Journal of Integrative Neuroscience

J. Integr. Neurosci. **2025**; 24(8): 31369
https://doi.org/10.31083/JIN31369

Review

Introduction to the Physiology, Anatomy, and Biochemistry of Autonomic Medicine

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Academic Editor: Gernot Riedel
Submitted: 25 November 2024 Revised: 19 February 2025 Accepted: 25 February 2025 Published: 28 August 2025

Abstract

Autonomic medicine is a rapidly evolving field focused on understanding diseases and processes that affect the autonomic nervous system (ANS). The ANS regulates essential involuntary physiologic processes such as heart rate, blood pressure, and digestion. This review introduces the key anatomical structures, physiological mechanisms, and biochemical processes underlying autonomic function. The anatomy section focuses on the peripheral components of the ANS, including the sympathetic and parasympathetic divisions. The physiological section explores the process of homeostasis and the intricate feedback systems that maintain this balance within the body. Finally, the biochemistry of autonomic signaling, focusing on the neurotransmitters acetylcholine, norepinephrine, and epinephrine, and their receptors, is reviewed. Pertinent clinical points are highlighted throughout, emphasizing the importance of the basic science to the clinical world. This review aims to provide a comprehensive basic science foundation for clinicians and researchers exploring the field of autonomic medicine.

Keywords: autonomic medicine; autonomic physiology; autonomic anatomy; autonomic biochemistry

1. Introduction

The body's potential to survive and thrive depends on its ability to maintain a consistent internal environment that is compatible with life. This includes physical factors (such as temperature), hemodynamic factors (such as blood pressure, blood volume, and cerebral perfusion), and metabolic factors (such as acidity, electrolyte levels, glucose levels, and oxygen levels). The different means and methods the body uses to keep these values within a certain viable range is called homeostasis. Each of the body's organs and systems contribute to this goal of homeostasis, but the chief director is the autonomic nervous system (ANS) [1–3].

Some of the primary functions under control of the ANS are the regulation of blood pressure and temperature, digestion, and the elimination of waste products (defecation, micturition) [1–3]. When the ANS malfunctions, these processes can be affected, pushing the body outside of its homeostatic goal. If the values deviate too far or for too long outside of the desired range, then deleterious consequences can occur (causing symptoms and disease). The study of the ANS, its mechanisms of promoting homeostasis, and what happens when this malfunctions is called Autonomic Medicine. To understand how to approach diagnosing and treating autonomic dysfunction, it is necessary to have a working knowledge of the basic science underlying the ANS. The purpose of this review is to provide an introduction to the anatomy, biochemistry, and physiology that underlies autonomic medicine, with important clinical applications scattered throughout.

2. Review

2.1 The Autonomic Nervous System

The nervous system is divided into the central nervous system (CNS; consisting of the brain and spinal cord) and the peripheral nervous system (PNS; everything else—nerve roots, ganglia, peripheral nerves, etc.) [4]. The autonomic nervous system consists of two analogous parts: The central autonomic network (CAN; the central component) and the peripheral autonomic nervous system (the peripheral component) [5]. The CAN is exponentially more complex than the peripheral autonomic nervous system and is still not fully understood. We direct the interested reader to a review by Benarroch [6]. Our primary focus will be on the peripheral autonomic nervous system.

2.2 The Divisions of the Autonomic Nervous System

The peripheral nervous system consists of the somatic nervous system and the autonomic nervous system [4,7]. The somatic nervous system controls "voluntary" motor function and the sensory aspects that we are aware of (e.g., sight, touch, taste, hearing). The ANS handles the "automatic" functions of the body, those that we do not have conscious thought or control over, such as regulating blood pressure and temperature, supporting digestion, and expelling waste (micturition, defecation)—i.e., maintaining homeostasis [7,8].

The ANS has many components, with different and often overlapping functions. John Langley was the first to describe the ANS as having three parts: The parasympathetic

nervous system, the sympathetic nervous system, and the enteric nervous system [9]. The parasympathetic and sympathetic systems are complementary to one another, and both interact with the enteric system. The sympathetic nervous system was later subdivided further into the sympathetic noradrenergic system (SNS), the sympathetic adrenergic system (described by Walter Cannon), and the sympathetic cholinergic system (described by Henry Dale) [3].

The sympathetic and parasympathetic systems are arranged as chains of neurons [10]. Preganglionic neurons arise from the brainstem or spinal cord and synapse on ganglionic neurons (clusters of cell bodies), whose axons then terminate in a synapse on the effector target. The effector target is most often smooth muscle associated with blood vessels or glands. While the preganglionic axons are myelinated, the postganglionic axons are unmyelinated and so have slower transmission [5,8].

The origin of the preganglionic neurons, the location of the ganglia, the relative lengths of the pre- and postganglionic axons, and the effector targets and functions differ depending on whether the chain is part of the parasympathetic or sympathetic system.

Clinical Correlation: Autoimmune Autonomic Ganglionopathy

In autoimmune autonomic ganglionopathy (AAG), an autoantibody affects the ganglia of the ANS, causing autonomic impairment. Symptoms arise from failure of the parasympathetic system (causing sicca symptoms, urinary retention, and erectile dysfunction), failure of the sympathetic system (causing orthostatic hypotension and anhidrosis), and failure of the enteric system (causing achalasia, gastroparesis, and ileus). Though the classical presentation is global autonomic failure, symptoms can be more limited and variable [11]. The onset is most often acute or subacute, but a more chronic/indolent course has been described [12].

There are seropositive and seronegative forms of autoimmune autonomic ganglionopathy. In seropositive AAG (50–70% of cases) [13], antibodies targeting the ganglionic nicotinic acetylcholine receptors are present. These bind receptors in the autonomic ganglia, leading to internalization of the receptor, and causing a block in autonomic signaling [13]. Levels greater than 1.0 nmol/L are highly specific for AAG. Lower levels are nonspecific, and very low levels (<0.2 nmol/L) can even be found in 2–4% of healthy controls or in patients with unrelated neurologic disease [11].

Treatment for AAG is with immunotherapy. It is also important to screen for lung cancer and thymoma, as these can be associated. Other paraneoplastic antibodies that can affect the ANS include anti-neuronal nuclear antibody (ANNA-1)/Hu, collapsin response mediator protein (CRMP-5)/CV2, P purkinje cell cytoplasmic antibody (CA-2), voltage gated potassium channel (VGKC), and P/Q calcium channel antibodies [12].

