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Neural control of the circulation

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Thomas GD. Neural control of the circulation. *Adv Physiol Educ* 35: 28–32, 2011; doi:10.1152/advan.00114.2010.—The purpose of this brief review is to highlight key concepts about the neural control of the circulation that graduate and medical students should be expected to incorporate into their general knowledge of human physiology. The focus is largely on the sympathetic nerves, which have a dominant role in cardiovascular control due to their effects to increase cardiac rate and contractility, cause constriction of arteries and veins, cause release of adrenal catecholamines, and activate the renin-angiotensin-aldosterone system. These effects, as well as the control of sympathetic outflow by the vasomotor center in the medulla and the importance of sensory feedback in the form of peripheral reflexes, especially the baroreflexes, are discussed in the context of cardiovascular regulation.

sympathetic; parasympathetic; adrenergic receptors; vascular resistance; vascular capacitance; baroreflex

PART OF THE DISCUSSION about the cardiovascular system in a general physiology course for students in graduate, medical, and health professions schools should include the topic of neural control of the circulation. As an introduction to this topic, it helps if the students have already learned about the autonomic nervous system and have a basic understanding of hemodynamic principals. Neural control is therefore best presented later in the course of the cardiovascular lectures; it follows quite logically after a discussion of local control of the circulation and provides an opportunity for students to think about how local and neural control mechanisms integrate to optimize the function of the cardiovascular system.

The goal of this brief review is to highlight key concepts about neural control of the cardiovascular system that students should incorporate into their rapidly expanding knowledge base. This information should help them to construct a working model of the circulation in their own minds that facilitates their understanding of how the cardiovascular system functions in health and to begin to think about how things can go awry in disease. It is ideal to have one to two full lectures to thoroughly cover the relevant concepts, but a fair amount of ground can be covered in less time by carefully choosing a few of the most salient points to emphasize.

Why Is Neural Control of the Circulation Important?

The peripheral circulation is regulated to distribute cardiac output to the various organs and tissues according to their individual metabolic or functional needs while maintaining arterial blood pressure within a relatively narrow range. Regional blood flows can be efficiently regulated at the local level by the intrinsic ability of vessels to respond to various me-

chanical forces (e.g., wall tension and shear stress) as well as chemical stimuli (e.g., tissue metabolites and O_2). Superimposed on this local control system is another level of regulation governed by changes in central neural activity that adjust cardiovascular function to meet the needs of the body as a whole. Such remote control is an important means to effect rapid changes in blood pressure, in the amount and distribution of cardiac output, and in the distribution of blood volume that are essential to maintain vital perfusion of the heart and brain in the face of physiological and environmental challenges. For example, the seemingly simple act of moving from a supine to standing position requires rapid adjustments in regional blood flows and blood volumes to maintain arterial pressure and prevent cerebral hypoperfusion and syncope. These cardiovascular adjustments cannot be achieved solely by local vascular control mechanisms but require the coordinating activity of central neural outflow to the heart and blood vessels.

Autonomic Nerves and Cardiovascular Control

The autonomic nervous system is responsible for involuntary control of most visceral organs, including the heart and blood vessels. Autonomic motor control is effected by thin, lightly myelinated preganglionic fibers originating within the central nervous system (CNS) at the level of the brainstem or sacral spinal cord in the case of the parasympathetic division and the thoracic or lumbar spinal cord in the case of the sympathetic division. Axons of these preganglionic fibers synapse in autonomic ganglia located outside of the CNS on the cell bodies of very thin, unmyelinated postganglionic fibers, which, in turn, innervate the effector tissues. Both parasympathetic and sympathetic preganglionic fibers are cholinergic, releasing the fast excitatory neurotransmitter acetylcholine, which binds to nicotinic acetylcholine receptors to evoke action potentials on the postganglionic fibers. This general anatomic pattern pertains to both divisions of the autonomic nervous system. However, one important difference is that the parasympathetic division consists of long preganglionic fibers that synapse on short postganglionic fibers arising from ganglia located close to the effector targets. In contrast, the sympathetic division consists of short preganglionic fibers that synapse on long postganglionic fibers arising from the paravertebral chain ganglia or collateral ganglia. Such an arrangement allows sympathetic preganglionic fibers to ascend or descend within the paravertebral chain before synapsing on postganglionic fibers. Consequently, sympathetic discharge can cause diffuse responses involving multiple regional effectors while parasympathetic discharge causes fairly localized responses.

