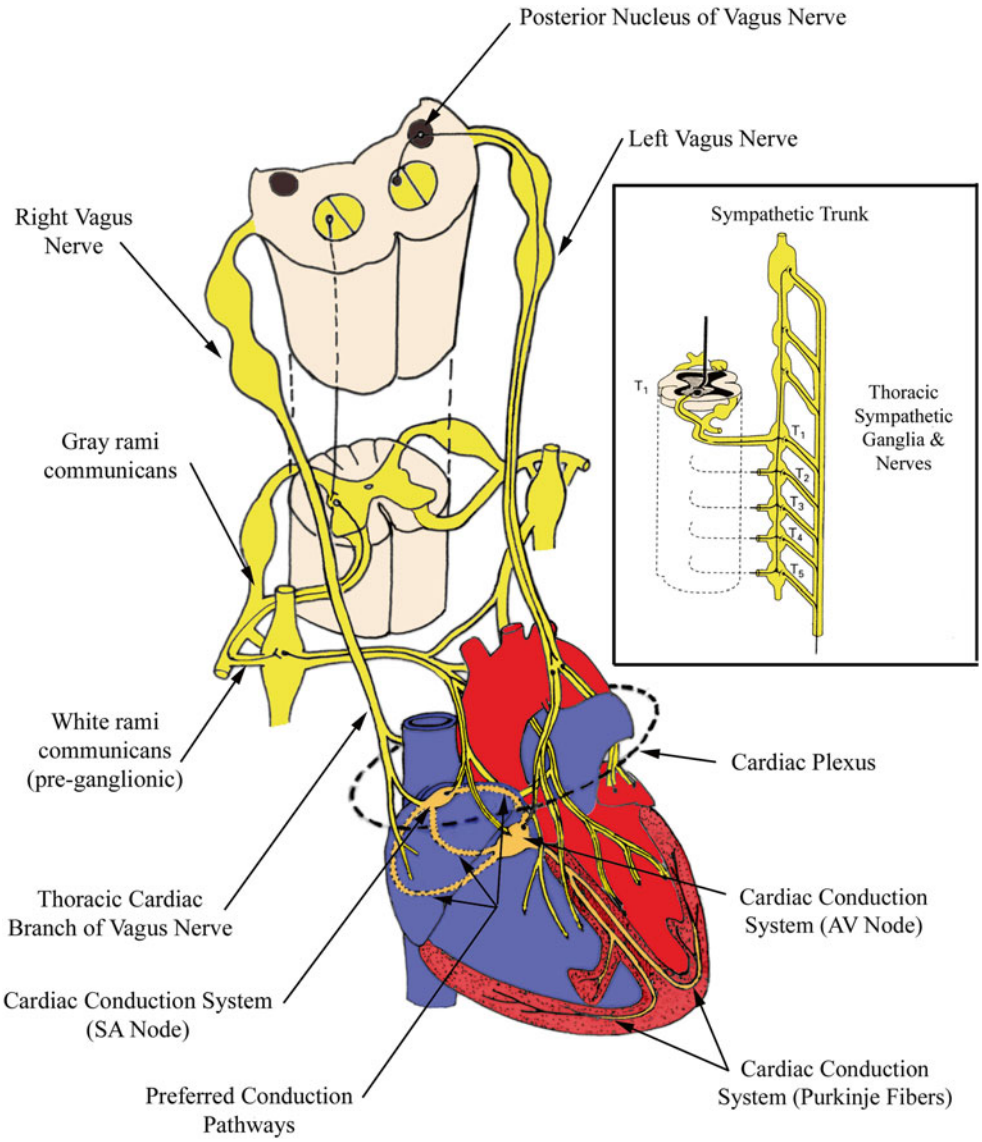

Fig. 14.4 Autonomic innervation of the heart. Vagal innervation of the right atrium can be observed. The area where many axons congregate just prior to innervation of the heart is depicted as the cardiac plexus. Sympathetic fibers branching from an arbitrary vertebral level of the paired sympathetic trunks is also illustrated. *AV* atrioventricular, *SA* sinoatrial. Modified from Martini [4]

pulmonary arteries. Still more neuronal bifurcations have been identified which extend to reach other areas of the heart, including both atria and the right and left ventricles. Sympathetic innervation of both the sinoatrial and atrioventricular nodes is important for control of heart rate, but has not been distinguished in greater concentration at these areas relative to elsewhere in the atria [5, 6]. Such nerves have been identified epicardially, often following the path of the coronary arteries and veins [5, 7]. In general, sympathetic innervation is more highly concentrated in the ventricles than in the atria [8]. Within the ventricles, a higher distribution is observed toward the base of the heart as opposed to the apex, with nerves in the epicardium at a slightly greater concentration than in the endocardium. This latter tendency is also evident in the atria [8].

14.3 Adrenal Medulla

The sympathetic nervous system also controls the hormonal secretions of the paired suprarenal (adrenal) glands lying within the abdomen, considered as components of the endocrine system. Specifically, preganglionic fibers, with their cell bodies located in the lower thoracic (T10–T12) segments of the spinal cord, travel to the adrenal medulla by means of the abdominopelvic splanchnic nerves. It is in the medulla, or central portions of these suprarenal glands, that both norepinephrine and epinephrine are released into the bloodstream [1]. The release of these *catecholamines* into the blood is considered a postsynaptic response initiated from this type of sympathetic

activation. Specifically, the cortex surrounding the medulla portions of the adrenal glands are responsible for producing multiple steroid hormones. As blood drains from the highly vascularized cortex to the medulla, the aforementioned hormones can be used to convert norepinephrine to epinephrine. The respective mechanisms of action for these two similarly structured catecholamines will be discussed later in this chapter.

14.4 Parasympathetic Anatomy

The parasympathetic (craniosacral) nervous system branches from four paired cranial nerves and the lower sacral segment of the spinal cord (S2–S4). The vagus nerve (cranial nerve X) is the main effector pathway for modulating cardiac function, i.e., controlled by input from the parasympathetic subdivision of the autonomic nervous system (Fig. 14.4). Efferent fibers of the vagus nerves originate in the medulla oblongata and weave through the neck alongside the carotid arteries to the thoracic and abdominopelvic cavities, bifurcating many times along the way to innervate an assortment of organs including the heart. More specifically, the efferent fibers of the cranial parasympathetic branch communicate with blood vessels of the head and other viscera; the sacral portion of the spinal cord innervates viscera of the lower abdominopelvic cavity like the urinary bladder and colon, as well as their respective blood vessels.

Unlike the short sympathetic preganglionic fibers, the parasympathetic division of the autonomic nervous system generally has very long preganglionic fibers and short postsynaptic fibers. Hence, the parasympathetic ganglia are often located very proximal to, or actually within, the target organ. As discussed previously, acetylcholine is this branch of the autonomic nervous system and is the primary neurotransmitter released at both preganglionic and postganglionic junctions.

