

# AUTONOMIC NERVOUS SYSTEM PHYSIOLOGY

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## HISTORICAL CONSIDERATIONS

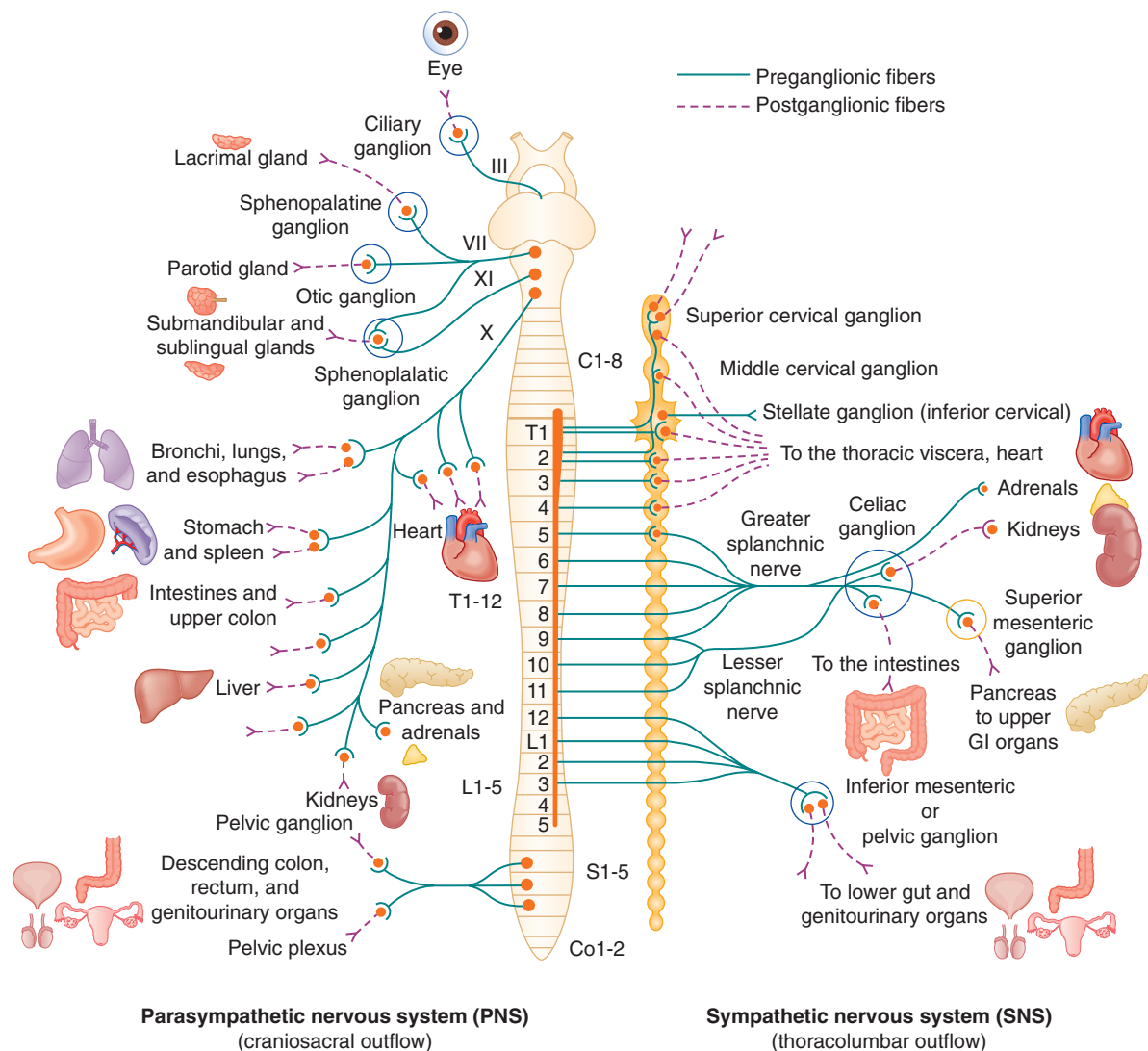
A specialized taxonomy of the autonomic nervous system (ANS) has been developing since the time of Galen (AD 130-200). In the early 1900s, Langley first referred to the ANS.<sup>1</sup> He used the term *sympathetic nervous system* (SNS) as described by Willis in 1665, and introduced the second division as the *parasympathetic nervous system* (PNS) in 1921.<sup>2</sup> Although Langley initially described only the visceral motor system (efferent fibers), the existence of visceral reflex arcs necessitated the inclusion of the sensory (afferent) portions of the ANS.<sup>3</sup> Early anesthesia textbooks dealt with the practice of anesthesia, elucidating basic considerations, pharmacology and techniques, but did not contain explicit information dealing with the ANS. The evolution of the comprehensive anesthesia textbook has led to extensive chapters on the ANS.<sup>2,4</sup>

The ANS maintains cardiovascular, thermal, and gastrointestinal homeostasis. A firm understanding of the basic anatomy and physiology of the ANS forms an important foundation for the practice of anesthesiology. ANS structure, function, and reflexes are critical to the support of the circulation under anesthesia. This chapter reviews anatomy and physiology of the ANS relevant to anesthesia.

## ANATOMY AND PHYSIOLOGY

ANS anatomy is comprised of central control and feedback areas, sensory receptors, peripheral effectors, and reflex conduction pathways. In addition, complex interactions occur between the ANS and the endocrine system (Chapter 30).<sup>4</sup> The renin-angiotensin system, antidiuretic hormone, glucocorticoid and mineralocorticoid responses, and insulin interact via an increasing number of receptor subtypes to maintain physiologic homeostasis (Figure 12-1).

