

TUCOM—OMS I

Autonomic Function Preview

Fundamentals of Osteopathic Medicine

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2025



For an osteopathic physician, the clinical importance of the autonomic nervous system (ANS) is central to understanding somatic dysfunction, spinal facilitation, and viscerosomatic integration (reviewed in 1), as well as the pharmacologic management of many disease states (reviewed in 2). Autonomics (A) is part of the ABC's of osteopathic medicine along with biomechanics (B), circulation (C), and screening (s). This exercise is intended to orient 1st year medical students to the importance of the autonomic nervous system in health and disease, as well as the specific receptors and signal transduction pathways that are involved in ANS control of body function. Next semester the drugs that stimulate and inhibit these receptors will be discussed. Learning the use of these drugs in the therapeutic management of diseases will continue throughout your four years of medical and during your clinical practice, as will the application of osteopathic principles and practices.

The material from this handout will be used for an individual and a team-based quiz during the Autonomic Function TBL ([explained on next page](#)). There will not be a pharmacology lecture for this material in this block, it will come later after you have had time to digest the enormity of the information provided. The OPP material is testable on the Fall Block 2 and 3 Didactic Skills exams, as well as any exam thereafter. Good luck!!!!!!!!!

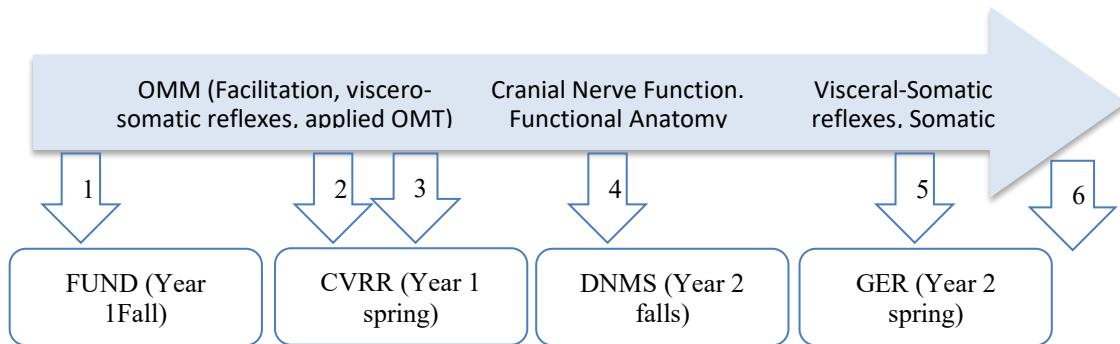
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Learning Design/Curriculum Integration

Learning Instructions

A full understanding of ANS function takes years to develop. To start on this learning path a progressive approach to the material will be used (See diagram below).



Step 1a: Students work through Autonomic Packet in the attempt to organize content and start to obtain awareness of the regulatory control provided prior to team-based learning event. It will be a huge if you can gain an awareness of receptor types, location, and functional control of organ function.

Step 1b: In lab learning exercise—TBL style (<http://www.teambasedlearning.org>). At start of the lab an individual quiz (IRAT) is given to give students time to think through questions. The same quiz is given in a team setting (GRAT). The team interaction is where the learning occurs—students teach each other. Providing the individual assessment also drives learning. Then answers are discussed. This is a low stakes environment.

Step 2: Students learn the drugs that alter ANS receptor function—classification, mechanism of action, and side effects. This is the vocabulary portion.

Step 3: Students use knowledge gained from step one and two to determine the best therapeutic management for various disease states (hypertension, ischemic heart disease, CHF, Asthma, COPD, migraine headaches, GI and GU issues).

Step 4, 5: Apply knowledge gained to disease states and drug side effects.