Within the heart, the majority of the parasympathetic ganglia are located near the sinoatrial node and within the conduction tissue surrounding the atrioventricular node [5]. Consequently, the right and left vagus nerves envelope a large and overlapping portion of the atria, where short postsynaptic fibers from both branches act on the conduction centers of the heart (Fig. 14.4). However, the endings of the right vagus primarily innervate the sinoatrial nodal region, while a great number of projections from the left are typically observed innervating the atrioventricular node [5]. In fact, high concentrations of vagal innervation situated within a localized region of epicardial fat near the atrioventricular node have been described for the human heart, and it is hypothesized that nerves located within this "pad" have little effect on behavior of the sinoatrial node [9]. Thus, it is likely that each region is controlled independently of the other. Parasympathetic junctions are also observed in the ventricles, but only at one-half to one-sixth as frequently as sympathetic innervation [8]. Nevertheless, nerves of the parasympathetic division of the autonomic nervous system outnumber those of the sympathetic division in the atria by some 30–60 % [8]. Interestingly, while sympathetic innervation has been described to occur at approximately an equal distribution between the endocardial and epicardial surfaces of the heart, vagal nerve endings are reportedly located at almost twice the density (1.7–1) transmurally (within the myocardium) when compared with their epicardial distribution [8].

14.5 Baroreceptors

The autonomic nervous system plays a vital role in the overall regulation of blood pressure within the human body. Specialized receptors sensitive to changes in arterial diameter are located at various strategic locations within the upper thoracic cavity and neck; these nerve clusters are commonly known as *arterial baroreceptors*. Substantial groupings of such baroreceptors can be found at the arch of the aorta and on the internal carotid arteries (just distal to where the common carotid bifurcates). This focal density of carotid baroreceptors is also referred to as a *carotid sinus*. The majority of receptors are located at areas within these arteries where the walls decrease in thickness, enabling pressure changes to be somewhat magnified at these locations (Fig. 14.5). Under even minimal pressure increases, these large arteries will elicit detectable wall dilatations. In contrast, under decreased pressure, their internal diameters will decline, also resulting in changes of the firing frequencies of these receptors. The axons of these afferent neurons travel from baroreceptors along parasympathetic corridors to the medullary cardiovascular center in the brainstem. Under increases in the mean pressure detected by these arterial baroreceptors, efferent sympathetic stimulation will decrease, which is accompanied by an increase in parasympathetic outflow to the heart. This neural activity is intended to return the mean blood pressure to a normal state. The opposite autonomic response would commence if the mean arterial pressure at the baroreceptor locations decreased. The synergistic functioning, briefly noted here between both divisions of the autonomic nervous system, will be discussed in much greater detail in the following sections. It should be noted that the direct application of pressure to an individual's neck at the site of the carotid sinus can induce a reflex decrease in blood pressure, even to the point of causing unconsciousness, i.e., the so-called *sleeper hold*.

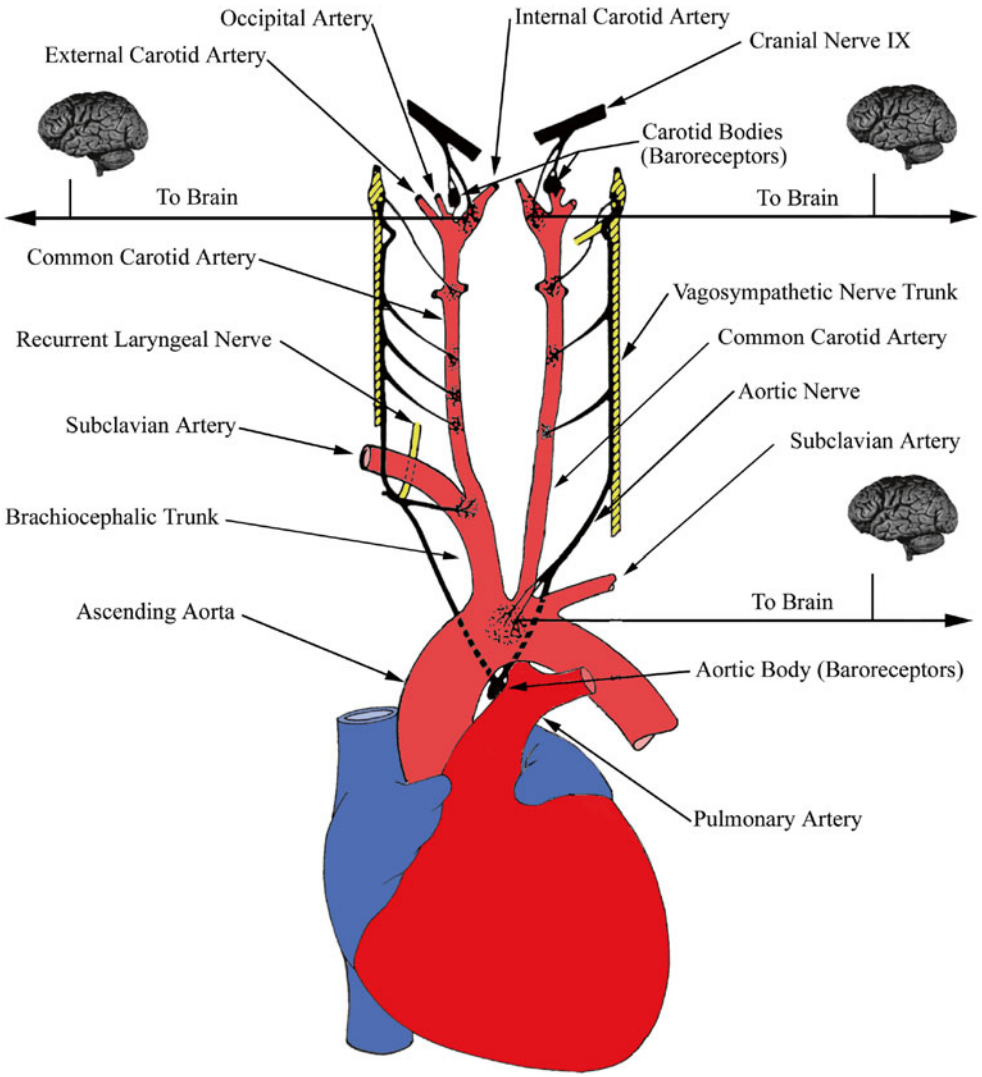

Fig. 14.5 Arterial baroreceptors. Receptors located at the bifurcations of the carotid arteries and aortic arch convey information to the brain and vasculature to help regulate pressure fluctuations. Modified from Mountcastle [10]

14.6 Homeostasis

The tendency to maintain the internal environment of the body at a relatively constant level is known as *homeostasis*. The heart itself exerts perhaps the greatest control on countless parameters involving the circulation of blood throughout the body. The heart communicates with the central nervous system via both branches of the autonomic nervous system. Both the sympathetic and parasympathetic divisions work together in synergistic control of their antagonistic influences, in order to prevent potentially harmful fluctuations in many vital bodily functions. While it is obvious that significant changes do occur, an array of physiologic responses involving the heart (homeostatic control mechanisms) mediated by the autonomic nervous system quickly reverses these changes to return within the reasonable ranges required to maintain overall health. In general, homeostatic control functions are the underlying determinants of the relative degrees of both parasympathetic and sympathetic activation.