There are no distinct centers of autonomic function in the cerebral cortex. However, input from various sensory systems can impact higher cortical centers, be processed, and result in efferent autonomic activity. Tachycardia and peripheral vasoconstriction heralding a “fight-or-flight” response or a vasovagal response (fainting) are well-known examples of this higher cortical sensory processing.<sup>5</sup> External stimuli representing a threat or danger are detected by the senses of hearing, touch, smell, or sight. These signals are sent to the



**Figure 12-1** Schematic representation of the autonomic nervous system consisting of the parasympathetic nervous system (*left*) and the sympathetic nervous system (*right*).

brainstem, where reflex responses are processed in the hypothalamus and the limbic forebrain. Higher cortical centers provide descending input to the paraventricular nucleus of the hypothalamus, which has projections to sympathetic and parasympathetic nuclei. Chronic stress alters these structures and their function leading to both sensitization and habituation of the stress response.<sup>6,7</sup>

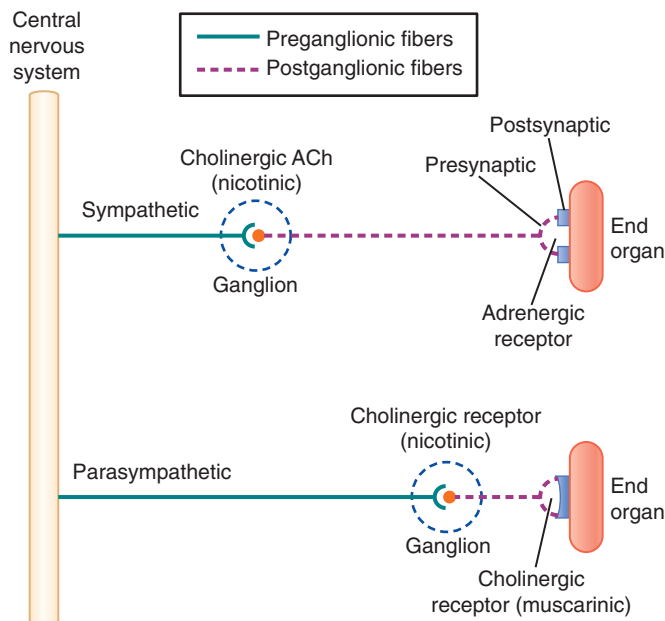
The hypothalamus is the midbrain center that processes sympathetic and parasympathetic functions, temperature regulation, fluid regulation, neurohumoral control, and stress responses. Hunger, sleep, and sexual function are also regulated by the hypothalamus, dependent upon both cortical input and complex feedback control. The anterior hypothalamus controls temperature, while the posterior hypothalamus is involved in water regulation. The hypothalamic-pituitary axis is a part of the ANS that ultimately regulates long-term blood pressure control and stress responses.<sup>7</sup>

The output centers of the ANS reside in the medulla oblongata and the pons of the brainstem. Immediate control of blood pressure, heart rate, cardiac output, and ventilation is organized and integrated in specific nuclei. Tonic impulses

from nuclei like the nucleus tractus solitarius maintain blood pressure and respond to afferent signals from the sensory side of the ANS. These afferent impulses from the vagus (X) and glossopharyngeal (XI) nerves result in vasodilation and bradycardia (see section on ANS reflexes).

The ANS is anatomically and functionally divided into two complementary systems, the SNS and the PNS (see Figure 12-1). The peripheral SNS is controlled by the thoracolumbar segment of the spinal cord, while PNS control arises from the brainstem nuclei and sacral segments (see Figure 12-1). Activation of the SNS produces diffuse physiologic responses, while the PNS exerts local control of innervated organs.<sup>8</sup>

Both systems have efferent pathways through peripheral ganglia; the SNS ganglia are located close to the thoracolumbar spine, and the PNS ganglia are situated near or inside the innervated organs (see Figure 12-1; Figure 12-2). Ganglia serve as synaptic relay stations, and in the SNS coordinate an efferent mass action response through signal amplification. Thus one preganglionic SNS fiber can activate 20 to 30 postganglionic sympathetic neurons and their fibers. In contrast, PNS preganglionic fibers terminate in ganglia located in



**Figure 12-2** Differences between the location of the ganglia in the sympathetic and parasympathetic branches of the autonomic nervous system. The 22 paired sympathetic ganglia are located close to the vertebral column in the sympathetic chain. The unmyelinated postganglionic fibers innervate their respective organs. The exception is the adrenal gland, where the sympathetic preganglionic nerve fibers travel directly to the adrenal medulla. The parasympathetic preganglionic fibers travel directly to the organ of innervation, to synapse with postganglionic neuronal cell bodies.

proximity to the innervated organs and affects only one to three postganglionic neurons.<sup>2</sup> The close proximity of PNS ganglia to their effector organs is the anatomic basis of the more focused and specific responses elicited by PNS activation.

Most organ systems are affected by both the SNS and the PNS. Different organ systems have their resting tone dominated by the SNS or the PNS, and this ratio can change depending on pathophysiologic states and can change over the lifetime of an individual. For instance, newborns are dominated by parasympathetic responses, hence bradycardia can be seen in 20% of unpremedicated infants during stressful situations such as anesthetic induction and airway manipulation, while it is uncommon in adults.<sup>9</sup> Vasoreactivity of the major blood vessels, arteries and arterioles is primarily responsive to the SNS, while PNS cardiovascular effects reside mainly at the level of the heart. Examples of the differential effects of the ANS in various organs and organ systems are summarized in Table 12-1.

In general, the SNS modulates the activity of vascular smooth muscle, cardiac muscle, and various glands (especially the adrenal gland); this modulation is critical for the fight-or-flight response. In contrast, the PNS modulates “rest-and-digest” functions such as salivation, lacrimation, urination, digestion, defecation, and sexual arousal.