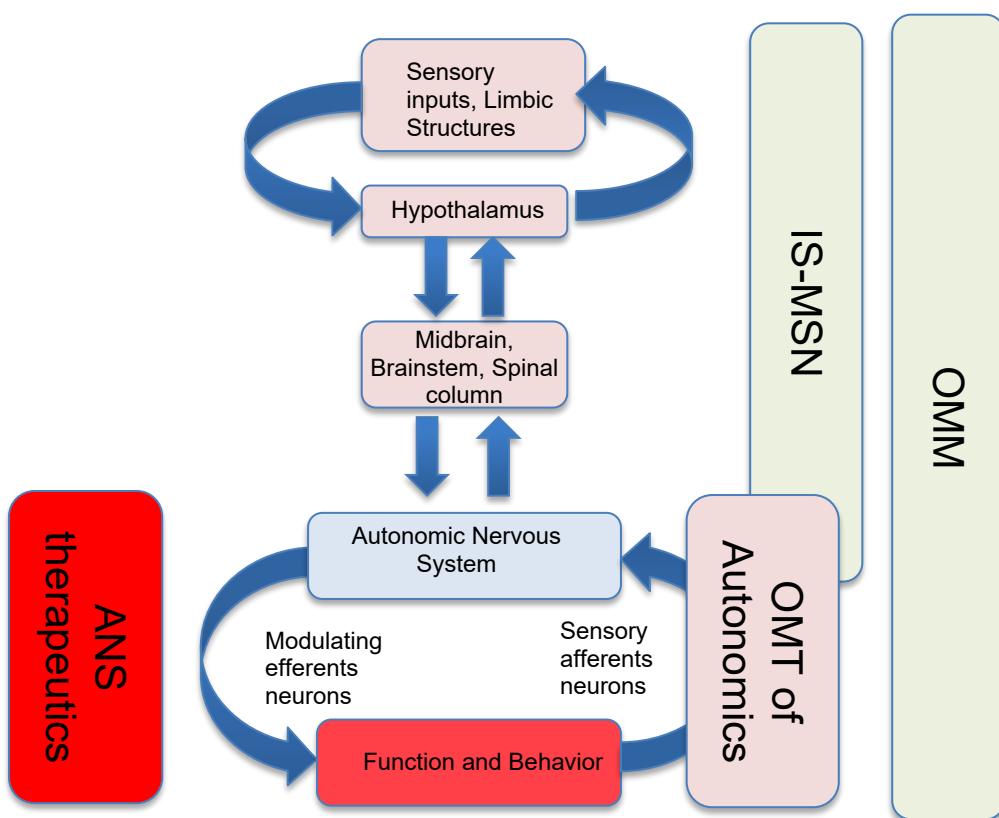
Step 6: Rocking the boards.

Step 7: Becoming an outstanding clinician.

Objectives for TBL. This document will provide you with the required material to necessary to know prior to the in-class portion of the TBL exercise. In class you will be given an individual quiz followed by a team-based quiz (TBL) and class discussion.

Autonomic Nervous System Curriculum Integration

The importance of the role of the Autonomic Nervous System (ANS) in health and disease cannot be overstated. Appropriate balance of the autonomic nervous system between the sympathetic and parasympathetic arms is vital to a homeostatic state of balance. In the OPP courses, you will learn how to modulate autonomic tone through manual manipulation. The peripheral sensory input is central to understanding somatic dysfunction and viscerosomatic reflexes. In the fundamentals course, you will learn intricacies involved in the homeostatic regulatory control of organ function mediated by ANS hormones and neurotransmitters and their respective cellular receptors. In the IS-MSN course, you will learn in detail the pathways that govern this system and its integration into the rest of the CNS. You are encouraged to read ahead if you are interested (1). In this exercise we will focus on the receptors and peripheral neurons involved in control of target organ function. It is at this level the use of pharmacologic agents becomes important.



Foundational Science objectives:

1. Classify, in general, the anatomical features of the autonomic nervous system
 - a. types of neurons (cholinergic or adrenergic) and principal neurotransmitters
 - b. The principle post-synaptic receptors at ganglionic and post-ganglionic junctions.
 - c. Innervation patterns.
2. Reconstruct the regulation of smooth muscle via autonomic signaling molecules.
3. Label the receptors involved in autonomic regulation as well as, their locations, function, and intracellular pathways.
 - a. Adrenergic receptors: alpha 1 and 2 as well as beta 1 and 2
 - b. Cholinergic receptors: Muscarinic--M₁, M₂, M₃, and nicotinic--N_n, N_m.
4. Differentiate how parasympathetic and sympathetic autonomic pathways control heart, smooth muscle, and liver function.
5. Reconstruct how changes in vascular tone produce compensatory feedback regulation of heart rate.
6. Interpret the consequences of the cellular types of feedback regulation on autonomic regulation.
7. Describe the autonomic regulation of eye function.

Osteopathic Principles and Practices objectives:

1. Recognize normal anatomy and physiology of the nervous system with particular attention to spinal reflex pathways
2. Define spinal facilitation (AKA central sensitization), including how it is created and maintained
3. Identify examples of the various types of spinal reflex pathways
4. Recognize the spinal regions pertinent to autonomic function with respect to the following: head/neck, heart, lungs, and regions of the gastrointestinal system and genitourinary system covered in the lecture materials
5. Recognize examples of allostasis and allostatic load, as well as autonomic imbalance and facilitation
6. Describe how to recognize, document, and treat facilitation, allostatic load, and autonomic imbalance with osteopathic manipulative treatment
7. Define and give examples of the following terms:

Allostasis, Allostatic load, Axoplasmic flow, Sympathicotonia, Parasympathicotonia, Cutaneous Red Reflex, Nociception, List what tissues have and lack nociceptive feedback, Homeostasis, Facilitation/central sensitization

The in-class discussion will focus on questions encountered during the TBL group quiz. After completing this exercise, the TBL, and assimilating material from lectures, the uses of several drugs to regulate blood pressure, airway resistance, cardiac, eye, gastrointestinal and urinary function will become clearer. These will be discussed in detail during the IS-CVRR (second semester course) and for the rest of your lives.