14.7 Hypothalamic Control

More specifically, the autonomic control of the heart is greatly influenced by activity within the portion of the brain known as the *hypothalamus*. Afferent fibers from the brainstem (medulla oblongata) and spinal cord convey information via the autonomic afferent system to the hypothalamic nuclei within the central nervous system [11], whereas impulses that leave the hypothalamus travel along efferent fibers to the various sympathetic and parasympathetic ganglia as noted above. Most parasympathetic response signals have been determined to originate from the anterior portions of the hypothalamus, while sympathetic activity stems primarily from the posterior portions [6, 11]. Direct electrical stimulation of specific sites within the hypothalamus can initiate preprogrammed, simultaneous, patterned changes in heart rate, blood pressure, and peripheral resistance [5] (Fig. 14.6).

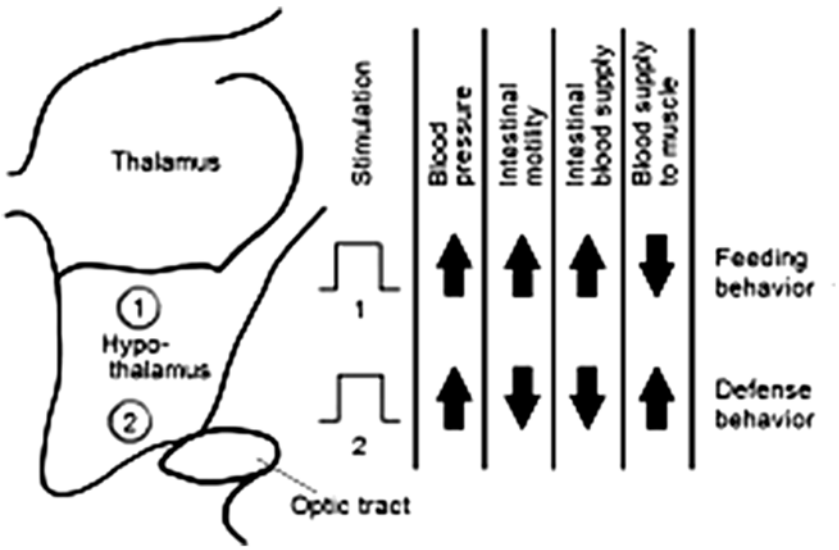

Fig. 14.6 The body's cardiovascular responses are more or less under involuntary control and are thus regulated by the autonomic nervous system (ANS). For example, stimulation of any region of the medial hypothalamus will induce characteristic changes in cardiovascular responses. These patterned responses are commonly associated with innate behavior responses that are also attributed to the hypothalamus, such as feeding or defensive behaviors, which in turn appropriately modulate other body systems under ANS control

As noted above, afferent axons from the aortic and carotid baroreceptors principally travel to the medullary cardiovascular centers, with neural pathways continuing onward to the hypothalamus [6]. Temperature regulation of the body is also centered within the hypothalamus. Thus, during exposure to cold, the hypothalamus initiates appropriate autonomic responses to maintain body temperature, such as vasoconstriction and shivering. The contraction of the peripheral vasculature motivates a redistribution of blood flow to vital organs like the heart and brain, in order to maintain their suitable function [2]. The shiver reflex induced by the hypothalamus increases heat production which, in turn, causes additional adjustments in blood flow and cardiac activity. The opposite outcome occurs during exposure to high degrees of heat, such that sweating is initiated via postganglionic sympathetic neurons and vasodilation of the vasculature supplying the skin is amplified. The regulation of bodily processes is an important responsibility of the hypothalamus, and it performs such tasks via the autonomic pathways, hence regulating countless systems within the body simultaneously. Keeping this relative state of constancy throughout the body regardless of extreme external changes is referred to as *homeostasis*; in nearly all cases, there are direct effects on cardiac performance.

In addition to the influence the hypothalamus has on autonomic pathways, emotional and hormonal changes are controlled in this region of the brain in order to promote homeostasis. The pituitary gland function is also mediated by the hypothalamus, initiating or suppressing hormonal release from this important part of the endocrine system to the rest of the body. Some of these hormones act as cotransmitters in the presence of acetylcholine or norepinephrine during synapses eliciting parasympathetic or sympathetic activity [2], dopamine being one example.

14.8 Effector Pathways to the Heart

Within the myocardium, parasympathetic nerve fibers release acetylcholine upon stimulation. Cardiac cells contain muscarinic receptors embedded within their lipid bilayer, which can activate G proteins found in their cytoplasm upon binding with acetylcholine. Activation occurs when a bound GDP (guanosine diphosphate) molecule is replaced by a GTP (guanosine triphosphate) structure. Subsequently, this response allows the altered protein to bind with potassium channels in the membrane and causes them to open, thus increasing potassium permeability (Fig. 14.7). As a result, heart rate will generally decrease due to an efflux of potassium ions (K^+) from cardiac cells, since the cellular membrane becomes more polarized as the potential moves closer to the K^+ equilibrium potential of −90 mV [6]. This hyperpolarization makes the spontaneous generation of action potentials more difficult and thus slows the rate of firing of the sinoatrial node. Activated G proteins will remain in such a state until GTP is hydrolyzed to form inactive GDP [2, 12].

The type of regulatory control in the case described above involves the direct opening of K^+ channels via G proteins within a cardiac muscle cell. It should also be noted that indirect opening of potassium channels may also occur after acetylcholine binds to the muscarinic receptors. Furthermore, activated G proteins may also cause some increase in the production of arachidonic acid, which acts as a secondary messenger that can result in increased K^+ permeability due to cleavage of membrane lipids [12].