2.3 The Parasympathetic Nervous System: An Overview

The parasympathetic nervous system (PNS) is often described as promoting the "rest and digest" functions of the body. It assists in cardioinhibition (slowing the heart rate, decreasing contractility), digestion (motility, secretions), urination, erection, defecation, lacrimation, and pupillary constriction. The main neurotransmitter used in the PNS is acetylcholine [14].

The parasympathetic preganglionic neurons are of "craniosacral" origin; they arise from the brainstem and sacral spinal cord (S2-4) [8]. From the brainstem, the parasympathetic preganglionic axons travel with several cranial nerves (CN) (III, VII, IX, X) to reach their respective ganglia [7,8]. These ganglia lie very close to their targets, making the preganglionic axon very long and the postganglionic axon very short. The cranial parasympathetic ganglia are all named. The cranial components of the parasympathetic nervous system are listed in Table 1 (Ref. [1,3,4,8,10]).

The pre-ganglionic axons travelling with CN III arise from the Edinger-Westphal nucleus in the midbrain [8,10]. These axons exit the skull through the superior orbital fissure and synapse on the ciliary ganglion in the posterior orbit; the post-ganglionic axons travel with the short ciliary nerves and terminate on the iris sphincter muscle (causing pupillary constriction, "miosis") and the ciliary muscle (contracting the lens, "accommodation") [7]. Sensory branches (from the nasociliary nerve, supplying the cornea, iris, and ciliary body) and sympathetic postganglionic axons also travel through the ciliary ganglion but do not synapse there [2].

The pre-ganglionic axons travelling with CN VII arise from the superior salivatory nucleus in the pons. These axons travel with a branch of CN VII (nervus intermedius) and synapse on the pterygopalatine ganglion (via the greater petrosal nerve) and the submandibular ganglion (via chorda tympani and lingual nerves) [2,7].

The post-ganglionic axons from the pterygopalatine ganglion terminate on the lacrimal gland and mucosa and/or glands of the paranasal sinuses, nasal cavity, pharynx, gingiva, and hard palate—triggering secretion in all of these. Sensory branches (from the maxillary branch of the trigeminal nerve) and sympathetic postganglionic axons also travel through this ganglion but do not synapse within it [2,7].

The post-ganglionic axons from the submandibular ganglion terminate on the submandibular, sublingual, and lingual glands, also triggering secretion [2,8].

The preganglionic axons travelling with CN IX arise from the inferior salivatory nucleus in the pons [8]. These axons synapse on the otic ganglion (near the foramen ovale), and the post-ganglionic nerves terminate on the parotid gland, triggering salivation. Sensory fibers (via the auriculotemporal nerve, providing sensation to the parotid gland), sympathetic fibers, and motor fibers (supplying ten-

Table 1. Cranial components of the parasympathetic nervous system.

Nucleus	Conducting cranial nerve	Ganglion	Effector	Action
Edinger-Westphal (midbrain)	III	Ciliary	Iris sphincter Ciliary muscle	Miosis Accommodation
Superior salivatory (pons)	VII	Pterygopalatine ganglion	Lacrimal glands Mucosa/glands of paranasal sinuses, nasal cavity, pharynx, gingiva, hard palate	Lacrimation Salivation
Superior salivatory (pons)	VII	Submandibular	Submandibular glands Sublingual glands Lingual glands	Salivation
Inferior salivatory nucleus (pons)	IX	Otic	Parotid glands	Salivation
Dorsal motor nucleus Nucleus ambiguus	X	On or near thoracic or abdominal targets	Gastrointestinal system Heart	Motility, digestion Heart rate control

sor tympani, tensor veli palatini, and medial pterygoid) also pass through this ganglion without synapsing [2].

The dorsal motor nucleus and the nucleus ambiguous give rise to the parasympathetic nerves of CN X (Vagus nerve). The ganglia where they synapse are on or near their thoracic or abdominal targets. The dorsal motor nucleus innervates primarily the gastrointestinal (GI) system, aiding in motility and digestion from the esophagus through the first half of the large intestine [8]. The nucleus ambiguus innervates primarily the heart, providing beat-to-beat heart rate control [2].

2.3.1 Clinical Correlation: The Pupillary Light Reflex

The pupillary light reflex [8,15] assesses the integrity of cranial nerves II and III and the parasympathetic system. When a light is shone in one eye, information travels via CN II to synapse on the pretectal area of the midbrain. This triggers bilateral input to the Edinger-Westphal nuclei to increase parasympathetic activity and cause constriction of both pupils. Malfunction at any part of this loop (ipsilateral CN II, midbrain, or CN III) will cause the same response (lack of pupillary constriction of the eye receiving the light input). Shining a light into only one eye, and assessing the pupillary responses of both eyes, can aid in localization of a lesion.

If light is shone in one eye and neither pupil reacts, the lesion is likely at the ipsilateral CN II (so that the light information never makes it to the midbrain). This can also occur in bilateral lesions in CN III, the EW nuclei, or the ipsilateral pretectal nuclei.

If light is shone in one eye and the ipsilateral pupil does not react but the contralateral pupil constricts, the lesion is likely at the ipsilateral CN III. If the extraocular movements are preserved, then likely only the parasympathetics of CN III are affected. This can also occur in an ipsilateral EW lesion.

If light is shone in one eye and the ipsilateral pupil constricts but the contralateral pupil does not, the lesion is likely within the contralateral CN III. This can also occur in a lesion of the contralateral EW nucleus.

2.3.2 Clinical Correlation: Respiratory Sinus Arrhythmia

The heart has an internal pacemaker (the sinoatrial node) so that even if it is disconnected from extra-cardiac influences, it will continue to beat within a range of 60–100 bpm. The parasympathetic nervous system closely regulates the heart rate via the vagus nerve acting on this pacemaker node. Vagal input is increased or decreased depending on different cardiovascular and pulmonary factors. Increasing vagal input will slow conduction and thus heart rate; removing vagal input will increase conduction and heart rate. Perhaps best demonstrating this concept is respiratory sinus arrythmia, where heart rate increases with inspiration and decreases with expiration [16,17]. Respiratory sinus arrhythmia is thought to have evolved as a way to efficiently increase pulmonary blood flow during inspiration (optimizing gas exchange) [18]. The Bainbridge reflex and the Herring-Breuer reflex are thought to be involved in this process.