Section 1: Autonomic Nervous System Overview

A. ANS General Function

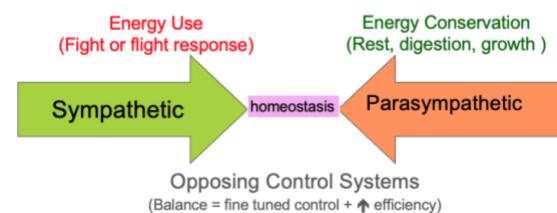
a. Homeostasis, Allostasis and the Mind-Body-Spirit

Homeostasis is defined as any self-regulating process by which biological systems maintain stability to optimize survival through continuously adjusting to external and internal conditions. The stability attained is a dynamic equilibrium, in which continuous change occurs yet relatively uniform conditions prevail. This self-regulating process was explored by French physiologist Claude Bernard in 1849 and the word homeostasis coined by American neurologist and physiologist Walter Bradford Cannon in 1926 ([2](#)).

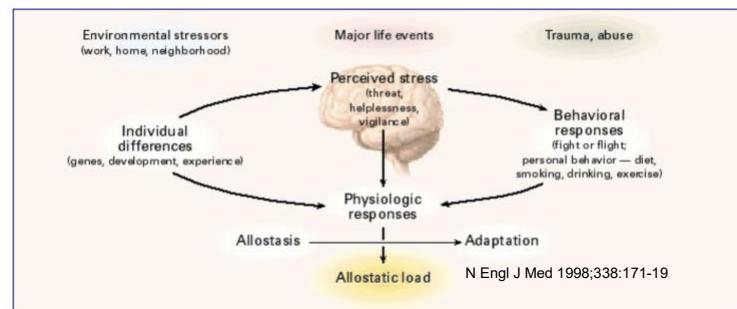
The general role of ANS is to participate, along with other local mediators and hormones, in the homeostatic control of body function. The principal targets of the ANS are the organs that contain smooth muscle, the heart, liver, kidneys, and secretory glands. Autonomic neurons that innervate organs produce immediate homeostatic responses by releasing neurotransmitters that activate organ cell surface receptors (the regulation of these receptors will be the focus of this handout). Hormones provide a more sustained long lasting and much slower response on organ dynamics. Local control is provided by release of autacoid and metabolites.

Homeostatic Balance

Definition: **Homeostasis** is the ability or tendency of an organism or a cell to maintain internal equilibrium by adjusting its physiological processes



Allostasis is the active process of maintaining homeostasis in response to stress or external changes by adapting and adjusting to the demands placed on the body. Unlike homeostasis, which focuses on maintaining internal balance within narrow limits, allostasis involves the organism's ability to adjust its internal environment to cope with a wider range of environmental challenges ([3](#)).



The autonomic nervous system (ANS) is essential to maintaining internal stability, or homeostasis, by integrating sensory input with dynamic efferent responses across multiple organ systems. However, under chronic or excessive stress, this finely tuned regulation may become maladaptive.

Understanding the concept of **allostatic load** is critical for osteopathic medical students and future physicians seeking to understand how the body adapts to internal and external challenges via neuroendocrine and autonomic mechanisms.

Definition: Any process that chronically or excessively drives the body away from homeostasis is referred to as **allostatic load**.

This process relies on the compensatory activation of **autonomic, endocrine, immune, and behavioral systems**, which work in tandem to produce mediators that promote short-term stability (e.g., catecholamines, cortisol, cytokines).

Allostatic load refers to the cumulative physiological burden imposed by repeated or sustained stress-mediated activation of adaptive systems, particularly the ANS and the hypothalamic-pituitary-adrenal (HPA) axis. Over time, this load may manifest as dysregulation in cardiovascular, metabolic, immune, and neuroendocrine function, increasing the risk for chronic disease ([\(6\)](#)).

The following table outlines common biomarkers of allostatic load, grouped by functional systems, and indicates their regulation by the ANS.