Modulation of G proteins is also an important aspect of the underlying sympathetic effects on cardiac behavior. Sympathetic fibers release norepinephrine at postsynaptic terminals of cardiac muscle cells, and receptors located within the cellular membrane bind with the norepinephrine

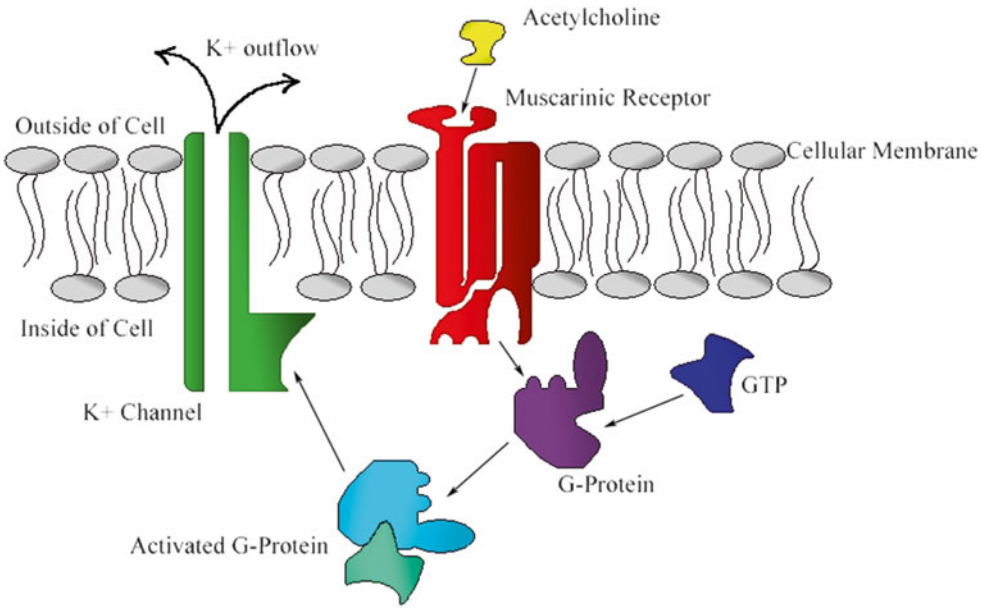

Fig. 14.7 The effect of acetylcholine on cardiac muscle cells. Potassium channels within a cellular membrane are opened as a result of binding an activated G protein. Acetylcholine released by parasympathetic neurons activates these G proteins by binding with muscarinic receptors within the membrane. The effect of norepinephrine on cardiac muscle cells is propagated in a similar manner, with differences as described in the text. *GTP* guanosine triphosphate

to stimulate β_1 adrenergic receptors. Next, G proteins replace GDP at their binding sites with GTP upon activation by the excited β_1 receptors, causing an increase in the production of cyclic AMP within the cardiac myocytes. The increased cAMP levels cause molecules of protein kinase A to phosphorylate large numbers of calcium channels within the cellular membrane. This addition of a phosphate group not only causes Ca^{2+} channels to remain open longer but also allows for a greater number of channels to open, thus contributing to the influx of calcium ions into each cell upon activation [6]. In other words, the threshold for depolarization will be more easily attained due to the greater number of available calcium channels, thus allowing greater calcium incursion during activation and resulting in higher contraction strength.

An advantage of the mechanisms of action involving G proteins is that autonomic modulation can be sustained without constant nerve fiber stimulation. That is, a burst of synaptic activity causing the release of either acetylcholine or norepinephrine can initiate the respective processes described above. For more details on cardiac receptors and intracellular signaling, refer to Chap. 15.

14.9 Specific Sympathetic and Parasympathetic Cardiac Controls

14.9.1 Heart Rate

The rate at which a normal adult heart completes cardiac cycles during rest is approximately 70 beats/min [6]. The heart rate is maintained at this relatively constant value via a continuous firing (resting-rate activation) of the vagus nerve, called *basal* (*or vagal*) *tone*. The heart rate will increase when vagal tone decreases and is further modulated by increased activity of sympathetic nerves to the heart, which releases norepinephrine and causes a rise in the sinoatrial nodal depolarization rate (Fig. 14.8). A rate increase of this nature is referred to as a *positive chronotropic effect*. As stated above, the fundamental cause of this increase in heart rate is due to an increase in activated calcium channels in myocardial cell membranes, increasing the speed at which depolarization occurs. This increased sympathetic outflow can be initiated by a large array of internal and external stimuli, including but not limited to: exercise, an increase in body temperature, trauma, and/or emotional stress. Additionally, a concurrent release of epinephrine from the adrenal medulla can further amplify these same effects on myocardial ion channels, although to elicit a significant rise in heart rate, the amount of the hormone liberated must be fairly substantial [6].

Parasympathetic discharge, in part, increases potassium ion permeability in cardiac myocytes, thus increasing the threshold for depolarization to occur spontaneously particularly within the sinoatrial node; as a result, the heart rate declines (Fig. 14.8). This autonomic neural input predominates during sleep and other sedentary states, eliciting an increase in cardiac cycle time and therefore enabling the heart to expend less energy [2]. In addition to decreasing the slope of the pacemaker potential, parasympathetic stimulation may also induce a so-called pacemaker shift [5]; true pacemaker cells can become more inhibited than the latent pacemakers, thus shifting the initiation of spontaneous depolarization from the true pacemakers to the latent ones [5].

Conduction velocity is the measure of the spread of action potentials through the heart. Parasympathetic stimulation above normal tonic activity also slows cardiac conduction velocity, and this response is termed *negative dromotropic*. It

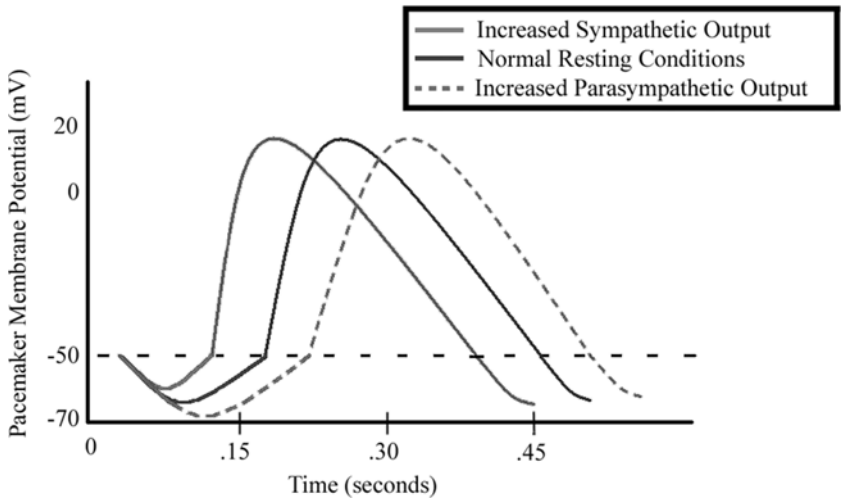

Fig. 14.8 The effects of changes in sympathetic and parasympathetic outflow to the heart. The heart will increase its rate of contraction during increased sympathetic neural stimulation. This decreases the time required for the cardiac pacemaker cells to reach threshold. In contrast, increased parasympathetic outflow will decrease the heart rate and increase the time to threshold

follows that an increase in conduction velocity, which commonly accompanies sympathetic stimulation, has a *positive dromotropic* effect. The atrioventricular node is the location within the heart where conduction speed variations are most notable. The reader is referred to Chap. 13 for more details on specific mechanisms of cardiac pacemaker mechanisms.

