AUTONOMIC NERVOUS SYSTEM

Brian M. Keech, MD

CHAPTER 4

1. Describe the autonomic nervous system.

The autonomic nervous system (ANS) is a network of nerves and ganglia that provide involuntary (i.e., unconscious) control of the physiological actions that maintain internal homeostasis and respond to stress. The ANS innervates structures within the cardiovascular, pulmonary, endocrine, exocrine, gastrointestinal (GI), genitourinary, skeletal muscle, and central nervous systems (CNS) and can influence metabolism and thermal regulation.

The ANS consist of three components: sympathetic nervous systemic (SNS), parasympathetic nervous system (PNS), and enteric nervous system (ENS). The ENS governs the function of the GI tract, is the largest component of the ANS, and can function independent of the CNS. The SNS produces widespread effects, whereas the PNS tends to produce more localized, discrete effects. The SNS and PNS generally have opposing effects on most organs. At rest, the PNS predominates (i.e., rest-and-digest), whereas in stressful situations, the SNS predominates (i.e., fight-or-flight).

2. What is the origin of the terms *sympathetic* and *parasympathetic*?

The origin of the term *sympathetic* (nervous system) comes from the Greek word "sympathy," which can be traced to the Greek physician and scientist, Claudius Galen (129–210 CE). Galen described the nervous system as the framework which facilitates a physiologic "sympathy," coordinating synergistic interactions among various organ systems. Parasympathetic (nervous system) comes from the Greek word "para" + "sympathy," where "para" denotes the meaning of "near, alongside, contrary, or against."

3. Review the anatomy of the sympathetic nervous system.

Preganglionic sympathetic neurons originate from the intermediolateral columns in the spinal cord (T1–L2). These myelinated fibers exit via the ventral root of the spinal nerve, travel into the sympathetic chain, and synapse with three types of ganglia (Fig. 4.1):

1) *Paravertebral sympathetic ganglia*—A chain of paired ganglia located lateral to the vertebral column (i.e., paravertebral), which runs from the skull to the coccyx forming the sympathetic trunk.
2) *Prevertebral sympathetic ganglia*—Unpaired ganglia that are located anterior to the vertebral column (i.e., prevertebral).
3) *Adrenal medulla*—A modified ganglia located within the adrenal gland. Although other ganglia function as relay stations with long postganglionic fibers that innervate specific organs, the adrenal medulla directly secretes catecholamines into the venous blood stream.

Preganglionic sympathetic neurons may ascend or descend the sympathetic chain multiple levels and a single preganglionic fiber may synapse with multiple ganglia. On average, one preganglionic sympathetic fiber synapses with approximately 20 ganglia. Whereas most preganglionic sympathetic fibers that enter the sympathetic trunk ultimately synapse with paravertebral sympathetic ganglia, some will not and instead continue through the sympathetic trunk and synapse with other ganglia (e.g., prevertebral ganglia or adrenal medulla). Preganglionic sympathetic fibers release acetylcholine at their synapse to stimulate nicotinic cholinergic postganglionic neurons (or chromaffin cells of the adrenal medulla).

Postganglionic adrenergic neurons synapse at target organs and release norepinephrine (NE, and epinephrine in the adrenal medulla), except in the case of sweat glands, where acetylcholine is released (Fig. 4.2).

4. List examples of specific sympathetic ganglia that are often used as a target for interventional pain management.

Stellate ganglia—Paired paravertebral sympathetic ganglia formed as a fusion of the inferior cervical ganglia and the first thoracic ganglia from the sympathetic trunk. They are located at the level of C7, anteromedial to the vertebral artery, and posterior to the carotid, internal jugular, and phrenic nerve. They provide most of the sympathetic innervation to the head, neck, and upper extremities. It is a common target for a nerve block to treat complex pain disorders, such as complex regional pain syndrome of the upper extremity.

Celiac plexus—A collection of prevertebral sympathetic ganglia located anterior to the aorta in the retroperitoneal space. It provides sensory and sympathetic outflow to the stomach, liver, spleen, pancreas, kidney, and GI tract up to the splenic flexure. It is a common target for a nerve block to treat complex abdominal pain disorders, such as pain from pancreatic cancer.