The axons of the postganglionic neurons that innervate cardiovascular tissues (cardiac and smooth muscles) branch extensively, and each branch comes in close contact with numerous effector cells. Found along these nerve branches are enlargements, or varicosities, that contain synaptic vesicles filled with neurotransmitters that are liberated with each action

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potential traveling along the postganglionic axon. This type of synapse, called a synapse en passant, allows a single neuron to innervate many effector cells. This is unlike the highly differentiated neuromuscular junction of skeletal muscle, where a single motor axon innervates a single muscle fiber and neurotransmitter release only occurs at the nerve terminal. The principal neurotransmitter released from the postganglionic parasympathetic fibers is acetylcholine, which binds to muscarinic acetylcholine receptors on target tissues. Effects of acetylcholine are discrete and short lived due to high local concentrations of acetylcholinesterase, which rapidly degrades the neurotransmitter and prevents its appearance in the bloodstream. Sympathetic fibers release norepinephrine, which binds to either α- or β-adrenergic receptors. Norepinephrine has more prolonged and wider ranging effects than acetylcholine. Its fate includes reuptake into the postganglionic terminal, where it can be repackaged in vesicles and released by subsequent action potentials, metabolism by monoamine oxidase or catechol-O-methyl transferase, or diffusion away from the nerve terminals into the bloodstream. Because it is difficult to directly record sympathetic outflow in humans, plasma concentrations of norepinephrine are often used as a surrogate measure of postganglionic sympathetic nerve activity. Caution is warranted, however, as blood levels will be affected by changes not only in the release of noreprinephrine but also in its reuptake and metabolism (clearance from the blood). Furthermore, plasma norepinephrine provides limited insight into regional differences in sympathetic nerve activity as it reflects the contribution of norepinephrine spillover from all potential sources (3).

With regard to autonomic control of the cardiovascular system, it is important to dispel a common fallacy of students that parasympathetic and sympathetic neurons exert equal but opposing effects on all target tissues. Parasympathetic neurons innervate the heart and a small number of blood vessels, limiting their influence largely to the control of cardiac function. In contrast, sympathetic neurons innervate the heart, blood vessels, adrenal glands, and kidneys, providing for widespread direct and indirect control of cardiac and vascular function. Thus, neural control of the cardiovascular system is governed mainly by the activity of the sympathetic nerves, with a limited but important cardiac effect of the parasympathetic nerves.

Autonomic Neural Control of the Heart

The autonomic nervous system exerts a profound influence on the heart due to its ability to modulate cardiac rate (chronotropy), conduction velocity (dromotropy), contraction (inotropy), and relaxation (lusitropy). The chronotropic and dromotropic effects are mediated by both parasympathetic and sympathetic fibers innervating the sinoatrial (SA) and atrioventricular (AV) nodes, whereas the inotropic and lusitropic effects are mediated mainly by sympathetic fibers innervating atrial and ventricular myocytes. The parasympathetic fibers, which travel in the vagus nerve, release acetylcholine, which activates M_2 muscarinic acetylcholine receptors to increase the K^+ conductance of nodal cells. The resultant membrane hyperpolarization decreases the spontaneous firing rate of the SA node and slows conduction in the AV node, thereby slowing the intrinsic heart rate. The sympathetic fibers release norepinephrine, which

binds to β-adrenergic receptors to activate adenylate cyclase, increase intracellular cAMP, and activate PKA. The β_1-adrenergic receptor is coupled to the heterotrimeric G_s protein and is considered the primary means for norepinephrine-induced increases in cAMP concentrations, whereas the role of the β_2-adrenergic receptor is more complex as it is coupled to both G_s and G_i (4). Activation of β-adrenergic receptors increases the slope of diastolic depolarization in the SA node and increases conduction in the AV node, causing heart rate to increase. In myocytes, it increases membrane Ca^{2+} currents and Ca^{2+} release from the sarcoplasmic reticulum (SR) during each action potential, resulting in increased force production. In addition, Ca^{2+} reuptake into the SR is enhanced, thereby accelerating relaxation. Together, the inotropic and lusitropic effects of sympathetic stimulation result in increased stroke volume.