### Sympathetic Nervous System

The SNS is formed from preganglionic fibers in the thoracolumbar segments (T1-L3) of the spinal cord arising from the intermediolateral gray column (see Figure 12-1). These myelinated fibers enter the paravertebral ganglia and travel a

**Table 12-1.** Autonomic Nervous System Receptor Types and Subtypes

RECEPTOR	EFFECTOR	RESPONSE TO STIMULATION
<b>Sympathetic Nervous System</b>		
$\alpha_1$	Smooth muscle (vascular, iris radial, ureter, trigone, bladder sphincters)	Constriction
$\alpha_2$	Presynaptic SNS nerve endings	Inhibition of NE release
$\beta_1$	Brain Heart	Neurotransmission Increase rate, contractility, conduction
$\beta_2$	Adipose tissue Blood vessels Bronchioles Kidney Liver	Lipolysis Dilation Dilation Renin secretion Gluconeogenesis, glycogenolysis
	Endocrine pancreas Uterus	Insulin secretion Relaxation
$D_1$	Blood vessels	Dilation
$D_2$	Presynaptic SNS nerve endings	Inhibition of NE release
<b>Parasympathetic Nervous System</b>		
$M_1$	Skeletal prejunctional nerve endings	Facilitate ACh release
$M_2$	Lung—presynaptic PNS nerve endings Visceral organs	Inhibits ACh release Increase
$M_3$	Lung smooth muscle, postsynaptic	Bronchoconstriction
$N_1$	PNS and SNS ganglion	Ganglionic blockade
$N_2$	Skeletal muscle	Muscle contraction

*ACh*, Acetylcholine; *D*, dopamine; *M*, muscarinic; *N*, nicotinic; *NE*, norepinephrine; *PNS*, parasympathetic nervous system; *SNS*, sympathetic nervous system.

variable distance up or down the sympathetic chain to synapse with the neuronal cell bodies of postganglionic sympathetic neurons. The unmyelinated postganglionic fibers then innervate their respective organs. An exception to this rule is the adrenal gland, where the preganglionic fibers do not synapse in the thoracic ganglia, but course through the sympathetic chain into the adrenal medulla. The chromaffin cells in the adrenal medulla are derived from neuronal tissue and essentially function as the postganglionic cells.

The stellate ganglion consists of postganglionic neurons that provide sympathetic innervation to the head and neck. Preganglionic fibers from the first four or five thoracic segments form this ganglion as well as the superior cervical and middle cervical ganglia. Blockade of this structure with local anesthetic blocks the sympathetic fibers coursing to the ipsilateral head and neck, resulting in Horner syndrome, characterized by ptosis, miosis, enophthalmos, and anhidrosis on the affected side.<sup>10</sup> This syndrome would be seen as a direct effect of a stellate ganglion block and possibly be experienced as a side effect of a brachial plexus block due to its close proximity to the stellate ganglion.<sup>10</sup> Similarly, blockade of the lumbar plexus produces a sympathetomy in the lower extremities, and peripheral nerve block often produces a sympathetomy in the affected limb because the postganglionic sympathetic nerve fibers travel along the somatic nerves.

## Parasympathetic Nervous System

Preganglionic fibers in the PNS arise from the midbrain, medulla oblongata, and sacral segments of the spinal cord. Cranial nerves II, VII, IX, and X carry preganglionic parasympathetic fibers directly to ganglia located near or directly in innervated organs. The sacral segments S2-S4 provide innervation to the rectum and genitourinary tissues (see Figure 12-1).

The vagus nerve (X) is the major carrier of parasympathetic neuronal traffic. These preganglionic fibers affect the heart, lungs, and abdominal organs with the exception of the distal portion of the colon. A combination of the distal location of the ganglion and the smaller 2- to 3-fold amplification factor between preganglionic and postganglionic fibers causes parasympathetic effects to be specific to each organ.

### CELLULAR PHYSIOLOGY

#### Preganglionic Neurons

Synaptic transmission through ANS ganglia is similar in both the SNS and the PNS. Preganglionic neurons in both the SNS and PNS are cholinergic. Acetylcholine (ACh) is stored in synaptic vesicles and released by a  $\text{Ca}^{2+}$  dependent process upon nerve terminal depolarization (Figure 12-3). ACh then interacts with postsynaptic receptors to depolarize the postsynaptic membrane. The principal ganglionic receptors are excitatory nicotinic ACh receptors, related to the ACh receptors at the neuromuscular junction (see Chapter 18). Thus many neuromuscular blocking agents have cardiovascular side effects mediated by their actions at the level of ANS ganglia. Recent advances in the pharmacology of these drugs have been directed at decreasing these ganglionic actions (see Chapter 19).

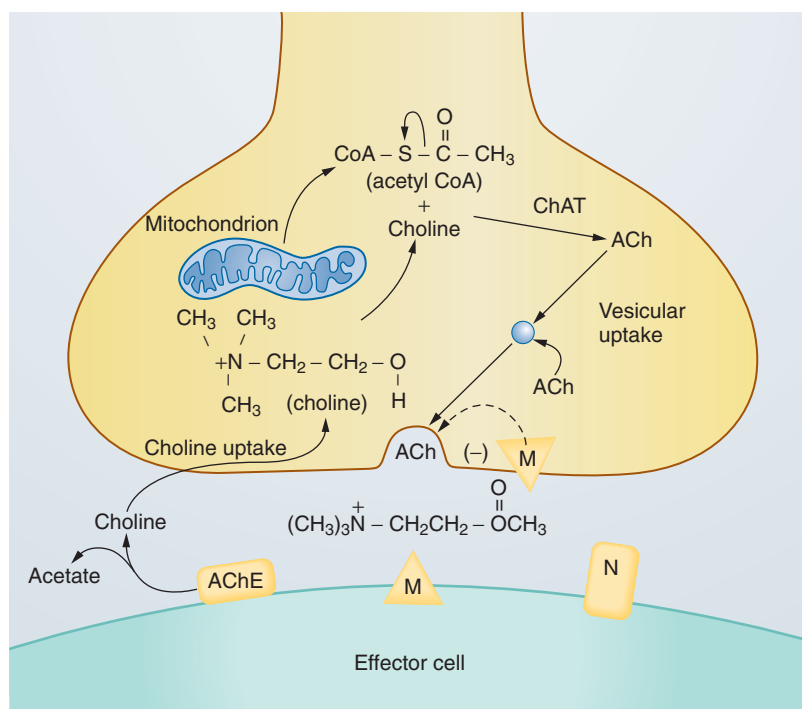
There are two distinct nicotinic receptor types, designated neuronal and muscle nicotinic ACh receptors (Figure 12-4).<sup>11</sup> Neuronal ACh receptors expressed in the autonomic ganglia are composed of  $\alpha 3\beta 4$  subunits, and are blocked by older neuromuscular blockers (e.g., gallamine), leading to ganglionic blockade. The neuromuscular junction has muscle nicotinic ACh receptors (composed of  $\alpha\beta\delta\epsilon$  subunits in adults) that are blocked selectively by the newer neuromuscular blocking agents, resulting in few side effects. Volatile anesthetics and ketamine are potent inhibitors both at  $\alpha 4\beta 2$  in the central nervous system and ganglionic  $\alpha 3\beta 4$  receptors.<sup>11</sup> The development of neuromuscular blocking agents has been focused on reduction of muscarinic side effects and elimination of ganglionic blockade. Structure-activity relationships indicate that the presence of quaternary ammonium moieties facilitates binding at the ACh site, while interionic distances may play a role in diminishing ganglionic as well as muscarinic cross-reactivity.<sup>12</sup>