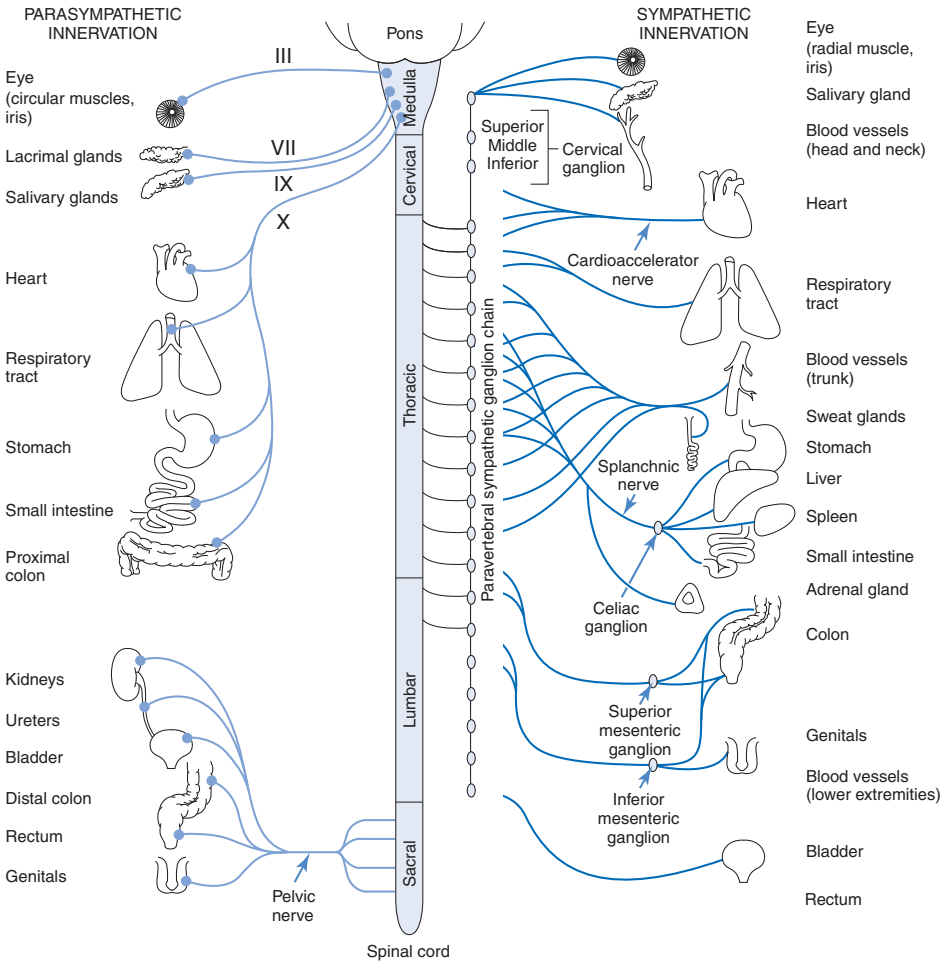

Fig. 4.1 Schema of the autonomic nervous system depicting the functional innervation of peripheral effector organs and the anatomic origin of peripheral autonomic nerves from the spinal cord. (From Bylund DB. Introduction to the autonomic nervous system. In: Wecker L, Crespo L, Dunaway G, et al, eds. Brody's Human Pharmacology: Molecular to Clinical. ed 5. Philadelphia: Mosby; 2010:95.)

5. Describe the anatomy and function of the parasympathetic nervous system.

Preganglionic parasympathetic neurons originate from cranial nerves III, VII, IX, and X and sacral segments 2 to 4 (see Fig. 4.1). Of these, the vagus nerve accommodates approximately 75% of PNS traffic. Preganglionic parasympathetic neurons, as opposed to preganglionic sympathetic neurons, synapse with postganglionic neurons close to the target end-organ facilitating fine, discrete physiological effect. Both preganglionic and postganglionic parasympathetic neurons release acetylcholine; these cholinergic receptors are subclassified as either nicotinic or muscarinic. The response to cholinergic stimulation is summarized in Table 4.1.

6. What are the adrenergic receptors and what is their response to agonism?

There are alpha-1 (α_1), alpha-2 (α_2), beta-1 (β_1), and beta-2 (β_2) adrenergic receptors. The α_1, β_1, and β_2 receptors are postsynaptic and are stimulated by the neurotransmitter NE. The α_2 receptors are presynaptic and are also stimulated by NE. Stimulation of α_2 receptors inhibits the presynaptic release of NE, reducing overall sympathetic response. Molecular pharmacologists have further subdivided these receptors, but this is beyond the scope of this discussion. The response to receptor activation at different sites is described in Table 4.1.

7. What are catecholamines? Which occur naturally? Which are synthetic?

Catecholamines are monoamines that stimulate adrenergic nerve terminals. NE, epinephrine, and dopamine are naturally occurring catecholamines, whereas dobutamine and isoproterenol are synthetic catecholamines.