The control mechanisms of heart rate are also, in part, dependent on gender [13]. For example, women have been shown to exhibit higher-frequency parasympathetic input (using spectral analysis procedures) than men of similar age, possibly indicating a more dominant control of heart rate via vagal stimulation than their male counterparts [13].

14.9.2 Stroke Volume and Contractility

Like heart rate, the amount of blood ejected from the ventricles during systole is greater when the heart is modulated by an increased sympathetic input (Fig. 14.9). The underlying mechanism for this increased stroke volume is enhanced cardiac myocyte contractility, and the magnitude of this response is strongly affected by preload and afterload conditions, as predicted by the Frank–Starling Law [6]. Such an increase in contractility is characterized as a *positive inotropic* effect. By and large, myocytes increase in length in proportion to their preload, and since they become more elongated, they also have the capability to shorten over this greater distance. The increased amount of shortening leads to an enhanced strength of contraction of the heart by also increasing the number of available cross-bridge formations between the actin and myosin molecules (see also Chap. 12). As described previously, sympathetic excitation also facilitates a larger and more rapid Ca^{2+} influx into cardiac cells, which further augments the degree of overall contraction during systole [12].

Combined with a larger preload, the increased contractility due to calcium ion influx will raise the stroke volume of

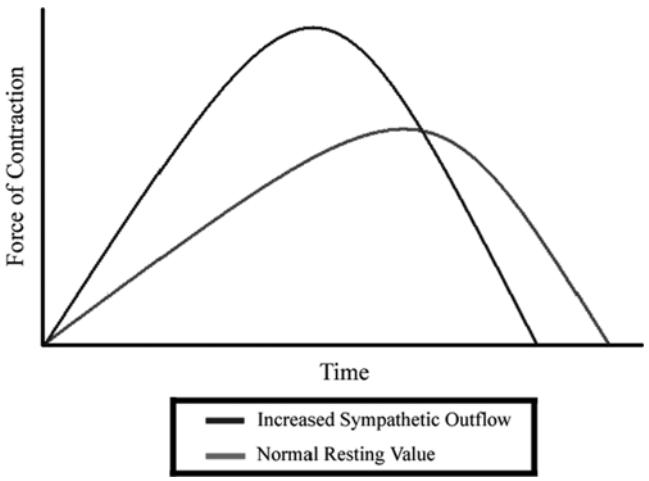

Fig. 14.9 Effect of increased sympathetic stimulation on contractility (see text for details)

the heart (Fig. 14.10). Likewise, the ejection fraction of blood from a given chamber of the heart also elevates accordingly [2]. However, stroke volume is also dependent on afterload created by the relative diameter of the peripheral arteries and will not increase as significantly under sympathetic stimulation if the afterload is elevated due to vasoconstriction. As expected from the often antagonistic nature of the autonomic nervous system, parasympathetic stimulation decreases contractility. However, the relative decrease in contractility is much less significant than the increase in this parameter that sympathetic input provides [2].

An important concept to note involves simultaneous increases in heart rate and stroke volume. Since cardiac output is the product of these two factors, its overall value typically increases with sympathetic stimulation. Conversely, cardiac output normally decreases with a higher rate of parasympathetic input. This happens when the body is in a seden-

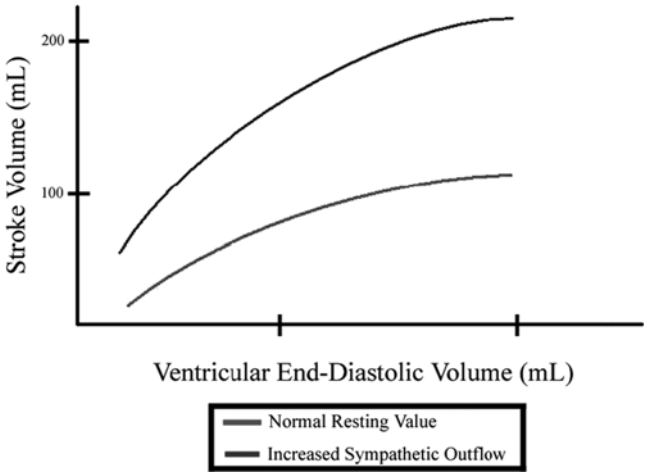

Fig. 14.10 The relative effects of increased sympathetic stimulation on altering stroke volumes (see text for details)

tary state; hence, tissue oxygen and metabolite requirements are not as high.

The time necessary for the heart to fully contract and relax decreases under sympathetic stimulation, due primarily to the larger proportion of the cardiac cycle that is made available for filling. While an increase in heart rate makes the total duration of the cardiac cycle shorter [2], the corresponding rise in contractility causes the muscular contractions to commence more rapidly and with greater force than under resting conditions. This translates to a decrease in the amount of time necessary for contraction of the heart during a complete cardiac cycle. Thus, the heart is relaxed for a greater portion of the cycle, enabling enhanced filling of the chambers to provide a greater volume of blood ejected for each contraction.

14.9.3 Baroreceptor Pressure Regulation

Arterial pressure, or afterload, is regulated in the short term by baroreceptors in the walls of the aorta and carotid arteries. In particular, baroreceptors sense both magnitude and the rate of stretch of arterial walls due to pressure fluctuations within the vessels [6]. The afferent fibers projecting from the baroreceptors convey this information concerning pressure shifts to the autonomic nervous system which, in turn, responds by either increasing or decreasing sympathetic and/or parasympathetic drive. A basal tonic activity can be identified from the receptors, which progresses to the higher cardiovascular centers. The frequency of impulses can be observed to increase or decrease in response to these pressure changes. Decreased arterial dilatation causes sympathetic nerves to increase their discharge rate and escalate the release of norepinephrine, thus increasing heart rate, stroke volume, and peripheral resistance [2]. The baroreceptor reflex functions as a negative feedback system [6], such that a decrease in arterial stretch will induce an increased sympathetic discharge, accordingly raising cardiac output (Fig. 14.11). This, in turn, will increase blood delivered to the vessels containing baroreceptors, increase pressure, and decrease the tonic activity of the receptors. Homeostatic control of arterial pressure is thus administered, since the decreased baroreceptor discharge rate will cause a lowered degree of sympathetic activity and revert the cardiac output back toward its basal value. In other words, the response of the baroreceptors ultimately removes the stimulus causing the initial response [6]. Carotid artery massage is sometimes suggested in an attempt to decrease overall sympathetic tone in the body, e.g., an individual eliciting an arrhythmia due to stress can sometimes convert back to a normal sinus rhythm with this maneuver.