Both nicotinic and muscarinic agonists and blockers interact at the level of the ganglia, the effects of which summate to either excite or inhibit the postganglionic neuron, and subsequently inhibit the effector organ. Thus the ganglionic synapse serves complex integrative and processing functions during normal physiology and while under the influence of anesthetic agents.

#### Postganglionic Neurons

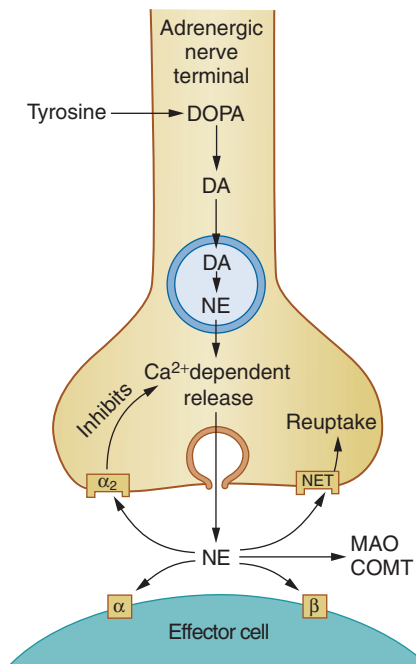
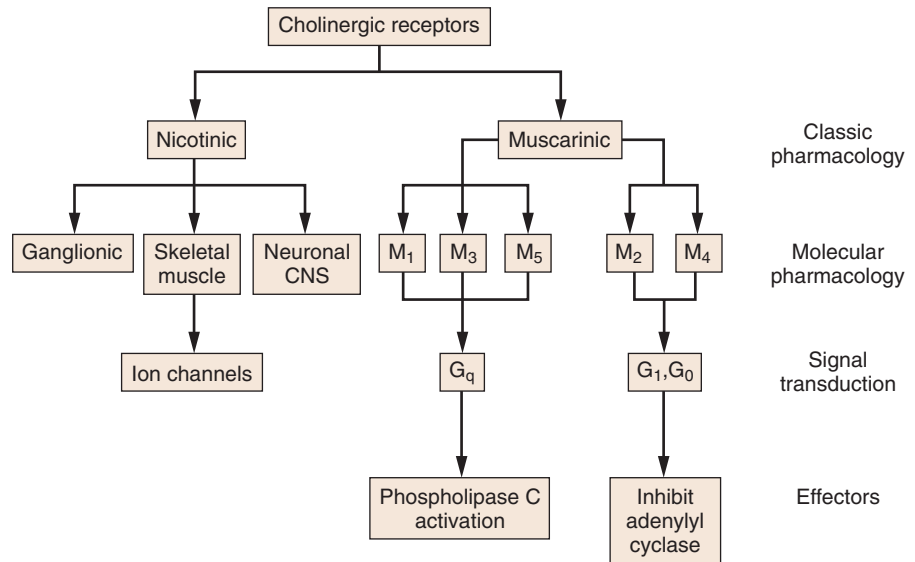
##### SYMPATHETIC NERVOUS SYSTEM

Epinephrine, norepinephrine, and dopamine are the classic neurotransmitters of sympathetic synaptic transmission released from postganglionic neurons (Figure 12-5); they interact with adrenergic receptors to effect sympathetic physiologic responses. As shown in Figure 12-6, these neurotransmitters and their receptors can be characterized at different levels. Building on the original observation by Ahlquist,



**Figure 12-3** The cholinergic synapse. Acetylcholine (ACh) is produced in the presynaptic terminal by the combination of acetyl CoA and choline through the action of choline acetyltransferase (ChAT). This neurotransmitter is stored in vesicles located in the presynaptic terminal and released upon nerve stimulation. ACh can bind to either nicotinic (N) or muscarinic (M) postsynaptic receptors to elicit an effector response (after summation in the postsynaptic membrane). In addition ACh interacts with presynaptic muscarinic receptors to provide negative feedback on ACh release. ACh is broken down in the synapse by acetylcholinesterase (AChE), and choline is taken up into the presynaptic terminal to be reused.

**Figure 12-4** Classification of cholinergic receptors. Receptor classification is pharmacologic or based on second messenger signal transduction.



**Figure 12-5** The adrenergic presynaptic terminal. Tyrosine (Tyr) is converted to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. DOPA decarboxylase produces dopamine (DA) in the cytoplasm, which is taken up into synaptic vesicles. Inside the synaptic vesicles, DA is converted to norepinephrine (NE) by dopamine β-hydroxylase. When NE is released from the presynaptic site by calcium (Ca<sup>2+</sup>)-dependent exocytosis, and the released neurotransmitter interacts with the effector cell adrenergic receptors and receptors located on the presynaptic membrane. Presynaptic α<sub>2</sub> receptors inhibit further NE release. Presynaptic β receptors enhance NE release. NE synthesis is controlled by a negative feedback loop at the level of tyrosine hydroxylase (not shown). Small amounts of NE escape into extraneuronal tissues where it is inactivated by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT).

adrenergic “receptors” are of two different types (alpha and beta), classified in terms of the overall physiologic response they elicit (the “classic pharmacology” approach).<sup>13</sup> Modern pharmacology further categorizes these receptors in terms of their molecular biology (e.g., DNA sequence and protein structure). From a mechanistic perspective, these receptors

can also be classified in terms of how their signals are transduced (i.e., which G-protein subtype is involved) and how the response is effected (i.e., what ion channels or enzymes are involved).