Given the ability to modulate both cardiac rate and stroke volume, the autonomic nerves provide an important remote mechanism to rapidly adjust cardiac output to meet short-term changes in the body's needs. In humans, there is a good deal of tonic vagal discharge and a moderate amount of tonic sympathetic discharge. The interplay of these tonic activities results in a resting heart rate that is $\sim$30% lower than the intrinsic heart rate of 90–100 beats/min and a cardiac output that is $\sim$30% higher than in the absence of sympathetic discharge. Additional vagal discharge can further reduce heart rate and decrease cardiac output, whereas additional sympathetic discharge can increase heart rate and stroke volume and increase cardiac output. Conversely, withdrawal of tonic vagal or sympathetic discharge has opposing effects to increase or decrease cardiac output, respectively.

Sympathetic Neural Control of Blood Vessels

Postganglionic sympathetic nerves are localized to the adventitial-medial border of most arteries, arterioles, and veins throughout the body. Venules and capillaries, which lack smooth muscle, are not directly innervated by sympathetic nerves. Norepinephrine released from the sympathetic nerve terminals binds to α_1- or α_2-adrenergic receptors located on vascular smooth muscle cells to increase intracellular Ca^{2+} either by causing release of Ca^{2+} from the SR or by increasing flux through plasmalemmal Ca^{2+} channels (4). This rise in Ca^{2+} causes contraction of the smooth muscle via the activation of calmodulin-dependent myosin light chain kinase and the subsequent phosphorylation of myosin light chain, which is required for the activation of myosin ATPase and binding of myosin to actin filaments. In vessels that contain more than one layer of smooth muscle, only the outermost cells receive sympathetic innervation. Smooth muscle cells of the inner portions of the medial layer contract due to the diffusion of norepinephrine and cell-to-cell communication mediated by gap junctions.

In addition to norepinephrine, vascular sympathetic nerves also may contain neuropeptide Y (NPY) or ATP, which can be released as cotransmitters. Both can produce constriction by activating vascular NPY Y_1 receptors or purinergic P_2X receptors, respectively, and increasing intracellular Ca^{2+}. NPY also may potentiate the constrictor effects of norepinephrine and ATP. The contribution of these cotransmitters to sympathetic

vasoconstriction varies among vascular beds and with the relative strength and pattern of sympathetic discharge (8).

Like the autonomic nerves that innervate the heart, the sympathetic nerves innervating the vasculature also display tonic activity, which sets a background level of vasoconstriction. Increasing sympathetic outflow beyond this tonic level causes more vasoconstriction, whereas withdrawing sympathetic tone causes less vasoconstriction, i.e., causes vasodilation. This latter point explains why autonomic control of most blood vessels can be effected solely by the sympathetic vasoconstrictor nerves without any innervation by parasympathetic vasodilator nerves. As pointed out in a previous *Refresher Course* report (7), this concept of baseline neural tone also is important for understanding the autonomic reflexes that control cardiovascular function, which will be briefly discussed later in this review.

The functional effect of sympathetically mediated constriction of the peripheral vasculature depends on the type of vessel involved. The arterioles, which constitute the major resistance vessels and are composed of one or more layers of smooth muscle, play a key role in regulating regional blood flows. To demonstrate the robust effect that constriction of the resistance vessels can have on blood flow, it is helpful to briefly review Poiseuille's formula, which predicts flow through a long narrow tube: flow = $(P_i - P_o)\pi r^4/8\eta L$, where $(P_i - P_o)$ is the pressure difference along the tube, r is tube radius, η is viscosity, and L is tube length. This is solely to remind students that flow varies directly (and resistance inversely) with the fourth power of the vessel radius. As a result, even small changes in vessel caliber can have relatively large effects on vascular resistance and blood flow. Sympathetic neural control of arteriolar resistance therefore offers a powerful mechanism to regulate regional blood flows to individual organs and tissues. As the arterioles are the major contributors to total peripheral resistance, sympathetic control also plays a principal role in the regulation of systemic blood pressure (blood pressure = cardiac output × total peripheral resistance).

Although most vascular beds are innervated by sympathetic nerves, they are not equally responsive to changes in sympathetic neural activity. In general, arterioles of the skin, muscle, renal, and splanchnic circulations show robust constriction in response to sympathetic activation, whereas cerebral and coronary arterioles are less responsive. Teleologically, such differential responsiveness serves to redistribute cardiac output by constricting nonessential vascular beds while preserving flow to vital organs in the setting of uniform discharge of the sympathetic nervous system. However, numerous factors can influence neurogenic constriction of vascular beds, individual vessels, and even different segments of the same vessel. These include the density of sympathetic innervation, density and subtype of adrenergic receptors, differences in norepinephrine kinetics, release of cotransmitters, and local factors such as the degree of basal tone, the concentrations of vasoactive tissue metabolites, and vessel size and structure (4, 6, 10).