Importantly, long-term pressure regulation is not accomplished via baroreceptor input, due to its adaptive nature (accommodation). That is, if pressure in the aorta and carotid arteries remains elevated for sustained periods, the tonic firing rates will eventually return toward resting values regardless of whether or not the pressures remain elevated. Long-term regulation of pressure involves numerous complex hormonal mechanisms, which are extensively influenced by the hypothalamic and medullary cardiovascular centers.

14.9.4 Arteriolar Pressure Regulation

Because the heart is responsible for delivery of blood to every part of the body, homeostatic control often involves changing the amount of blood provided by the circulatory system to a given tissue, organ, or organ system. For example, the gastrointestinal system normally receives approximately 20 % of the blood pumped by the heart during each cardiac cycle. However, during times of intense stress or exertion, the blood provided to this area may drastically decrease, while the proportion of blood provided to the heart and skeletal muscles may increase notably. Such changes in blood supply are commonly mediated by changes in resistance of the peripheral vasculature (see also Fig. 1.8 in Chap. 1).

At rest, the smooth muscle cells in the walls of arterioles throughout the body remain slightly contracted due to a combination of influences from the central nervous system, hormonal distributions within the vasculature, and/or localized organ effects. The relative degree of contraction within the arterioles is referred to as their basal tone. The stretching of the arterioles due to pulsatile blood pressure is thought to be the cause of the constant state of stress within such vessels [6]. Arterioles innervated by sympathetic fibers possess an increased contractile tone, termed the *neurogenic tone*, due to the sustained activation of these fibers. Control of the vascular

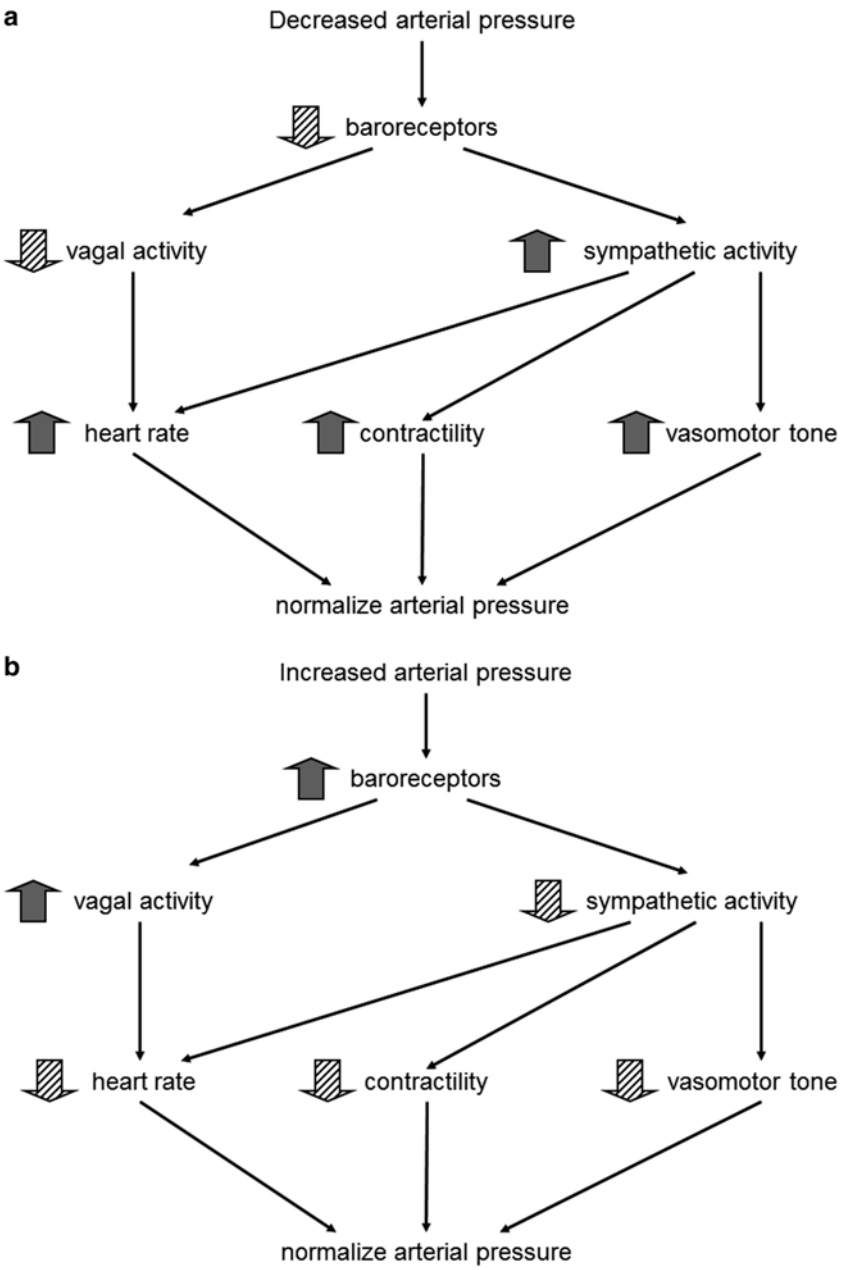

Fig. 14.11 The negative feedback control of blood pressure. In *Panel a*, there is decreased pressure detected by the baroreceptor, and in *Panel b* there is an elevated pressure. The relative responses that occur in order to maintain an overall normal systemic pressure are indicated

peripheral resistance is achieved by varying the firing frequency within these sympathetic fibers. More specifically, postganglionic fibers release the neurotransmitter norepinephrine, which binds to alpha (α_1) adrenergic receptors within the smooth muscle cells in arteriolar walls. Thus, an increase in the firing activity of these neurons produces an increase in norepinephrine levels which, in turn, binds with more α_1 receptors and causes an overall decrease in the diameters of arterioles. In contrast, a lowering of the basal tonic activity causes vasodilation, since less neurotransmitter is available for binding, causing the smooth muscle cells to relax.

The relative firing rates of arteriolar sympathetic neurons innervating a given tissue are also modulated by the need for blood elsewhere in the body. For example, if a hemorrhage occurs in the abdomen which results in significant bleeding, sympathetic activity to that area will increase, causing less blood to flow to these damaged tissues in an attempt to preserve adequate levels of flow to the heart and brain. It should be noted that other regulators exist for the control of vasomotion and the tonic activity of the sympathetic system. Local increases in extracellular cation concentrations, acetylcholine levels, and even norepinephrine itself can act to prevent extreme vasoconstriction. Adrenergic receptors that are pharmacologically different from those in smooth muscle cells [6] have been identified on postganglionic sympathetic neurons themselves and are given an α_2 designation. These

receptors bind with the neurotransmitter and inhibit its release if the amount previously liberated is excessive (negative feedback).