The Bainbridge reflex occurs when an increase in cardiac preload results in an increase in heart rate; this increase in preload can be either an increase in blood volume (stimulating atrial stretch receptors) or inferior vena cava distension [19]. The Hering-Breuer reflex occurs when sustained lung inflation stimulates pulmonary stretch receptors, triggering expiration. When pulmonary stretch receptors are activated, cardiac vagal tone is inhibited, via vagal efferents, accelerating heart rate [20].

During inhalation, the diaphragm contracts, moving downward and expanding the intrathoracic cavity. Intrathoracic pressure decreases causing an increase in blood flow to the heart when then triggers the Bainbridge reflex. This leads to withdrawal of parasympathetic input and an in-

crease in heart rate. Simultaneously, the pulmonary stretch receptors increase firing, also leading to cardiac vagal inhibition and an increase in heart rate (Hering-Breuer reflex).

During exhalation, the diaphragm relaxes, collapsing the chest wall and decreasing the size of the intrathoracic cavity, which increases intrathoracic pressure. This increased pressure inhibits venous return to the heart (reducing cardiac preload). The pulmonary stretch receptors also reduce firing. Both of these trigger an un-inhibition of the cardiac vagal efferents, decreasing the heart rate.

When combined, these rhythmic changes in heart rate that occur with inhalation and exhalation are called respiratory sinus arrhythmia. This response is best seen in young, active individuals. It decreases with age, diabetes, and cardiovascular disease [21,22]. As the sympathetic nervous system is thought to have little to no role in this (as the response would take too long), measuring the variation in heart rate with respiration is used to measure cardiovagal integrity (max heart rate at inspiration – max heart rate at expiration).

The sacral component of the parasympathetic nervous system arises from cell bodies in the lateral gray horn of the S2-4 spinal cord region (corresponding to the T12-L1 vertebral levels). These axons exit the spinal column as S2-4 spinal nerves and then form plexuses (along with sympathetic nerves) before branching off to synapse within the walls of their targets. When activated, these increase motility of the intestines and ureters and aid in defecation and micturition [2].

2.4 The Sympathetic Nervous System: An Overview

Broadly speaking the sympathetic nervous system oversees the "fight or flight or freeze" responses and is the complementary system to the parasympathetic nervous system's "rest and digest". The sympathetic nervous system has been described as having three components [3], depending on which neurotransmitter is used at the effector: The SNS, the sympathetic cholinergic system, and the sympathetic adrenergic system. The three components of the sympathetic system utilize different neurotransmitters, have different targets, and so have different effects.

The sympathetic systems arise from the interomediolateral columns of the thoracic and lumbar regions of the spinal cord (T1-L2) [8]. The preganglionic axons leave the spinal canal through the anterior root, through the anterior rami and white rami connectors, and then enter the sympathetic ganglia. There are paravertebral, prevertebral, and previsceral sympathetic ganglia [7,14].

The paravertebral ganglia are mostly unnamed and exist as an ordered chain that runs parallel on either side of the spinal column [10]. Preganglionic sympathetic axons can synapse directly at their level of entry into this chain; can ascend or descend to a different level and synapse there; or can pass through without synapsing [8]. The paravertebral sympathetic ganglia include three cervical (superior, middle, and inferior), 10–12 thoracic, four lumbar, and four to five sacral ganglia [10,14].

The superior cervical ganglia are adjacent to C2-3; postganglionic axons arising from here travel with the carotid arteries to supply the head and neck, as well as heart [10]. The middle cervical ganglia lie adjacent to C6; postganglionic axons from here travel to the heart and neck. The inferior cervical ganglia can exist as a standalone structure or can be fused with the first thoracic ganglion (and then called the stellate ganglion). It is adjacent to C7. Postganglionic axons from here provide innervation to the lower neck, heart, arm, and posterior cranial arteries [2].

The prevertebral ganglia lie midline, anterior to the aorta. These include the celiac, aortico-renal, and mesenteric ganglia. The celiac ganglia provide innervation to the stomach, liver, gallbladder, spleen, kidney, ovaries, and parts of the colon (ascending and transverse). The mesenteric ganglia also provide innervation to the GI system, including the small intestine and parts of the colon (ascending and transverse) [2].

Just as in the parasympathetic system, the preganglionic axons of the sympathetic system are myelinated while the postganglionic axons are unmyelinated [8]. As the myelinated preganglionic axons of the sympathetic system are short, synapsing almost immediately on their respective ganglia, the unmyelinated postganglionic axons will stretch longer distances throughout the body to terminate on their ultimate targets. This contrasts to the parasympathetic system, where preganglionic myelinated axons are much longer, and postganglionic unmyelinated axons are shorter. This myelinated versus unmyelinated concept is important as it could have clinical implications. As a larger proportion of the sympathetic pathway is unmyelinated, it can be more vulnerable to metabolic insults (like hyperglycemia) than the parasympathetic system.

The SNS uses acetylcholine at its ganglionic synapse (as do all components of the ANS) but at its final target uses norepinephrine [4]. Targets of the SNS include the smooth muscle in blood vessel walls (leading to vasoconstriction and increased blood pressure), the heart (increasing heart rate and force of contractility), and the iris constrictor (pupil dilation) [3].

The sympathetic cholinergic system uses acetylcholine as its sole neurotransmitter, in both the ganglionic synapse and at the final target (sweat glands). This system is involved in thermoregulation and, when activated, will cause sweating to cool the body [3].

The sympathetic adrenergic system is a special case. The preganglionic neurons that are part of this system do not synapse on any of the sympathetic ganglia; they pass through the ganglia without synapsing, ultimately making their way to the adrenal gland, where they synapse on chromaffin cells of the adrenal medulla, using acetylcholine as the neurotransmitter [1,3]. When activated, this will trig-

ger the release of primarily epinephrine. Epinephrine enters the blood stream and circulates widely throughout the body, acting on any adrenergic receptor it comes across. This is the only system of the ANS that uses this type of hormonal transmission. Epinephrine can act on the adrenergic receptors in the blood vessel walls (leading to vasoconstriction and increased blood pressure), the heart (increasing heart rate and contractility), the pupil (leading to pupil dilation), the liver (triggering glycogenolysis), and sweating of the palms, soles, etc. [3].