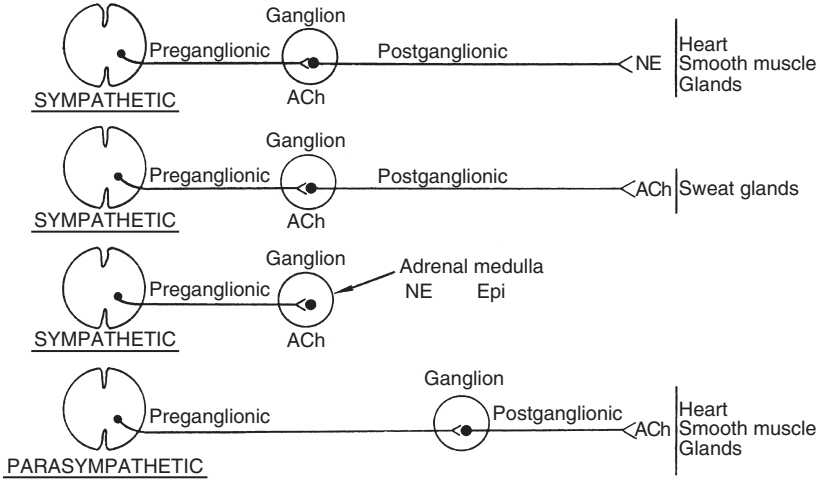

Fig. 4.2 Neuronal anatomy of the autonomic nervous system with respective neurotransmitters. *ACh,* Acetylcholine; *Epi,* epinephrine; *NE,* norepinephrine. (From Glick DB. The autonomic nervous system. In: Miller RD, ed. Miller's Anesthesia. 8th ed. Philadelphia: Elsevier Saunders; 2015:347.)

Table 4.1 End-Organ Effects of Autonomic Stimulation

ORGAN	ADRENERGIC RESPONSE	RECEPTOR	CHOLINERGIC RESPONSE	RECEPTOR
Cardiac (chronotropy)	Increased	β_1	Decreased	M_2
Cardiac (inotropy)	Increased	β_1		
Veins	Vasoconstriction	α_1		
Arteries (most)	Vasoconstriction	α_1		
Arteries (skeletal muscle)	Vasodilation	β_2		
Lung	Bronchodilation	β_2	Bronchoconstriction	M_3
Uterus	Relaxation	β_2	Contraction	M_3
Gastrointestinal tract	Relaxation	α_2	Contraction	M_3
Pupil	Dilation (mydriasis)	α_1	Constriction (miosis)	M_3
Kidney (renin secretion)	Increased	β_1		
Bladder (detrusor muscle)	Relaxation	β_2	Contraction	M_3
Pancreas (insulin release)	Decreased	α_2		
Fat cells (lipolysis)	Increased	β_1		
Liver (glycogenolysis)	Increased	α_1, β_2		
Salivary glands (secretion)	Increased/Decreased	α_1/α_2	Increased	M_3
Sweat glands (secretion)	Increased	M_3		

8. Review the synthesis of dopamine, norepinephrine, and epinephrine.

The amino acid tyrosine is actively transported into the adrenergic presynaptic nerve terminal cytoplasm, where it is converted to dopamine by two enzymatic reactions: hydroxylation of tyrosine by tyrosine hydroxylase to L-DOPA and subsequent decarboxylation by aromatic L-amino acid decarboxylase to dopamine. Dopamine is transported into storage vesicles, where it is hydroxylated by dopamine β-hydroxylase to NE. Epinephrine is synthesized in the adrenal medulla from NE, through methylation by phenylethanolamine *N*-methyltransferase.

9. How are catecholamines metabolized?

Although NE is primarily removed from the synaptic junction by reuptake into the presynaptic nerve terminal, a small amount enters the circulation and undergoes metabolism. Catecholamines are metabolized in the blood, liver, and kidney by the enzymes monoamine oxidase and catecholamine *O*–methyltransferase. The important metabolites of epinephrine and NE are metanephrine and normetanephrine, respectively.

10. Why is it important to know the metabolites of epinephrine and norepinephrine?

Because the half-life of catecholamines is ultrashort ($t_{1/2} \approx 2$ minutes), it is difficult to directly measure catecholamines when diagnosing catecholamine secreting tumors, such as a pheochromocytoma. The catecholamine metabolites, metanephrine and normetanephrine, have a much longer half-life ($t_{1/2} \approx 1$–2 hours) and are often measured to diagnose pheochromocytoma. Catecholamine metabolites can be measured directly from the plasma or from a 24-hour urine sample.

11. What enzyme metabolizes acetylcholine?

Acetylcholine (ACh) is rapidly metabolized to choline and acetate by acetylcholinesterase (AChE), an enzyme located within the junctional cleft.