Blood flow through the coronary arterioles is primarily regulated by local metabolic controls that are highly coupled with oxygen consumption. That is, subtle increases in oxygen consumption by the heart will result in an increase in blood flow through the coronaries. Elevated sympathetic activity of the systemic vasculature typically induces a subsequent decrease in the diameter of the peripheral arteries. However, upon sympathetic excitation, vasodilatation predominates in the coronary arterioles instead of vasoconstriction, since oxygen consumption is raised significantly by concurrently inducing higher heart rates and levels of contractility. The factors motivating metabolic regulation therefore outweigh the vasoconstrictive effects of sympathetic innervation of the coronaries.

Blood flow to the skeletal muscle is controlled in a similar manner to that of the coronary arteries, in that local metabolic factors play a vital role in regulating vessel resistance. While increased sympathetic activity may decrease the blood flow to a resting skeletal muscle by a factor of four [6], a muscle undergoing exercise (and thus in the presence of elevated sympathetic activity) can elicit an increase in blood flow almost 20 times that of normal resting values [6]. However, this muscle response must occur in conjunction with a drastic decrease in the blood flow to other tissues or organs, such as those of the abdominal cavity or nonexercising muscles. This course of action allows the total peripheral resistance to remain at a functional level. Homeostatic control during exercise also exists at the skin. In order to cool the body from the increased metabolic heat production, sweat glands become active and cutaneous blood flow increases significantly over the normal resting value in order to dissipate excess body heat. The active vasodilatation is the result of metabolic activity overcoming the increased sympathetic outflow to skin arterioles.

During the digestion of food, remaining sympathetic activity predominates at the vasculature of skeletal muscles and there are increases in blood flow to the stomach and intestines. Parasympathetic discharge to the heart increases, while the sympathetic stimulus declines, lowering the heart rate. This concentration of blood to the abdominal organs facilitates the movement of nutrients to areas of the body in need; this is a good example of how both branches of the autonomic nervous system work together to sustain a level of balance throughout the entire body.

The suprarenal glands can also contribute to vasomotion. Since norepinephrine is released directly into the bloodstream from these endocrine glands, arteriolar constriction in the systemic organs can result. The *fight or flight* response in humans, elicited under stressful or exciting circumstances, originates from the hypothalamus via hormones that travel to the pituitary gland and later the adrenal cortex, where the agent cortisol is released into the bloodstream and adrenal medulla. It is in the medulla that cortisol activates the enzyme necessary to convert norepinephrine to epinephrine, which is released into the bloodstream to amplify increased sympathetic activity [2, 3]. Blood flow to the skin and other internal organs (like the stomach and intestines) is greatly decreased by increasing sympathetic (and decreasing parasympathetic) tonic activity, while flow to skeletal muscles and the heart increases considerably. This process can be thought of as simply delivering blood to the areas of the body most in need to deal with the demanding circumstances. The direct release of these agents into the bloodstream allows for their rapid circulation, which helps contract arterioles along with conventional sympathetic outflow. The "adrenaline rush" one experiences during periods of great tension or exhilaration comes from the adrenal glands.

Flow regulation through the veins and venules in the body is carried out by many of the same mechanisms as that for arterioles. While veins have smooth muscle in their walls, complete with α_1 receptors that respond to norepinephrine, their basal tonic activity is much lower than that observed in arterioles. Thus, venules at rest can be considered to be in a more dilated state. The wall thickness of veins is also significantly less than that found in arteries, which enables the consequences of physical effects to be more prominent in veins. That is, the overall blood volume associated with veins can be greatly affected by compressive forces. For example, in the skeletal muscle, the degree of muscle contraction around the vessel can push large amounts of blood back toward the heart, which enables quicker filling within the right atrium and enables sustained physical activity. If skeletal muscles surrounding veins are relaxed, the venous system can act as a blood reservoir (see also Fig. 1.4 in Chap. 1).

The vasculature within skeletal muscles and the liver can play a unique role relative to homeostasis, via noninnervated β_2 receptors located in their arteriolar walls. Increased blood levels of epinephrine can activate these receptors which, along with G proteins [6, 12], act to catalyze an intracellular chemical reaction resulting in decreased cytoplasmic levels of Ca^{2+} and a hyperpolarization of the cellular membranes. This in turn decreases the contractile machinery sensitivity to Ca^{2+}, thus causing vasodilatation [6]. Vasodilatation in the presence of epinephrine is in contrast to the decrease in vessel diameter caused by the chemically similar compound norepinephrine. β_2 receptors are more sensitive to epinephrine than α_1 receptors [6]. Thus, a small elevation in the concentration of epinephrine in the bloodstream (e.g., provided by the adrenal medulla) can cause vasodilatation. However, if the level of catecholamine increases, the more numerous α_1 receptors will be activated and cause vasoconstriction. It is important to note that there is no neural input to β_2 receptors; therefore, norepinephrine has no effect on their activation.

It can be seen that the parasympathetic and sympathetic effects of the heart and vasculature often elicit opposite physiologic responses yet work in conjunction to synergistically maintain homeostasis.

14.10 Cardiac Denervation

Denervation can be divided into two categories—preganglionic and postganglionic. Preganglionic denervation can be caused primarily by disease or injury of the vasomotor centers in the brain or spinal cord above T10; it leaves intact the postganglionic nerve fiber and many reflexes that occur at the ganglionic level. Preganglionic denervation results not only in loss of centrally mediated cardiac reflexes but also leads to abnormalities in the control of peripheral vascular tone as well as an inability to control blood pressure with changes in body position. Shy–Drager syndrome is a classic example of preganglionic denervation affecting the cardiovascular system [14].

Postganglionic denervation of the heart occurs as the result of several neurodegenerative processes, after certain types of cardiac surgery and/or after cardiac transplantation. Loss of the postganglionic nerve cell body results in Wallerian degeneration of the distal nerve, with loss of axonal integrity and neurotransmitters. Loss of neurotransmitters at the neural junction with the distal target (e.g., cardiac conduction tissue or cardiac myocytes) in turn leads to an increase in neurotransmitter receptor number and density. This, combined with a loss of neurotransmitter metabolism by the degenerated neurons, makes both the cardiac conduction system and muscle hypersensitive to circulating catecholamines (so-called denervation hypersensitivity). It should be noted that cardiac denervation is also considered as a potential means to alter the occurrence of arrhythmias in such patients [15].

Cardiac transplantation is the most complete form of cardiac denervation, resulting in loss of both sympathetic and parasympathetic innervation, with subsequent Wallerian degeneration of the intracardiac nerve fibers [16]. Diabetes is the most common cause of denervation in the general non-transplant population [17]. More specifically, a diabetic neuropathy can result in loss of both sympathetic and parasympathetic efferent and afferent pathways; hence, heart rate variability will diminish. As with other neurodegenerative diseases, neuronal loss is typically patchy and permanent. Infiltrative diseases such as amyloidosis may also lead to cardiac denervation.