As a final side note: There are postganglionic sympathetic nerves that have targets in the kidney; these postganglionic neurons release dopamine and control the rate of blood filtration in the kidney [2].

2.4.1 Clinical Correlation: Horner's Syndrome

Classical Horner's syndrome [8,23] consists of the triad of unilateral ptosis, miosis, and anhidrosis. This occurs due to a lesion in the sympathetic pathways supplying the face. A lesion can occur at any point in this long pathway:

Hypothalamus $\rightarrow$ cervical cord (C8-T1) $\rightarrow$ sympathetic preganglionic neurons (that travel through the brachial plexus and over the pulmonary apex) $\rightarrow$ superior cervical ganglia (near the bifurcation of the common carotid artery) $\rightarrow$ postganglionic axons (that travel with the internal carotid artery (ICA), through the cavernous sinus, and with ophthalmic branch of CN V into the orbit).

Lesions at different locations throughout this path can lead to either a full or partial Horner's syndrome which can aid with clinical localization. If the lesion occurs proximal to the superior cervical ganglion, then sudomotor pathways will be affected (full Horner's syndrome). After the superior cervical ganglion, the sudomotor fibers separate from the other sympathetic tracts; the former travel with the external carotid artery while the latter travel with the ICA. If the lesion affects the ICA or distal (cavernous sinus, first branch of CN V, orbit), then the sympathetic sudomotor fibers will be spared and, clinically, the patient will have a partial Horner's (ptosis, miosis).

2.4.2 Clinical Correlation: Thermoregulatory (Cholinergic) and Adrenergic Sweating

Sweating (diaphoresis) is the body's primary means of cooling itself. Sweating can be triggered by overheating and by emotion [1].

The hypothalamus serves as the body's thermostat. When heat-sensitive neurons there sense an increase in body temperature outside of the desired range, they activate the sympathetic sudomotor pathway. The postganglionic sympathetic sudomotor axons release acetylcholine, which acts on muscarinic receptors, leading to stimulation of eccrine sweat glands and sweating.

Emotional sweating is restricted to the palms of the hands, soles of the feet, armpits, and the forehead [24]. Rather than acetylcholine acting on muscarinic receptors, sympathetic nerves innervating these sweat glands release norepinephrine that acts on adrenergic receptors. Sweating here is triggered by emotion and stress, not thermoregulation.

2.5 How does the Autonomic Nervous System Communicate?

With the exception of the final step of the sympathetic adrenergic system, the parasympathetic and sympathetic systems use neurotransmitters acting at nearby targets for local effects [3]. Neurotransmitters are stored within vesicles inside the cell. When it is time for their release, the vesicle will move towards the cell membrane and then fuse with the membrane via the help of a soluble NSF attachment protein receptor (SNARE) complex [3]. The SNARE complex is made of many different proteins (including SNAP, syntaxin, and synaptobrevin); it attaches to the vesicle and pulls it closer to the membrane. Once the vesicle has fused with the membrane, an opening (pore) forms, and the neurotransmitter contents are expelled into the synaptic terminal [3].

Clinical Correlation: Toxins and the SNARE Complex

Two of the deadliest toxins, botulinum and tetanus toxins, both target the SNARE complex. These are produced by two Clostridium species of bacteria (C. botulinum and C. tetani, respectively).

C. tetani is found in the soil and often infects contaminated wounds. This toxin targets the spinal inhibitory interneurons, cleaving the SNARE complex (synaptobrevin) and preventing the release of gamma aminobutyric acid (GABA). This leads to overactivity of skeletal muscles, and the characteristic spasms of tetanus toxicity [25,26].

C. botulinum is found in the soil and water, and characteristically can cause disease with IV drug use, with wound contamination, or after ingestion of improperly canned foods or (in an infant) honey. Botulinum toxin targets cholinergic cells, also cleaving the SNARE complex. The exact SNARE target differs depending on the type of botulinum toxin, but they all ultimately prevent the release of acetylcholine. Symptoms include flaccid paralysis (from the affect at the neuromuscular junction) and autonomic dysfunction. Exposure to type B botulinum toxin can even rarely present as pure autonomic failure, with orthostatic hypotension, constipation, erectile dysfunction, urine retention, and hypohidrosis [27–29]. Botulinum toxin has found a medical purpose, though, in the treatment of increased muscle tone (as with dystonia and spasticity), hyperhidrosis, hypersalivation, migraine, and in cosmetic procedures to reduce wrinkles [30]. Though the effects at the SNARE complex are permanent, the injections must be repeated, as the axons will regenerate, sprouting new synaptic terminals.

Table 2. Overview of the parasympathetic and sympathetic nervous system.

	Parasympathetic	Sympathetic (cholinergic)	Sympathetic (noradrenergic)
Pre-ganglionic origin	Brainstem Sacral spinal cord	Thoracolumbar spinal cord	Thoracolumbar spinal cord
Preganglionic Axon	Long, myelinated	Short, unmyelinated	Short, unmyelinated
Ganglionic neurotransmitter	Acetylcholine	Acetylcholine	Acetylcholine
Ganglionic receptors	Nicotinic	Nicotinic	Nicotinic
Post-ganglionic axon	Short, unmyelinated	Long, unmyelinated	Long, unmyelinated
Post-ganglionic neurotransmitter	Acetylcholine	Acetylcholine	Norepinephrine
Effector receptors	Muscarinic	Muscarinic	Adrenergic

2.6 Neurotransmitters of the Autonomic Nervous System

The primary neurotransmitters used in the ANS are acetylcholine, norepinephrine, and epinephrine. Table 2 (Ref. [1–4,10]) depicts an overview of the different neurotransmitters of the autonomic nervous system.

Acetylcholine serves as the primary neurotransmitter within all autonomic ganglia, within the adrenal gland (SAS), and at the final target synapses of the PNS and sympathetic cholinergic system. Acetylcholine is made within the cytoplasm of cholinergic neurons, using choline and acetyl coenzyme A, via choline acetyltransferase. The acetylcholine is then transported into vesicles via VAChT (vesicular acetylcholine transporter) [31]. This transporter's function depends on an ATP-fueled proton gradient; as protons leak from the (acidic) vesicle, acetylcholine will enter. After release into the synaptic junction, acetylcholine is rapidly metabolized by AChE (acetylcholinesterase), regenerating both acetate and choline. The metabolism of acetylcholine is so efficient that there is essentially no leakage of it outside of the synapse, meaning it cannot be measured in the blood as other neurotransmitters can [3].