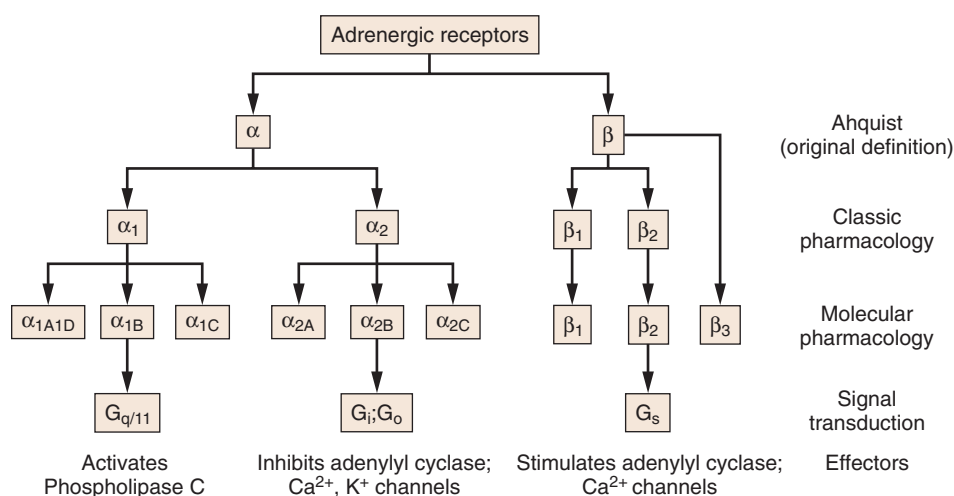
For example, norepinephrine released from sympathetic postganglionic neurons stimulates both α- and β-adrenergic receptors, eliciting classic adrenergic responses. Alpha-2 (α<sub>2</sub>) receptors located presynaptically, provide a negative feedback loop to modulate further release of neurotransmitter (Figure 12-5). The postsynaptic receptors regulate effector cells through second messenger signaling. The various and widespread physiologic actions of adrenergic and dopaminergic receptors are summarized in Table 12-1.

Synthesis of the adrenergic neurotransmitters takes place in the presynaptic varicosities of postganglionic sympathetic neurons. The steps in the enzymatic synthesis of norepinephrine are depicted in Figure 12-5. The neurotransmitters are stored and released from synaptic vesicles, and reuptake into presynaptic nerve endings assists in the termination of transmitter action. In addition, diffusion of transmitters away from the synaptic cleft and metabolism by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) quickly terminate the action of norepinephrine.

## PARASYMPATHETIC NERVOUS SYSTEM

Acetylcholine is the primary neurotransmitter at the postganglionic effector sites of the PNS. The postsynaptic receptors for ACh are classified as nicotinic or muscarinic. As with the adrenergic receptors, cholinergic receptors can be classified in terms of classic pharmacology, molecular biology and/or cellular mechanisms (Figure 12-4). Nicotinic receptors, which function at the neuromuscular junction, are also present in autonomic ganglia (see earlier).

Muscarinic receptors mediate the majority of PNS physiologic effects (Table 12-2). After release into the synaptic cleft, the action of ACh is quickly terminated by the extracellular enzyme acetylcholinesterase (AChE) through hydrolysis (see Figure 12-3). AChE is postsynaptically membrane-bound; hydrolysis produces choline and acetate. Choline is taken up by the presynaptic nerve endings to be reused, while acetate diffuses away from the synaptic cleft.



**Figure 12-6** Classification of adrenergic receptors. Receptor classification is pharmacologic or based on second messenger signal transduction.

**Table 12-2.** Homeostatic Balance Between the Parasympathetic and Sympathetic Nervous Systems by Organ System

ORGAN SYSTEM	EFFECTOR	SNS STIMULATION	PNS STIMULATION
Cardiovascular	Sinoatrial node	Increase heart rate	Decrease heart rate
	Atrioventricular node	Increase conduction velocity	Decrease conduction velocity
	His-Purkinje fiber	Increase automaticity, conduction	None or minimal
	Myocardial tissue	Increase contractility	None or minimal
	Coronary arterioles	Constriction ( $\alpha_2$ ), Dilation ( $\beta_2$ )	Dilation and constriction
Gastrointestinal	Salivary glands	Little increase in secretion	Stimulates secretion
	Gall bladder	Relaxation	Contraction
	Smooth muscle	Inhibits	Stimulates
	Sphincters	Constricts	Relaxes
Ophthalmologic	Iris	Mydriasis	Miosis
	Ciliary muscle	Relaxation (for far vision)	Contraction (for near vision)
Pulmonary	Bronchial smooth muscle	Relaxation	Contraction
Genitourinary	Bladder walls	Relaxes smooth muscle	Smooth muscle contraction
	Bladder sphincter	Contraction	Relaxation
	Ductus deferens, seminal vesicle, prostatic and uterine musculature	Contraction of smooth muscle	Vasodilation and erection
Thermal regulation	Blood vessels	Constriction	Dilation
	Sweat glands	Diaphoresis (postganglionic sympathetic fibers are cholinergic)	Little effect

PNS, Parasympathetic nervous system; SNS, sympathetic nervous system.

There are five distinct subclasses of muscarinic receptors, three of which have pharmacologic significance in the PNS, designated  $M_1$ ,  $M_2$ , and  $M_3$ .<sup>14</sup>  $M_1$  receptors exist in autonomic ganglia and the CNS, and are present in the airway.  $M_1$ ,  $M_2$ , and  $M_3$  receptors have effects on the airway smooth muscle with the majority of receptors being  $M_2$  and  $M_3$ .  $M_2$  receptors are located presynaptically and function as part of a negative feedback loop to limit release of ACh.  $M_3$  receptors are located postsynaptically and mediate bronchoconstriction.