14.10.1 Effects of Denervation on Basal Cardiac Function

Loss of tonic parasympathetic vagal inhibition of sinus node depolarization causes a rise in one's basal heart rate and loss of heart rate fluctuation with respiration, known as *respiratory sinus arrhythmia*. The resting heart rate of transplant patients typically is 95–100 beats/min. Further, the reflexes that are mediated primarily through the vagal nerves are absent, including carotid sinus slowing of heart rate, the pulmonary inflation reflex, and the Bezold–Jarisch reflex.

In contrast, resting inotropic state of the cardiac muscle and myocardial blood flow remain somewhat normal after denervation; basal ventricular function is changed minimally. Further, in such patients the measures of systolic contractility (such as dp/dt, ejection fraction, and cardiac output) are usually preserved. Preservation of pump function after denervation may be related in part to an upregulation of beta catecholamine receptors on both myocytes and the conduction system, leading to an amplification of the responses to blood-borne catecholamines [18].

Additionally, coronary blood flow is unchanged at rest and increases normally with exercise. Coronary flow reserve (a measure of maximal coronary blood flow) is normal, although in transplanted animals the responses to ischemia are blunted [19, 20].

Afferent sensation to pain (e.g., from ischemia), chemoreceptor stimulation (e.g., from ischemia, hyperosmolar contrast media), and stretch receptor stimulation (e.g., from pressure overload) are all initially absent. This aspect of denervation is important because coronary occlusion due to transplant-related coronary arteriopathy is common and the absence of anginal pain removes an important warning symptom.

14.10.2 Effects of Denervation on Exercise Hemodynamics

Cardiac denervation results in a blunting of the chronotropic response to exercise. With exercise, heart rate rises due to an increase in plasma catecholamines (released primarily from the adrenal glands) rather than from direct sympathetic stimulation of the sinus node. The heart rate increase is delayed; i.e., heart rate may peak well after the cessation of exertion and remains elevated until the circulating catecholamines can be metabolized (Fig. 14.12).

Exercise or stress also results in a delayed increase in inotropic state, similar to the changes in chronotropic response. Unlike resting ventricular function, peak inotropic state and ejection fraction are typically reduced.

14.10.3 Reinnervation

Sympathetic neural reinnervation of the heart has been observed in nearly all animals undergoing autotransplantation and in most patients undergoing orthotropic transplantation. Reinnervation typically occurs over the aortic and atrial suture lines (left more than right), extending from the base of the heart to the apex. Yet, the rate of reinnervation is typi-

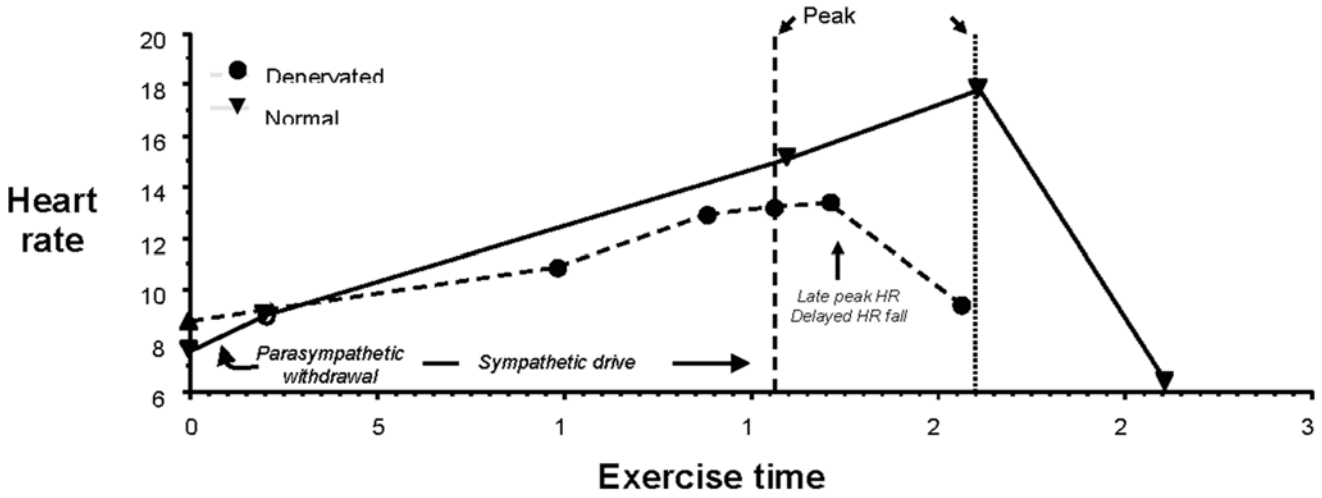

Fig. 14.12 The heart rate response to treadmill exercise is shown for normally innervated subjects (solid line) relative to patients with cardiac denervation after heart transplantation (dashed line). The denervated patients elicit higher resting heart rates, but heart rates rise more slowly with exercise because the induced increase in heart rate is dependent primarily on circulating catecholamines. After cessation of exercise, heart rates in the denervated patients continue to rise briefly and then fall slowly as circulating catecholamines are metabolized

cally slow (years), and in humans it is patchy and most often incomplete. Yet, it has been noted that the anterior wall typically reinnervates earlier and more densely than the rest of the left ventricle [21]. The sinus node reinnervates to some degree in over 75–80 % of patients.

Reinnervation results in partial normalization of the chronotropic and inotropic response to exercise [22, 23]. Reinnervated patients have been observed to exercise longer and have higher maximal oxygen consumption. Additionally, cardiac pain sensation (i.e., angina) also returns, although the regional nature of reinnervation results in reduced or patchy sensation to ischemia in most transplant recipients [24]. Parasympathetic reinnervation has been reported in a small number of transplant recipients; it is accompanied by return of respiratory mediated fluctuation in heart rate and carotid sinus slowing of heart rate.

It should be noted that in some transplant patients, the native sinus node is left intact, yet due to the suture line, these individuals require pacing therapy. There are known causes in which the activity in natively innervated nodes is sensed by a pacing system, which then rate adjusts the ventricular pacing accordingly, Hence, a more functional control of heart rate is maintained relative to the intrinsic activity within the autonomic nervous system.

14.11 Summary

The autonomic nervous system, and the role it plays in governing the behavior of the cardiovascular system, is intrinsically complex and important for sustaining life. The antagonistic nature of the parasympathetic and sympathetic branches of this system allows rapid and essential changes in cardiac parameters such as heart rate, contractility, and stroke volume in order to deliver metabolites and nutrients to tissues and organs that need them at any given time. Increased sympathetic outflow relative to normal resting conditions most often causes an excitatory response in physiologic parameters (such as heart rate and/or smooth muscle contraction), whereas parasympathetic stimulation usually results in calming adjustments (decreased heart rate, contractility, and/or vasodilatation).

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