The neurotransmitters norepinephrine and epinephrine, and their predecessor dopamine, arise from the amino acid tyrosine [3].

Tyrosine $\rightarrow$ DOPA (3,4-dihydroxyphenylalanine)$\rightarrow$ Dopamine $\rightarrow$ Norepinephrine $\rightarrow$ Epinephrine

In the cytoplasm of dopaminergic and noradrenergic neurons, tyrosine is converted to DOPA via tyrosine hydroxylase in a reaction that requires oxygen, iron, and tetrahydrobiopterin (BH4). DOPA is then converted to dopamine via L-aromatic amino acid decarboxylase (LAAAD or dopa decarboxylase), which requires vitamin B6 [3].

In the noradrenergic neurons in the brain, CNS, and adrenal medulla, after conversion from DOPA to dopamine, the dopamine is then transported into a vesicle via type II vesicular monoamine transporter (VMAT 2). As with the acetylcholine transporter, VMAT 2 depends on an ATP-fueled proton gradient; as protons leave the acidic vesicle, dopamine enters. Inside the vesicle, dopamine is converted to norepinephrine via dopamine beta-hydroxylase, which requires copper, vitamin C, and oxygen [3].

After norepinephrine is released at the synaptic terminal, it is recycled and re-enters the cytoplasm via the norepinephrine transporter (NET). Inside the cytoplasm, it is either reloaded into the vesicle via vesicular monoamine transporter 2 (VMAT2) or is metabolized by monoamine oxidase (MAO, on the outer mitochondrial membrane) [3].

In the adrenergic cells of the adrenal medulla, norepinephrine will either leak from vesicles or will be taken up from outside the cell via norepinephrine transporter (NET) on the cell membrane. phenylethanolamine N methyoltransferase (PNMT), a cytoplasmic enzyme, then converts norepinephrine to epinephrine. Inside the adrenal gland, epinephrine and norepinephrine are metabolized to metanephrine and normetanephrine, respectively [3].

The recycling and metabolism of norepinephrine and epinephrine are not as effective as acetylcholine metabolism. Because of this, norepinephrine and epinephrine are measurable in the blood.

2.6.1 Clinical Correlation: Organophosphate Poisoning

Organophosphates irreversibly bind and neutralize AChE so that it is unable to metabolize acetylcholine. The resulting cholinergic excess affects the ANS (causing miosis, diarrhea, vomiting, and sweating), the neuromuscular junction (uncontrolled muscle contraction), and higher cortical processes (altered mental status). When respiratory muscles are affected, suffocation and death can occur [32]. Organophosphate poisoning is seen with insecticide exposure or in chemical warfare. Treatment is with an acetylcholine receptor (muscarinic) antagonist, such as atropine [3].

Reversible AChE inhibitors have found a medical purpose in treating conditions like dementia (donepezil, rivastigmine) and myasthenia gravis (pyridostigmine) [33].

2.6.2 Clinical Correlation: Levodopa

Another name for DOPA is levodopa, a medication used in Parkinson's Disease [34]. In idiopathic Parkinson's Disease, dopamine producing neurons of the substantia nigra are lost, leading to dopamine deficiency in the basal ganglia. This causes difficulty regulating movement which manifests as bradykinesia (a decrease in the amplitude, amount, and speed of voluntary movement). Lev-

odopa/DOPA (the precursor to dopamine) is given to people with Parkinson's Disease to replace what is essentially a dopamine deficiency, as insulin is given to patients with type I diabetes mellitus (The full underlying pathophysiology is more complex, but this is a simplistic view). When levodopa is converted to dopamine within the CNS, there is improvement or even resolution of the bradykinesia.

LAAAD, the enzyme that catalyzes the conversion of levodopa/DOPA to dopamine exists throughout the body and not just within the CNS. When levodopa is converted to dopamine outside of the CNS, it can lead to severe nausea and vomiting. This was a significant adverse effect that limited early dosing of this medication. To avoid this, levodopa is almost always given with carbidopa. Carbidopa blocks the action of LAAAD, but only in the periphery, as it is unable to cross the blood brain barrier (see Fig. 1 below). When carbidopa is combined with levodopa, the conversion to dopamine in the periphery is greatly reduced (limiting nausea) while leaving the CNS process unaffected. When carbidopa was first paired with levodopa on the market, it was given the brand name "Sinemet", meaning "without emesis" in Latin.

2.6.3 Clinical Correlation: Vitamin C and Orthostatic Hypotension

As vitamin C is required for the production of norepinephrine, vitamin C deficiency, in theory, could cause dysfunction in the SNS and result in orthostatic hypotension [35]. This phenomenon has been documented in two case reports where severe vitamin C deficiency (scurvy) presented with orthostatic hypotension [36,37]. High dose vitamin C has been studied in ICU populations where it has been shown to increase the plasma NE, though did not change clinical outcomes or mortality [38].

2.6.4 Clinical Correlation: Catecholamine Levels in Diagnosis

Serum catecholamine levels [39] can aid in the evaluation of patients with autonomic symptoms. Levels of dopamine, norepinephrine, and epinephrine and their metabolites can be tested when lying and standing. Standing levels of norepinephrine (NE) should be higher than supine levels, due to activation of the SNS during standing.

Pure autonomic failure (a peripheral cause of autonomic failure) will typically have low levels of NE, with blunted orthostatic changes. In multiple systems atrophy (a central cause of pure autonomic failure), NE levels are typically normal, with a blunted orthostatic change. Elevated levels of norepinephrine can occur in pheochromocytomas; elevated standing levels of NE can be seen in hyperadrenergic postural orthostatic tachycardia syndrome (POTS).

As noted above, as acetylcholine is so efficiently metabolized within the synaptic cleft, essentially no acetylcholine escapes to the systemic system. Acetylcholine will not be measurable in the serum and so is not used in the clinical setting.