In contrast to arteries and arterioles, veins contain less smooth muscle and receive a sparser sympathetic innervation. They are more distensible and able to accommodate large volumes of blood and therefore serve primarily as capacitance vessels. Because volume varies directly with the square of the vessel radius, changes in the caliber of the veins is an effective means to change tissue volume. Sympathetic constriction of capacitance vessels is therefore an important mechanism to decrease tissue blood volume. Blood that is forced out of the veins returns to the heart, increasing end-diastolic volume and, via the Frank-Starling mechanism, increasing stroke volume and cardiac output. As ~20% of blood volume is located in the veins of the splanchnic circulation, translocation of blood from this venous reservoir due to sympathetic venoconstriction is a particularly effective way to quickly redistribute blood from the venous side to the arterial side of the circulation.

Adrenergic Receptor Subtypes and Sympathetic Neural Control

As discussed above, the basic conceptual framework for sympathetic control of the cardiovascular system is that neurally released norepinephrine acts on β-adrenergic receptors in the heart to modulate cardiac function and on α-adrenergic receptors in the blood vessels to modulate arteriolar resistance and venous capacitance. This foundation can readily be expanded upon by introducing additional roles of the α- and β-adrenergic receptors as time permits. Nine subtypes of adrenergic receptors (α_{1A}, α_{1B}, α_{1D}, $\alpha_{2A/D}$, α_{2B}, α_{2C}, β_1, β_2, and β_3) have now been identified by molecular cloning, but the functional role of each receptor subtype has not been fully elucidated (4). Whereas both postjunctional α_1- and α_2-adrenergic receptors have been implicated in sympathetic vasoconstriction, the specific receptor subtypes that are involved appear to vary among vascular beds, between large and small vessels, between arteries and veins, and even among species. In general, α_{1A}-, α_{1D}-, $\alpha_{2A/D}$-, and α_{2B}-receptor subtypes have been implicated most often in the regulation of vascular smooth muscle. There are also prejunctional α_2-adrenergic receptors on the sympathetic nerve terminals that provide feedback inhibition of norepinephrine release and CNS α_2-adrenergic receptors in the brain stem that act to inhibit central sympathetic outflow. Activation of these neural adrenergic receptors, which are thought to be mainly $\alpha_{2A/D}$- and α_{2C}-receptor subtypes, reduces sympathetic vasoconstriction.

Many blood vessels also express all three β-adrenergic receptor subtypes with the β_2-receptor subtype predominating in most. Activation of vascular β-adrenergic receptors causes vasodilation; however, these receptors are not thought to be directly innervated by sympathetic nerves in most vessels and instead are activated by circulating catecholamines. Prejunctional β_2-adrenergic receptors that facilitate norepinephrine release also have been identified, but the physiological significance of these receptors remains controversial.

Sympathetic Neurohumoral Control

In addition to the rapid, direct effects of the sympathetic nerves to constrict arteries and veins and to modulate cardiac function, the sympathetic nervous system also exerts more prolonged, indirect effects on the cardiovascular system by activation of several powerful humoral systems. These include the sympathoadrenal system and the renin-angiotensin-aldosterone system (RAAS).

Sympathetic preganglionic neurons innervate chromaffin cells of the adrenal medulla, which essentially act as postganglionic neurons to synthesize and release mainly epinephrine (~80%) along with norepinephrine (~20%) into the bloodstream. These circulating catecholamines contribute to cardio-

vascular regulation by activating cardiac and vascular adrenergic receptors. The physiological effects of circulating norepinephrine are similar to those of neurally released norepinephrine: vasoconstriction mediated by α-adrenergic receptors and cardiac intropy mediated by β-adrenergic receptors. Epinephrine activates both α- and β-adrenergic receptors, but the net effect on vessels possessing both receptor types depends on the concentration of epinephrine present, the relative numbers of each receptor type, and the relative sensitivities or affinities of each receptor type. High concentrations of epinephrine can cause vasoconstriction in skeletal muscle, but with physiological levels the resistance vessels of skeletal muscle, cardiac muscle, and liver dilate, whereas those of the kidney, skin, and gastrointestinal tract constrict. Thus, one of the important physiological responses to epinephrine is redistribution of cardiac output among organs.