### ENTERIC NERVOUS SYSTEM

The gastrointestinal tract is innervated by sympathetic and parasympathetic efferents arising from preganglionic and postganglionic sites. These neural inputs, along with visceral afferents, interact with intrinsic neural elements (often referred to as the enteric nervous system) to control gut function. The SNS contributes nerve fibers from cell bodies located within the prevertebral sympathetic ganglia, and from celiac, inferior mesenteric, and pelvic ganglia. Vagal

(parasympathetic) innervation consists of both sensory and motor fibers. The vagal efferents end on smooth muscle within the walls of the gut, interacting with the intrinsic myenteric ganglion to control motility (see Chapter 27). Efferent outflow from the sympathetic and the parasympathetic systems modulate blood flow, secretory activity, and motility.<sup>15,16</sup> Vagal afferent traffic responds to normal gut function, while sympathetic afferents respond to painful stimuli such as distention and injury.

Anesthetic effects on the enteric nervous system can be divided into direct pharmacologic effects on the intestinal smooth muscle, and effects due to spinal or epidural anesthesia. Muscarinic cholinergic receptors in the gut can be modulated by acetylcholinesterase inhibitors and anticholinergics used for reversal of neuromuscular blockade.<sup>17</sup> Postoperative ileus can be decreased by the use of thoracic epidural anesthesia.<sup>18</sup> Autonomic dysfunction causing gut dysmotility occurs because the SNS exerts more influence in the postoperative period than the parasympathetic system. This inhibitory

sympathetic reflex can be interrupted by division of the splanchnic nerves, destruction of afferent sensory nerves, or chemical sympathectomy via thoracic epidural anesthesia. The result is a shortened time to resolution of postoperative ileus.<sup>18</sup>

### Second Messengers in the Autonomic Nervous System

Interaction of neurotransmitters with their postsynaptic receptors results in signal transduction, which translates receptor binding into an effector cell response. In the adrenergic system, transduction is mediated by G proteins, which then regulate adenylyl cyclase and phospholipase C to generate second messengers and/or directly modulate various ion channels (see Chapter 1). In contrast, nicotinic ACh receptor binding leads to opening of its intrinsic ion channel, which leads to changes in the cell electrical potential. Muscarinic ACh receptors are G protein-coupled receptors similar to adrenergic receptors. Second messenger responses to muscarinic receptor stimulation depend on the effector site and the muscarinic receptor subtypes expressed (see Table 12-2).

### ADRENAL MEDULLA

The paired adrenal medullae are specialized portions of the SNS. Chromaffin cells are homologous to the sympathetic ganglion neurons and are similarly derived from the neural crest. The adrenal medulla can be thought of as a functional sympathetic ganglion in direct communication with the systemic circulation. Stimulation of the SNS results in the release of epinephrine and norepinephrine from the medulla into the bloodstream, eliciting a diffuse (nontargeted) sympathetic response from various effector organs expressing adrenergic receptors. In this way, the adrenal gland represents the general effector of the SNS, an amplification essential to the stress response.<sup>19</sup>

## AUTONOMIC NERVOUS SYSTEM REFLEXES

The ANS maintains homeostasis using the SNS and PNS as counteracting regulators (see Table 12-2). The relative tone of each of the two subsystems varies with age, sex, organ system, and environmental effects such as stress.<sup>20</sup> The challenge facing anesthesiologists is to maintain homeostasis while the ANS is modulated by medications, coexisting disease, surgical stimulation, and anesthetic drugs. Understanding of the pathways of ANS reflexes, and the anesthetic/surgical circumstances under which they are accentuated or attenuated, provides a conceptual framework for maintaining homeostasis during anesthesia and critical care.

### Central Nervous System Reflexes

#### CUSHING'S TRIAD

Cushing's triad is the physiologic association of increased intracranial pressure, bradycardia, and hypertension.<sup>21</sup> Intracranial hypertension leads to sympathetically mediated increases in blood pressure; the apparent disparity in reduced heart rate is probably due to medullary ischemia. Activation of parasympathetic medullary centers via the baroreceptor reflex (see later) slows the heart but does not overcome sympathetically mediated hypertension. The result is homeostatically increased blood flow to the brain.

### AUTONOMIC HYPERREFLEXIA

Alternatively termed *autonomic dysreflexia*, this condition results from chronic disruption of efferent impulses down the spinal cord, as in spinal cord trauma or tumor impingement.<sup>22</sup> Autonomic hyperreflexia is uncommon if the level of disruption is below T5. Inciting stimuli such as bladder distention, bowel distention, or surgical stimulation can produce an exaggerated sympathetic response. This occurs because there is a loss of normal inhibitory impulses from areas above the level of the lesion. A portion of the exaggeration in the response is due to adrenergic receptor supersensitivity secondary to denervation. Management of the quadriplegic or high paraplegic patient consists of either spinal or general anesthesia combined with careful manipulation of blood pressure due to the alterations in the ANS.<sup>23</sup>

### THERMOGENESIS REFLEX

Autonomic control of thermoregulation in mammals consists of reflex pathways from sensory cells originating in diverse tissues including the skin, core organs, and the central nervous system. These signals are processed by the hypothalamus, which maintains body temperature within a narrow range of a few tenths of a degree around 37°C. Daily circadian rhythms result in a sinusoidal variation of about 1. The output of the hypothalamus controls effector responses including peripheral vasculature action (vasodilation or vasoconstriction), sweating, and shivering.<sup>24</sup>

The preoptic area (POA) in the anterior hypothalamus receives thermal afferent signals from peripheral receptors as well as sensors located in the core (spinal cord, some organs). Efferent traffic goes to the principal thermoregulatory effectors: (1) cutaneous blood vessels, which vasoconstrict to reduce heat loss and vasodilate to facilitate heat loss; (2) brown fat and skeletal muscle for thermogenesis and shivering; and (3) sweat glands to provide for evaporative heat loss.<sup>25</sup>

Sweating is controlled by cholinergic fibers that can be blocked by muscarinic antagonists like atropine, or by peripheral nerve block.<sup>26</sup> Shivering can be blocked by the use of neuromuscular blockers, and can be diminished in old age and neuromuscular diseases. Shivering does not occur in newborns and is limited in infants. Nonshivering thermogenesis occurring in newborns and infants is modulated by norepinephrine from adrenergic nerve terminals. Vasoconstriction is controlled by the ANS at the level of the arteriovenous shunts, and is the result of sympathetic nerve traffic and not circulating catecholamines.