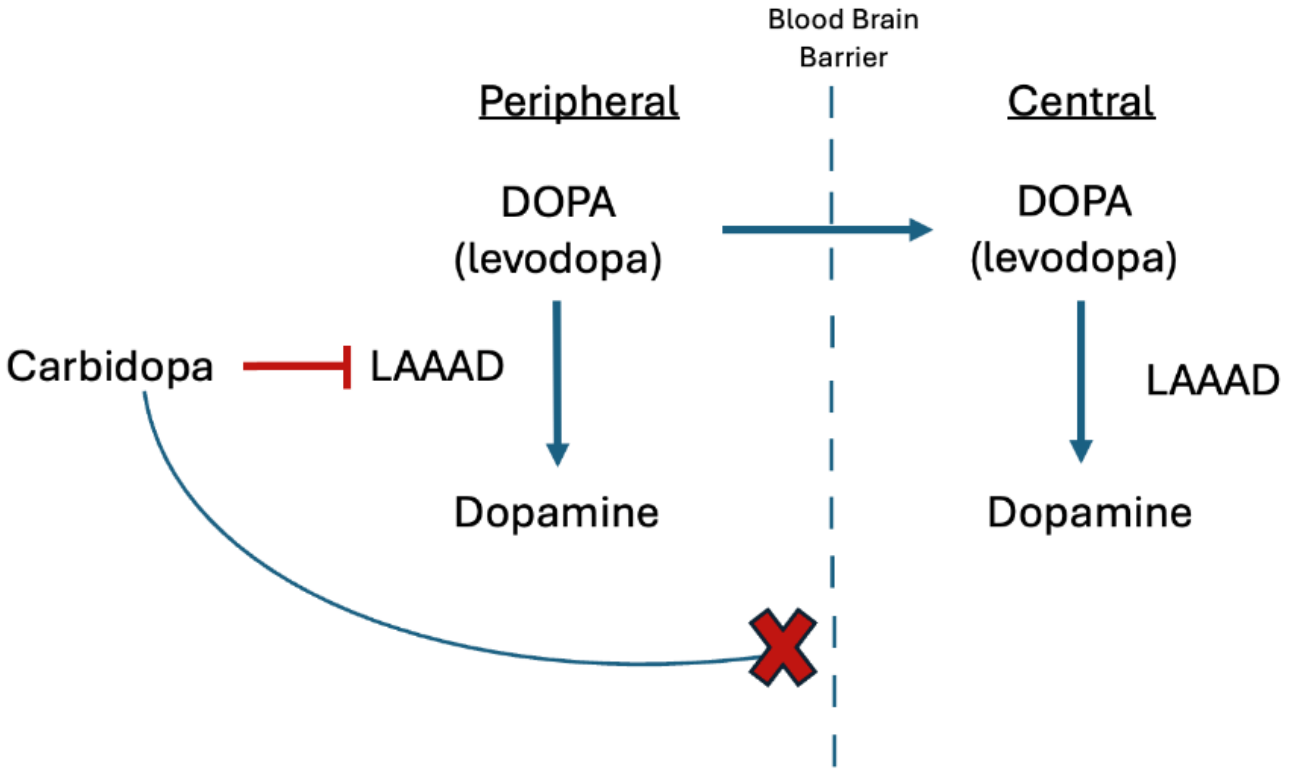

Fig. 1. The effects of carbidopa. DOPA, 3,4-dihydroxyphenylalanine; LAAAD, L-aromatic amino acid decarboxylase.

Table 3. Muscarinic receptors, locations, and actions.

	Excitatory or inhibitory	Location	Action
M1	Excitatory	gastrointestinal (GI) system	Gastric acid secretion
			Non-parotid salivation
M2	Inhibitory	Cardiac sympathetic nerves	Reduced norepinephrine (NE) release
		Bladder neck	Aiding micturition
		Heart	Reduced heart rate
			Reduced heart contractility
		Bronchi	Constriction
M3	Excitatory	Iris constrictors	Miosis
		Ciliary muscle	Accommodation
		Sweat glands	Secretion
		Parotid/non-parotid salivary glands	Salivation
		Lacrimal glands	Lacrimation
		Bronchi	Constriction
		Head, neck, and viscera blood vessels	Dilation
		GI system	Motility
			Intestinal secretion
		Bladder	Aiding micturition
		Rectal smooth muscle	Defecation
		Erectile tissues	Erection
M4	Inhibitory	Postganglionic cholinergic nerves	Inhibitory autoreceptors

2.7 What are the Receptors and Effectors of the Parasympathetic and Sympathetic Nervous Systems?

The primary receptors of the ANS are adrenergic and cholinergic receptors [2].

Cholinergic receptors can be nicotinic or muscarinic.

The preganglionic neurons of parasympathetic and sympathetic systems are all cholinergic, releasing acetylcholine onto nicotinic receptors of the autonomic ganglia (or the adrenal gland for the SAS). The parasympathetic ganglionic neurons are also cholinergic, releasing acetylcholine onto the muscarinic receptors of their targets. There are 5 types of muscarinic receptors: M1, M2, M3, M4, and M5 that are distributed throughout the central and peripheral nervous system. Most cells will have multiple receptor subtypes [2]. Muscarinic receptors can give excitatory or inhibitory responses. All five receptor subtypes are present in the brain, which could explain the cognitive effects of anticholinergic agents [40–43]. The various muscarinic receptor locations and actions are listed in Table 3 (Ref. [2,14,44–46]).

The sympathetic ganglionic nerves can be cholinergic or adrenergic.

In the sympathetic cholinergic system, the ganglionic neurons release acetylcholine which acts on muscarinic receptors. M3 receptors are present in sweat glands and, when activated, increase sweating [2]. The sympathetic cholinergic system is activated in thermoregulatory conditions to keep the body from overheating.

The sympathetic adrenergic and noradrenergic system utilize adrenergic receptors [2,3]. Adrenergic receptors can be alpha (α1, α2) and beta (β1, β2, β3). Stimulation of α1 receptors leads to increased activity at the target; stimulation of α2receptors leads to decreased activity at the target.

α1receptors are located on the iris (leading to pupil dilation), vessels in skeletal muscle, skin, cranium, and viscera (constriction), bladder neck (urine retention), and erectile tissue and vas deferens (ejaculation) [2,3].