Another key neurohumoral system that is regulated by the sympathetic nervous system is the RAAS. Some of the postganglionic sympathetic nerves that travel to the kidney innervate the juxtaglomerular granular cells found in the walls of the afferent arterioles. Increased renal sympathetic nerve activity stimulates β_1-adrenergic receptors on juxtaglomerular cells to cause release of renin into the bloodstream. Circulating renin acts in concert with angiotensin-converting enzyme to convert angiotensinogen into angiotensin II, which can modulate cardiovascular function by *1*) acting on the adrenal cortex to stimulate the secretion of aldosterone, which increases renal Na^+ and water reabsorption, thereby increasing blood volume; and *2*) causing constriction of arterioles, which increases peripheral resistance and blood pressure. Both of these effects of angiotensin II are mediated by the activation of angiotensin type 1 receptors. Angiotensin II also can enhance sympathetic neurotransmission by effects at the level of the ganglia and nerve terminals as well as by influencing central neural processing via the circumventricular organs (2).

Central Integration of Autonomic Outflow

The activity of the autonomic nerves that regulate cardiovascular function is determined by a network of neurons located in the medulla oblongata that receive inputs from *1*) other central structures including the hypothalamus, cerebral cortex, and medullary chemoreceptors; and *2*) peripheral reflexes arising from baroreceptor, chemoreceptor, mechanoreceptor, thermoreceptor, and nociceptor afferents located in the blood vessels, heart, lungs, skeletal muscles, skin, and viscera (5). The descending signals from higher brain centers and afferent sensory signals from the large systemic arteries, cardiopulmonary region, and some of the viscera have their first synapse in the nucleus tractus solitarius (NTS) in the dorsomedial region of the medulla. Other afferent inputs from the skin and skeletal muscles are transmitted to the medullary vasomotor centers via the spinal cord. Neural pathways from the NTS project to the ventrolateral medulla (VLM), which is the primary central site that regulates sympathetic outflow. The rostral VLM contains excitatory neurons that synapse on the sympathetic preganglionic neurons in the intermediolateral (IML) gray column of the spinal cord, whereas the caudal VLM contains inhibitory neurons that project to the rostral VLM. Medullary control of vagal outflow to the heart is also mediated by NTS neurons that synapse on preganglionic para-

sympathetic neurons in the dorsal motor nucleus of the vagus and the nucleus ambiguus.

Even a brief discussion of the various neural inputs to the medullary vasomotor center should stimulate an appreciation of the importance of this region for autonomic control of the cardiovascular system (5). Of the peripheral reflexes that provide feedback regulation of autonomic outflow, the arterial baroreceptor reflex is arguably one of the most important given its role in blood pressure homeostasis and should be covered in an introductory-level physiology course. If time permits, cardiopulmonary reflexes that regulate blood volume and arterial chemoreflexes that regulate ventilation can also be discussed.

Arterial Baroreflex

The arterial baroreflex is a classic example of a negative feedback system and is designed to buffer beat-to-beat fluctuations in arterial blood pressure from an internal set point or baseline. This sympathoinhibitory reflex is stimulated by acute changes in arterial blood pressure that are sensed by stretch receptors (baroreceptors) in the vessel wall of the carotid sinus and aortic arch. Afferent baroreceptor discharge is relayed from the carotid sinus via the glossopharyngeal nerve and from the aorta via the vagus nerve, together commonly referred to as the buffer nerves, to the NTS, which evokes changes in efferent sympathetic and parasympathetic outflow to the heart and blood vessels that adjust cardiac output and vascular resistance to return blood pressure to its original baseline. Thus, increases in arterial pressure stimulate afferent baroreceptor discharge, causing reflex inhibition of efferent sympathetic outflow to the blood vessels and heart and activation of parasympathetic outflow to the heart. The resultant decreases in vascular resistance, stroke volume, and heart rate will reduce arterial pressure back to baseline. Decreases in arterial pressure have the opposite effect, evoking reflex increases in peripheral resistance, stroke volume, and heart rate to restore arterial pressure.

As the arterial baroreceptors are very sensitive to the rate of stretch of the vessel wall, their discharge increases rapidly during early systole and decreases during late systole and early diastole. These phasic responses become more evident at lower blood pressures, when the overall frequency of baroreceptor discharge is reduced, and less evident at higher pressures, when the frequency of discharge is increased. The relationship between afferent baroreceptor discharge and arterial pressure is sigmoidal, with a threshold pressure for activation of baroreceptors at ~50 mmHg and a maximal response at ~180 mmHg. Within the normal operating range, it should be noted that the most sensitive part of this relationship (i.e., the steepest portion of the curve) occurs just above and below baseline blood pressure, which is usually ~100 mmHg. A similar, but inverse, relationship exists between arterial pressure and efferent sympathetic nerve activity or heart rate. By juxtaposing the afferent and efferent baroreflex response curves, it is easy to appreciate that even small changes in arterial pressure from baseline will evoke large, but directionally opposite, changes in afferent baroreceptor discharge and efferent sympathetic nerve activity. This should reinforce the concept that the baroreflex is an extremely effective feedback mechanism to rapidly buffer fluctuations in baseline blood pressure.