All general anesthetics impair thermogenesis reflexes. Sweating threshold is slightly increased and vasoconstriction and shivering thresholds are decreased markedly. These effects of anesthetics can lead to hypothermia during surgery if heat loss through radiation, conduction, convection, and evaporation is not minimized.<sup>27</sup>

### Cardiac Reflexes

#### BARORECEPTOR REFLEX

Stretch receptors in the walls of the carotid artery and aorta sense an increase in pressure (either endovascular or external, such as carotid massage). Afferent impulses are carried via the nerve of Hering and the vagus nerve to the medulla. In the medulla the excitatory baroreceptor inputs interact at the nucleus of the solitary tract to disinhibit inhibitory

interneurons, which then send increased signals to the rostral ventrolateral medulla and onward to the intermediolateral nucleus.<sup>28</sup> A decrease in heart rate, blood pressure, myocardial contractility, and total peripheral vascular resistance is mediated by efferent vagal activity (see Chapter 21). This effect is seen during anesthesia when phenylephrine, an  $\alpha_1$  receptor agonist, is administered intravenously, causing a rise in blood pressure and a fall in heart rate. Halothane attenuates this reflex.<sup>29</sup>

#### CHEMORECEPTOR REFLEX

Central chemoreceptors are sensitive to increases in arterial  $\text{CO}_2$  and decreases in arterial pH. Hypercarbia elicits a rapid and vigorous increase in minute ventilation (see Chapter 25). Volatile anesthetics, opioids, and nitrous oxide attenuate this response in a dose-dependent fashion. Even subanesthetic concentrations of volatile anesthetics have an effect on the ventilation response, thus patients given halogenated agents in the operating room can continue to have an impaired response to hypercarbia in the postanesthesia care unit.<sup>30</sup> Peripheral chemoreceptors are present in the carotid body; volatile anesthetics also produce dose-dependent attenuation of the ventilatory response to hypoxia mediated by these receptors.<sup>31</sup> Hypoxia elicits afferent impulses from the carotid and aortic bodies through Hering's nerve and the vagus to the nucleus tractus solitarius, increasing respiratory rate, tidal volume, and thus minute ventilation. Sympathetic activation causing increased heart rate and cardiac output can also occur.<sup>32</sup>

#### BAINBRIDGE REFLEX

An increase in central venous pressure (CVP) activates stretch receptors in the atria. Afferent impulses through the vagus nerve impact cardiovascular centers in the brain, which then inhibit tonic parasympathetic output, resulting in tachycardia.<sup>33</sup> The Bainbridge reflex can be seen during childbirth when autotransfusion increases CVP.<sup>34</sup>

#### BEZOLD-JARISCH REFLEX

This cardiac reflex is characterized by hypotension, bradycardia, and dilation of the coronary arteries (see Chapter 21). The Bezold-Jarisch reflex occurs in response to noxious stimuli detected in the ventricle; historically this was studied using *Veratrum* alkaloids applied intravenously. Chemoreceptors located in the ventricles respond to myocardial ischemia, resulting in an increase in blood flow to the myocardium and a decrease in the work of the heart. This appears to be a cardioprotective reflex. The pathway for this cardioprotective reflex begins with receptors in the ventricles of the heart, which detect mechanical and chemical stimuli. Afferent unmyelinated C-fibers travel through the vagus to enhance the baroreceptor reflex mechanisms, inhibit sympathetic output and inhibit vasomotor tone leading to peripheral vasodilation. The significance of this reflex in the presence of anesthetics continues to be debated, particularly in relation to regional anesthesia. As a cardioinhibitory reflex, the Bezold-Jarisch reflex might be functioning in parallel with the baroreceptor reflex but is probably not a predominant cause of physiologic change in humans.<sup>35</sup>

#### VALSALVA MANEUVER

Forced expiration against a closed glottis leads to multiple ANS-mediated responses. Increased intrathoracic pressure

leads to a decrease in venous return, causing an abrupt decrease in cardiac filling and blood pressure. The baroreceptor response leads to an increase in heart rate and inotropy through sympathetic stimulation. Upon glottic opening, the increase in venous return leads to an increase in blood pressure (contractility is still increased). This is detected by the baroreceptors, causing a parasympathetically mediated decrease in heart rate.<sup>36</sup>

#### OCULOCARDIAC REFLEX (TRIGEMINAL NERVE MEDIATED REFLEXES)

The trigeminal nerve (V) is associated with several autonomic reflexes; the best known is the oculocardiac reflex. Pressure on the globe or pulling on the extraocular musculature elicits afferent signals in the short and long ciliary nerves. These signals converge upon the Gasserian ganglion, causing a parasympathetic response, notably severe bradycardia. Release of the stretch results in a return of normal heart rate. This muscarinic receptor-mediated response can be blocked with glycopyrrolate or atropine, or by retrobulbar nerve block. In addition to the oculocardiac reflex, parasympathetic activation has been reported during intranasal stimulation and is an important part of the diving reflex.<sup>37,38</sup>

### EMERGING DEVELOPMENTS

#### Effects of Anesthetics on Autonomic Nervous System

General anesthetics tend to suppress the ANS, as they do the central nervous system. Many specific drugs used in anesthesia directly or indirectly interact with systems, organs, and receptors of the ANS, which then modify the function of the ANS. For instance, administration of the  $\alpha_2$  agonist clonidine decreases the dose of halothane required to produce general anesthesia.<sup>39</sup> This was followed by further investigation into the use of dexmedetomidine as an agonist of  $\alpha_2$  receptors in the central nervous system as an anesthetic adjunct.<sup>40</sup>