α2 receptors are located throughout the GI system (inhibiting secretions) and on the presynaptic terminals of sympathetic noradrenergic nerves (inhibitory autoreceptors) and parasympathetic cholinergic nerves (reducing AcH release) [2,3].

β1 receptors are located in the heart (increasing heart rate and contractility). β2 receptors are in the bronchi (bronchodilation), skeletal muscle vessels (vasodilation), GI system (inhibiting motility), the bladder detrusor (relaxing muscle, urine retention), and rectal smooth muscle (relaxing muscle, inhibiting defecation). β3receptors are also in the bladder wall (relaxing muscle, inhibiting micturition) [2,3].

In the SNS, ganglionic neurons release norepinephrine which acts on adrenergic receptors. Norepinephrine will act on both alpha receptors (α1, α2) and the β2 receptor. The SNS is activated primarily with orthostatic stress (standing) [2,3].

The end result of activation of the sympathetic adrenergic system is release of epinephrine into the circulation. Epinephrine is distributed widely throughout the body and can activate any of the adrenergic receptors [3]. The sympathetic adrenergic system is activated in situations that stress the body physically (hypoglycemia, hypotension, exercise,

hypothermia) or emotionally. Epinephrine release causes constriction of blood vessels in the skin, conserving heat and causing the characteristic "paleness" someone can have with overactivation of this system. Epinephrine will also lead to breakdown of glycogen, increasing serum glucose [47].

Clinical Correlation: Orthostatic Hypotension

Upon standing, gravity-dependent pooling of blood occurs in the dependent portions of the body (primarily the lower limbs and splanchnic circulation). A baroreflex-mediated increase in sympathetic activity and decrease in parasympathetic activity occurs, leading to vasoconstriction and increased peripheral vascular resistance, and an increased heart rate. Together, this leads to stability of standing blood pressure. Orthostatic hypotension (OH) [48] occurs when there is a sustained drop in blood pressure of >20/10 (systolic blood pressure/diastolic blood pressure) with standing. For every two-point drop in systolic blood pressure, there should be a one-point increase in heart rate. OH is often multifactorial, including neurogenic or non-neurgenic etiologies. There is some debate about whether all patients with OH have a neurogenic component, just existing on a spectrum of severity, or not [49].

In non-neurogenic orthostatic hypotension, the fall in blood pressure is not due primarily to autonomic failure. Upon standing, there is reactive vasoconstriction (due to sympathetic activation) and a rise in heart rate (due to parasympathetic withdrawal). On autonomic testing, cardiovascular adrenergic systems will be preserved. Non-neurogenic orthostatic hypotension can occur in the setting of decreased intravascular volume (dehydration, hemorrhage), cardiac pump failure (heart failure, valve disease), and medication effects, to name a few.

In neurogenic orthostatic hypotension, there is failure of the sympathetic system. Upon standing, there is no reactive vasoconstriction to offset gravity effects, and so blood pressure falls. Most often, the expected compensatory rise in heart rate will be blunted or absent (though rarely this can be preserved) [50]. Neurogenic OH can occur with autonomic disorders of central or peripheral origin, including the synucleinopathies (multiple systems atrophy, dementia with Lewy bodies, Parkinson's disease, and pure autonomic failure) and autonomic neuropathies (such as with diabetes). Blood pressure responses to Valsalva maneuver can be helpful in determining neurogenic vs non-neurogenic etiology [50].

2.8 Are the Parasympathetic and Sympathetic Nervous Systems Enemies?

Though they have competing functions, the PNS and SNS do not function antagonistically. Rather, they work synergistically to maintain homeostasis. One of the best examples of this is the regulation of blood pressure.

Blood pressure is one of the most tightly controlled variables in the body, as it determines the amount of blood flow to each organ. Blood pressure can be neither too high nor too low or else the brain and other organs could be damaged. The ANS monitors blood pressure (particularly cerebral blood flow) via baroreceptors. Baroreceptors are stretch-sensitive pressure sensors; there are arterial and venous baroreceptors, and both are activated via distortion.

Arterial baroreceptors are sensitive to high pressure; they are located within the carotid sinus (in the carotid wall at the bifurcation of the common carotid artery) and in the aortic arch [1,48]. When blood pressure is elevated outside of the desired range, there is increased stretch of the arterial walls, leading to distortion (and increased firing) of these baroreceptors. This information travels with CN IX (from the carotid sinus) and CN X (from the aortic arch) to the Solitary Nucleus in the medulla [1,48]. This leads to inhibition of the sympathetic nervous system (via inhibition of rostral ventrolateral medulla, which normally tonically activates the sympathetic system) and activation of the parasympathetic nervous system (via CN X)—causing a decrease in heart rate, decrease in vasoconstriction, decrease in heart rate contractility, and so a decrease in blood pressure. As blood pressure drops, there is less distortion (and less firing) of the baroreceptors. There is less activation of the Solitary Nucleus, leading to disinhibition of the RVLM, increasing sympathetic innervation and activity.

If blood pressure drops too low, the venous baroreceptors are activated. These are low pressure-sensitive baroreceptors in the large veins and atria. When these are activated, there will be an increase in the secretion of antidiuretic hormone (ADH), renin, and aldosterone. These will increase fluid retention, increasing blood volume, increasing blood pressure.

Clinical Correlation: Baroreceptor Failure

The baroreceptors can fail. This can occur when the baroreceptors are injured (such as with radiation or surgery to the neck) or in the setting of severe carotid atherosclerosis (which stiffens the vessels and ruins the efficacy of a stretch-sensitive mechanoreceptor). Baroreceptor failure [51] can manifest as labile blood pressure with hypertensive crises that occur in times of physical or emotional stress, episodic hypotension, and/or orthostatic hypotension. With the absence of the baroreceptor, the checks and balances system that monitors the sympathetic system is lost, leading to uncontrolled sympathetic activity and hypertension. Treatment is aimed at trying to avoid triggers and with centrally acting adrenergic attenuators (such as the α-agonist clonidine).

2.9 Malfunction of the Autonomic Nervous System

If any part of the ANS malfunctions—whether by overactivity or underactivity—symptoms will arise. The ANS can be affected by medications or disease processes.