12. What problems could result from acethylcholine accumulation in the junctional cleft?

Inhibition of AChE, such as with neuromuscular blocking reversal agents (e.g., neostigmine) will result in accumulation of ACh, causing the following side effects: bradycardia, salivation, lacrimation, urination, defecation, and emesis. In general, these side effects can be mitigated with anticholinergic agents, such as glycopyrrolate. However, excessive accumulation may result in cholinergic crisis, causing severe bradycardia, bronchoconstriction, blindness, and muscular paralysis in addition to the aforementioned. The latter more severe side effects may be seen with pesticides (e.g., organophosphates) or in chemical warfare (e.g., Sarin gas).

13. How should cholinergic crisis be treated?

Cholinergic crisis should be treated with atropine and intubation for respiratory support. Atropine will antagonize muscarinic receptors located within the cleft at parasympathetic innervated organs; however, it will not antagonize nicotinic receptors located within the neuromuscular junction. Paralysis caused by cholinergic crisis requires intubation and respiratory support, until the offending agents abates.

14. What are the indications for using β-adrenergic antagonists?

β-Adrenergic antagonists, commonly called *β blockers*, are antagonists at β_1 and β_2 receptors. β blockers are a common treatment for hypertension, angina, and dysrhythmias. Perioperative β blockade is essential in patients with coronary artery disease, and the use of these medications has been shown to reduce death after myocardial infarction.

15. Review the mechanism of action for β antagonists and their side effects.

β_1 and β_2 antagonism decreases the activation of adenylate cyclase, resulting in decreased production of cyclic adenosine monophosphate (cAMP). β blockers may be cardioselective (relatively selective β_1-antagonist properties), or noncardioselective. β_1-Blockade produces negative chronotropic and inotropic effects, decreasing heart rate, contractility, cardiac output, and myocardial oxygen requirement. β_1-Blockers also inhibit renin secretion, thereby reducing fluid retention and angiotensin II. Because volatile anesthetics also depress myocardial contractility, intraoperative hypotension may result with perioperative β-blocker administration. Abrupt withdrawal of these medications is not recommended because receptor upregulation can lead to hypertension, tachycardia, and myocardial ischemia. Because of their benefits in ischemic heart disease, patients receiving β-blocker therapy should continue their usual regimen the day of surgery.

β blockers interfere with the translocation of potassium ions across the cellular membrane and can cause hyperkalemia. β blockers may also decrease signs of hypoglycemia (i.e., tachycardia and tremor); thus it should be used with caution in diabetic insulin-dependent patients.

16. Review the effects of β_2 antagonism.

For our purposes, β_2 receptors are located on vascular and bronchial smooth muscle. β_2-Blockade produces peripheral vasoconstriction, bronchoconstriction, and inhibits insulin release and glycogenolysis. Because of this, selective β_1 blockers should be used in patients with peripheral vascular disease, chronic obstructive pulmonary disease, or reactive airway disease because of concerns for vascular and bronchial constriction, respectively.

17. Can β blockade be used to attenuate the surgical stress response?

The adrenergic response to intense perioperative stimuli, such as tracheal intubation or surgical incision, can be attenuated with β antagonism. However, it is unclear if this attenuation is sufficient to protect patients from the possible harm associated with the adrenergic response to intense perioperative stimulation. At present, the adrenergic response to surgical stress is probably best managed through a combination of anesthetic agents, opioids, and, when appropriate, β antagonists.

18. How might complications of β blockade be treated intraoperatively?

Bradycardia and heart block will usually respond to atropine or glycopyrrolate; refractory cases may require β_1-agonism with epinephrine, dobutamine, or isoproterenol. Other treatment options include glucagon, calcium, insulin and glucose, and even lipid emulsion therapy.

19. Review α_2 agonists and their role in anesthesia.

α_2-Agonists inhibit adenylate cyclase and decrease cAMP production, thereby decreasing sympathetic outflow from presynaptic nerve terminals in the CNS. The α_2-agonist used most commonly in the perioperative setting is dexmedetomidine. It produces excellent sedation, contributes to analgesia, lowers anesthetic requirement, and reduces heart rate and blood pressure, all without significantly depressing ventilation. Side effects include bradycardia, which can easily be treated with glycopyrrolate. Clonidine, another α_2 agonist, is used as an antihypertensive. It can lead to rebound hypertension if stopped abruptly, leading up to surgery.