A property of the arterial baroreflex that merits discussion, if time permits, is that it can be reset to operate around a new

baseline blood pressure (2, 7). This resetting can be acute or temporary, for example, during exercise, when the efferent baroreflex function curve shifts to the right and upward without a reduction in sensitivity. This adaptive response permits blood pressure, efferent sympathetic nerve activity, and heart rate to remain at higher levels during the period of exercise and then to decrease back to baseline levels at the end of exercise. Resetting can also be chronic, for example, during the development of hypertension as the baroreflex function curve gradually shifts to the right to operate around the new prevailing blood pressure. Over time, as arterial pressure remains elevated, the sensitivity of the baroreflex may also be reduced, rendering it less able to buffer acute pressure fluctuations.

Cardiopulmonary Baroreflex

Stretch receptors are also found in the low pressure portions of the circulation, primarily in the walls of the atria and pulmonary arteries, where they respond to changes in central blood volume. Similar to the baroreceptors in the large systemic arteries, these receptors are activated by distension of the vessel wall giving rise to afferent signals transmitted via the vagus nerve to the vasomotor center and resulting in reflex inhibition of efferent sympathetic outflow. Thus, the cardiopulmonary baroreceptors serve to minimize changes in arterial blood pressure in response to changes in blood volume. In addition, increased discharge of the cardiopulmonary baroreceptors decreases renal sympathetic outflow and pituitary release of vasopressin, thereby decreasing Na^+ and water reabsorption by the kidneys, increasing urine volume, and ultimately reducing blood volume. As changes in blood volume affect cardiac output and arterial pressure, this provides an additional mechanism by which the cardiopulmonary baroreflex contributes to blood pressure regulation.

Arterial Chemoreflex

Chemoreceptors located in carotid bodies at the bifurcation of the common carotid arteries and in aortic bodies in the region of the aortic arch respond to changes in arterial P_{O_2}, P_{CO_2}, and pH. Although primarily involved in regulating ventilation, they can also influence systemic vascular resistance because afferent signals are conveyed to both the respiratory and vasomotor centers in the medulla. Decreases in P_{O_2} and pH or increases in P_{CO_2} cause increased afferent chemoreceptor discharge, which excites the respiratory center to reflexly increase ventilatory rate and volume and excites the vasomotor center to reflexly increase sympathetic outflow. If blood pressure is within its normal range, the chemoreflex does not evoke a powerful cardiovascular response because of the predominant effect of the inhibitory arterial baroreflex. However, if blood pressure is low, generally below 80 mmHg, activation of the chemoreflex potentiates the vasoconstriction evoked by the baroreflex and helps to restore blood pressure to normal. In patients with obstructive sleep apnea, excessive sympathetic outflow caused by repeated chemoreflex activation by hypoxia and hypercapnia is associated with an increased risk of hypertension (1, 5).

Summary

The role of the autonomic nerves in cardiovascular regulation merits discussion in a general physiology course as neural control provides a powerful mechanism to effect rapid changes in cardiac and vascular function that are essential to maintain blood pressure and to appropriately distribute cardiac output in response to physiological and environmental challenges. Key concepts to convey include the following: *1*) the limited influence of the parasympathetic cholinergic nerves to cause bradycardia coupled with the widespread influence of the sympathetic adrenergic nerves to enhance cardiac rate and contractility, increase arteriolar resistance, decrease venous capacitance, and increase blood volume via renal Na^+ and water reabsorption; *2*) the predominant role of the sympathetic neurotransmitter norepinephrine acting on vascular α-adrenergic receptors and cardiac β-adrenergic receptors; and *3*) the importance of tonic sympathetic discharge and its modulation by peripheral reflexes, especially the baroreflexes. Useful resources include the Berne and Levy (10) and Guyton and Hall (6) textbooks of physiology and recent review articles, some of which also address the effects of aging (9, 12) and disease (1, 5, 11) on the neural control of the circulation.

DISCLOSURES

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