Sometimes, though, in cases of "autonomic dysfunction", the autonomic nervous system itself is intact; it is merely responding to deleterious stimuli. The ANS does not discern between different etiologies of a stimulus; it will respond to a given stimulus in the same way, no matter the cause. For instance, if someone has tachycardia upon standing, there can be a tendency to blame the ANS for "malfunctioning". However, there are many physiologic reasons the ANS could be overactive:

- With dehydration, when someone stands, their blood pressure will drop, activating the sympathetic system and increasing norepinephrine which will cause a rise in the heart rate. This is not a pathologic response. This is a compensatory response to support the blood pressure.

- With heart failure, cardiac contractility can be reduced so that when someone stands, blood pressure falls, activating the sympathetic system, increasing norepinephrine and heart rate. Again, this is a compensatory response to support blood pressure.

- If someone is in pain when they stand, the pain and emotional stress will activate the sympathetic system, increasing heart rate.

- If someone is sufficiently anxious, then emotional stress can also activate the sympathetic system, increasing heart rate.

In none of these scenarios is the ANS "malfunctioning". The ANS is responding, as it should, to different stimuli—hypotension, stress, and pain. The sources of the stimuli, in these instances, are the pathologic processes and are what should be addressed. Treating only the symptoms (i.e., giving beta blockers to control tachycardia) would not fix the underlying problem; it would only suppress the messenger, the ANS.

2.9.1 Clinical Correlation: Hyperadrenergic POTS

POTS is a clinical syndrome defined as an orthostatic rise in heart rate of >30 points in adults (>40 points in those under 20 years of age) accompanied by symptoms; this can be done via active stand test or passive head-up tilt. POTS itself is not a diagnosis but a description of symptoms, and it is important to identify the underlying etiologies. POTS is often multifactorial [52], with contributing factors including hypovolemia, deconditioning, increased venous pooling, and hyperadrenergic states. The latter, 'hyperadrenergic POTS', occurs when standing NE is >600 pg/mL [52]. One rare cause of hyperadrenergic POTS is a loss-of-function mutation in the norepinephrine transporter gene (*NET*), which decreases norepinephrine recycling and leads to overactivation of the SNS [53].

2.9.2 Clinical Correlation: Heart Failure and the Sympathetic System

In heart failure with reduced ejection fraction, the heart does not pump as efficiently as it should, often leading to hypotension. This can lead to chronic activation of the sympathetic, arginine vasopression (AVP), and renin-angiotensin aldosterone systems, increasing levels of norepinephrine, antidiuretic hormone, and angiotensin II, which (through fluid retention and vasoconstriction) help increase the blood pressure.

The chronic free water retention (courtesy of ADH) and increased fluid intake (courtesy of angiotensin II) also lead to hyponatremia, the degree of which is sometimes used as a marker of heart failure severity.

The increased contractility and increased afterload (from the increased norepinephrine) can lead to remodeling changes and disease progression, which worsen mortality [54].

2.10 Symptoms of an Overactive or Underactive Parasympathetic and Sympathetic Nervous System

When the parasympathetic nervous system is overactive, there can be miosis (worsening night vision), increased lacrimation, hypersalivation, GI distress (diarrhea, vomiting), bronchoconstriction, bradycardia, urination, erection, and increase in gastric acid and insulin secretion [1,3].

When the parasympathetic nervous system is underactive (parasympathetic failure), there can be dry eye and mouth, mydriasis (photophobia), bronchodilation, constipation, urinary retention, erectile failure, and a constant heart rate without variability [1,3].

When the sympathetic system is overactive, there can be hyperhidrosis, pallor, mydriasis (photophobia), hypertension, tachycardia, constipation, bronchodilation, and tremor [1,3].

If the sympathetic system is underactive (sympathetic failure), there can be hypohidrosis, ptosis, miosis (worsening night vision), and orthostatic hypotension [1,3].

2.11 What about the Enteric Nervous System?

The enteric system is the lesser known of the three main divisions of the ANS. The enteric system can function independently but is also affected by the parasympathetic and sympathetic systems.

Neurons of the enteric system surround the entire GI tract (from esophagus to anus) and control GI motility and secretion. The myenteric plexus (Auerbach's plexus) runs within the layers of the muscularis. The submucosal plexus (Meissner's plexus) runs within the submucosa beneath the muscularis. Many neurotransmitters are used in the enteric system, including acetylcholine, dopamine, and serotonin.

Clinical Correlation: Hirschsprung's Disease

Hirschsprung's disease is a congenital disorder where the precursors of ganglion cell (neural crest cells) fail to fully migrate to the distal portions of the GI system, leading to the partial absence of Meissner's and Auerbach's plexuses [55]. The affected areas will be atonic, leading to blockage. This affects the GI system in variable degrees. In some, only the most distal section (rectum) is affected,

causing constipation. In others, the affected area stretches proximally into the colon, leading to intestinal obstruction. Diagnosis is made via biopsy, identifying the lack of ganglion cells. Treatment is surgical, and prognosis generally good [56].

2.12 What About the Central Autonomic Network?

The CAN is exponentially more complex than the peripheral autonomic nervous system and is not fully understood. In brief, the CAN regulates the outflow of information to the ANS—increasing or decreasing activation of its component parts in response to various stimuli. There are cortical centers (prefrontal cortex, anterior and midcingulate cortex, and insular cortex), subcortical centers (central nucleus of the amygdala, paraventricular nucleus of the hypothalamus); and brainstem centers (periaqueductal gray in the midbrain, parabrachial nucleus at the junction of the midbrain/pons, locus coeruleus in the dorsal pons, raphe nuclei in the rostral ventrolateral medulla, dorsal motor nucleus of the vagus, nucleus ambiguous, and nucleus of the solitary tract in the medulla) [1,5].

3. Conclusions

Autonomic medicine is a multidisciplinary field, drawing on the knowledge of cardiology, neurology, gastroenterology, and urology. Symptoms arising from over- or under-activity of the ANS can affect any of these organ systems and can, at times, seem overwhelming. A thorough understanding of the anatomy, physiology, and biochemistry of the autonomic nervous system is crucial for clinicians who wish to effectively diagnose and manage these patients.

Author Contributions

FS, KS and PS made substantial contributions to the conception and design of the review, collection of resources, and production of the review with tables and images. FS, KS and PS contributed to writing the manuscript and making editorial changes. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We gratefully acknowledge the assistance and support of our colleagues and patients who support and teach us daily.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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