Anesthetics depress the ANS, in part by attenuating homeostatic reflexes and by decreasing the normal variability in measurements seen due to the balance between the sympathetic and parasympathetic systems. Heart rate variability, pulse-to-pulse interval and pulse plethysmography amplitude have been used to characterize the state of the ANS.<sup>41,42</sup> Administration of a potent opioid such as fentanyl decreases normal beat-to-beat variability, depresses sympathetic tone and promotes vagal activation.<sup>43</sup> Potent inhaled anesthetics such as desflurane depress the ANS as measured by heart rate variability.<sup>44</sup> Xenon, an anesthetic that has less hemodynamic depression than potent inhaled agents, causes increased parasympathetic and decreased sympathetic activity compared with total intravenous anesthesia (TIVA) with propofol.<sup>45</sup> Thus, while inhaled anesthetics have variable effects on the ANS, depression of the SNS appears to dominate.

General anesthesia and regional anesthesia also affect the ANS differently. The balance of sympathetic with parasympathetic tone in the upper body (unaffected by a lumbar epidural block) and the lower body, or the change in the balance between the intraoperative and postoperative state can have consequences in critical cardiac patients.<sup>46</sup> Continued ANS dysfunction in the intensive care unit complicates the perioperative course in the surgical patient.<sup>47</sup>



## Autonomic Failure

Aging, diabetes mellitus, and dysautonomia can result in failure or dysfunction of the ANS that affects perioperative management.

**Aging.** The cardiovascular effects of aging are characterized by hypertension and orthostatic hypotension, two conditions regulated by the ANS.<sup>48</sup> In addition, loss of temperature control can lead to heat stroke or hypothermia. All of these conditions lead to an inability of the older patients to adequately adapt to environmental stress. While the amount of circulating epinephrine and the number of  $\beta$ -adrenergic receptors are not reduced in older adults, the amount of norepinephrine is increased. This leads to a cyclic decline in responsiveness of adrenergic receptors as circulating plasma norepinephrine increases and receptors downregulate, requiring more stimulation.<sup>48</sup> Because older adults have decreased levels of plasma renin and aldosterone and increased levels of atrial natriuretic factor, they are prone to salt-wasting and hypovolemia.<sup>49</sup> The resultant labile blood pressure, particularly with orthostatic changes, makes pharmacologic management challenging. For instance,  $\beta$ -adrenergic agonists have a markedly decreased effect on heart rate, cardiac output, and vasodilation as a result of reduced affinity of the  $\beta$ -adrenergic receptor and a decline in the efficacy of second messenger coupling.<sup>48</sup>

Temperature regulation in older patients is also altered as a consequence of changes in the ANS, and as a result of reduced ability to respond physiologically with shivering and vasoconstriction. Older patients have reduced muscle mass so they are unable to generate heat effectively. They also have reduced subcutaneous fat (even though total fat as measured as a proportion of body weight is increased), leading to a decrease in thermal insulation.<sup>50</sup> Thermoregulatory control of skin blood flow in the elderly is also altered as a result of changes in the ANS. Reflex vasoconstriction and vasodilation are impaired due to diminished sympathetic output and reduced vascular responsiveness.<sup>51</sup> As a consequence, older adults can experience more stress directly related to hypothermia and hyperthermia.

## DIABETES MELLITUS

Autonomic neuropathy is common among diabetic patients. Between 20% and 40% of insulin-dependent diabetics have significant peripheral neuropathy, characterized by labile blood pressure, thermoregulatory deficits, and gastroparesis (possibly vagal nerve dysfunction).<sup>52</sup> This constellation of problems can require modification of the typical anesthetic plan, including pretreatment to mitigate the consequences of aspiration of stomach contents, cardiovascular support, and proactive efforts to prevent hypothermia. Perhaps in part because of autonomic dysfunction, diabetic patients experience more stress and are at increased risk for peri-operative complications.

## AUTONOMIC DYSAUTONOMIA

Dysautonomia can occur as a result of a genetic defect (e.g., familial dysautonomia, Shy-Drager syndrome), viral infection (Gullain-Barré syndrome), malignancy (Lambert-Eaton syndrome), or unknown reasons. Orthostatic hypotension and a decreased beat-to-beat variability in heart rate are common signs. This can lead to rapid changes in blood pressure and

an exaggerated response to sympathomimetic drugs under anesthesia due to an alteration in adrenergic receptor number or function.<sup>53</sup>

### KEY POINTS

- The ANS maintains cardiovascular, metabolic, thermal, and gastrointestinal homeostasis.
- Central control of the ANS is primarily mediated in the hypothalamus and medulla oblongata.
- Emerging from the spinal cord, the SNS acts primarily by the effector neurotransmitter norepinephrine to increase critical organ blood flow (i.e., muscles, heart, brain) in response to external challenges. The distribution of sympathetic ganglia close to the central nervous system facilitates a rapid amplification of this generalized fight-or-flight response.
- Emerging from select cranial and sacral nerves, the PNS acts primarily by the effector neurotransmitter acetylcholine (and muscarinic cholinergic receptors) to modulate activities that occur when the body is at rest (e.g., salivation, urination, defecation, sexual function). The distribution of parasympathetic ganglia close to effector organs facilitates the more focused rest-and-digest functions of the parasympathetic system.
- The adrenal medulla is functionally a sympathetic ganglion in direct communication with the systemic circulation that contributes to the amplification of the fight-or-flight response by delivering epinephrine and norepinephrine throughout the body.
- ANS reflexes (e.g., baroreceptor reflex, oculocardiac reflex) have important implications for anesthetic management.
- Anesthetics generally depress the ANS, in part by attenuating homeostatic reflexes.
- Autonomic dysfunction associated with aging, diabetes, and other disease states can have important implications on anesthetic management, especially as it relates to the support of the circulation during anesthesia.

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