20. Discuss the role of muscarinic antagonists in the reversal of pharmacological neuromuscular blockade.

Nondepolarizing muscle relaxants can be reversed with AChE inhibitors, which increases ACh at the neuromuscular junction (nicotinic receptor). However, AChE inhibitors also increase ACh at the parasympathetic innervated organs (muscarinic receptor) causing bradycardia, defecation, secretions, and bronchospasm. To minimize these latter side effects, muscarinic antagonist (e.g., glycopyrrolate) should be coadministered with AChE inhibitors (e.g., neostigmine).

21. Which muscarinic antagonist is most frequently given in the operating room to reverse neuromuscular blockade? Why?

Glycopyrrolate is the muscarinic antagonist that is most frequently administered. It is a quaternary amine (i.e., polar molecule) and therefore does not readily cross the blood-brain barrier, unlike atropine, a tertiary amine (i.e., nonpolar molecule) that readily crosses the blood-brain barrier, causing undesirable CNS anticholinergic effects, such as sedation, confusion, and delayed emergence from anesthesia.

22. What is the significance of autonomic dysfunction?

Patients with ANS dysfunction or dysautonomia are at risk of severe hypotension intraoperatively and aspiration from gastroparesis. Diabetes mellitus and chronic alcohol abuse are risk factors for autonomic dysfunction.

23. How does spinal cord injury affect the autonomic nervous system?

Spinal cord injury can cause various problems of the ANS depending on the site, extent, and timing of the lesion. Autonomic reflexes that are normally inhibited by supraspinal feedback are lost following a high (T6 or above) spinal cord injury. As a result, minor stimuli can produce exaggerated SNS responses.

Initially, for a period of days to weeks, injured patients may experience spinal shock, a condition where the peripheral vascular bed is vasodilated, and compensatory tachycardia predominates. As the injury becomes chronic, hypotension may result in bradycardia, as the vagus nerve is the only component of the baroreceptor reflex that remains intact. In addition, an upregulation of adrenergic receptors may occur, making patients exquisitely sensitive to exogenously administered vasopressors.

Pressure stimuli below the level of the lesion can lead to a dramatic rise in blood pressure and reflexive decline in heart rate, a condition known as *autonomic dysreflexia*, and can be managed by administering vasodilators and/or deepening your anesthetic. Regional anesthesia should strongly be considered in these patients to blunt the exaggerated sympathetic response to painful stimuli.

24. What is a pheochromocytoma, and what are its associated symptoms? How is pheochromocytoma diagnosed?

A pheochromocytoma is a catecholamine-secreting tumor composed of chromaffin tissue, producing either NE or epinephrine. Most are intraadrenal, but some are extraadrenal (within the bladder wall is common), and about 10% are malignant. Computed tomography scan is very accurate in diagnosing and localizing the tumor. Signs and symptoms include paroxysms of hypertension, sudden severe headache, palpitations, flushing, and diaphoresis. Pheochromocytoma is confirmed by detecting elevated levels of catecholamine metabolites (i.e., metanephrine and normetanephrine) in the plasma or from a 24-hour urine.

KEY POINTS: AUTONOMIC NERVOUS SYSTEM

1. Sympathetic nerves originate from the spinal cord at T1–L2.
2. Parasympathetic nerves originate from cranial nerves III, VII, IX, X, and from the spinal cord at S2–S4.
3. The stellate ganglion provides sympathetic innervation to the upper extremity, whereas the celiac plexus (a collection of prevertebral ganglia) provides sympathetic and sensory innervation to the abdominal organs. These are frequent targets for interventional pain procedures, such as complex regional pain syndrome or pancreatic cancer.
4. Patients on β-blockers should take them on the day of surgery and continue them perioperatively. Because the receptors are upregulated, withdrawal may precipitate hypertension, tachycardia, and myocardial ischemia.
5. Patients with high spinal cord injuries (T6 and above) are at risk for autonomic dysreflexia, a condition associated with excessive sympathetic response to painful stimuli below the level of the lesion.
6. Pheochromocytoma is a catecholamine-secreting tumor causing paroxysmal episodes of hypertension, tachycardia, sudden headache, and diaphoresis. It is diagnosed by detecting elevated levels of metanephrine and normetanephrine in the plasma or from a 24-hour urine.

Suggested Readings

Glick DB. The Autonomic nervous system. In: Miller RD, ed. Miller's Anesthesia. 8th ed. Philadelphia: Elsevier Saunders; 2015: 346–386.
Mustafa HI, Fessel JP, Barwise J, et al. Dysautonomia. Perioperative implications. Anesthesiology. 2012;116:205–215.
Neukirchen M, Kienbaum P. Sympathetic nervous system. Evaluation and importance for clinical general anesthesia. Anesthesiology. 2008;109:1113–1131.