Type	Allostatic Load Markers	Regulated by ANS
CV and Respiratory	Systolic and diastolic blood pressure, heart rate, peak expiratory flow	Yes, directly through neuronal and hormonal control
Anthropomorphic	Waist to hip ratio, BMI	Indirectly, via sympathetic effects on adipose metabolism and feeding behavior
Neuroendocrine	Gut-regulating hormones (GLP-1, PYY, Ghrelin, CCK), Adipose hormones (leptin, adiponectin, resistin), Metabolic-regulating hormones (Insulin, glucagon, thyroid), GH	Yes, both sympathetic and parasympathetic neurotransmitters influence secretion via liver, gut, and pancreas
Metabolic	HbA1c, HDL, triglyceride, total cholesterol (TC), HDL/TC, albumin, glucose	Yes, see above
Immune	Insulin-like growth factor 1, IL-6, Fibrinogen, CRP	Yes, indirectly via ANS-modulated cytokine signaling and HPA axis interactions
Stress	Cortisol, ANS (norepinephrine, epinephrine)	Yes, via direct adrenal medulla and hypothalamic-pituitary-adrenal (HPA) axis activation

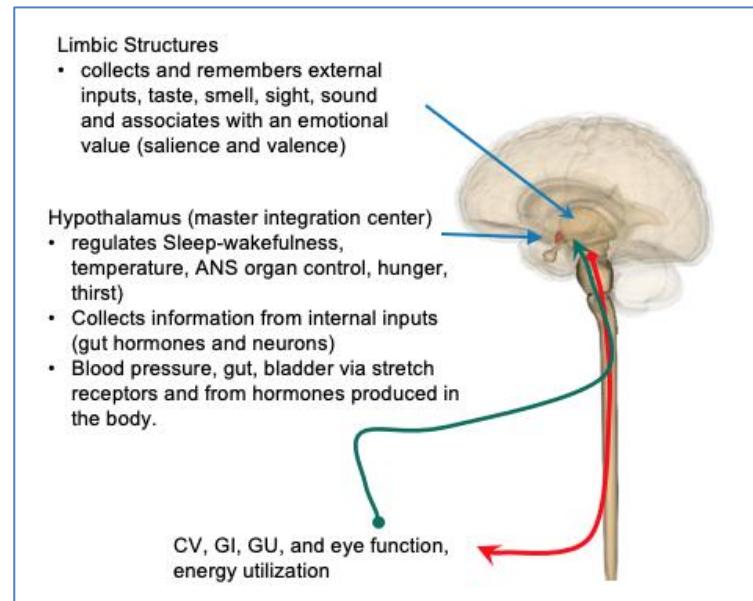
Mind-Body-Spirit: Dr. Still's Vision and Modern Neurobiology

In the late 19th century, **Dr. Andrew Taylor Still**, the founder of osteopathy, developed the importance of the interconnection between the body and mind as a key component underlying osteopathic principles and practice. In the Philosophy of Osteopathy, Dr. Still wrote: *First the material body, second the spiritual being, third a being of mind which is far superior to all vital motions and material forms, whose duty is to wisely manage this great engine of life. This great principle known as mind, must depend for all evidence on the five senses, and on this testimony, all mental conclusions are bad, and all orders from this mental court are issued to move to any point or stop at any place. Thus to obtain good results, we must blend ourselves with, and travel in harmony with nature's truths* (4).

Dr. Andrew Taylor Still taught that true health depends on the harmonious integration of mind, body, and spirit, with the body possessing an innate capacity for self-regulation and healing. Long before modern neuroscience mapped the precise neural circuits, Still understood that the human organism continuously blends external input and internal cues to maintain balance and adapt to life's demands.

Today, we know that this connection is biologically rooted in the central autonomic network, where sensory information, emotion, and cognition converge to guide physiologic responses.

Limbic Structures — like the hippocampus, nucleus accumbens, and amygdala — filter and attach emotional weight (emotional importance “salience” **and** positive or negative value “valence”) to what we see, hear, taste, and feel. This explains why stress, memory, or comforting sensory inputs can so powerfully shape the body’s state. The limbic system feeds this information directly to the **hypothalamus**, bridging emotion with physical function.



The **Hypothalamus**, the master regulator, integrates signals from:

- Internal body receptors (e.g., stretch receptors in the heart, gut, bladder)
- Hormonal messengers (like gut peptides and adrenal hormones)
- Limbic and cortical centers, adding emotional and cognitive context

It then fine-tunes **autonomic, endocrine, and behavioral outputs** — adjusting heart rate, digestion, sleep, hunger, and energy use — to keep the body in **dynamic equilibrium**, echoing Still's idea of the body's inherent wisdom.

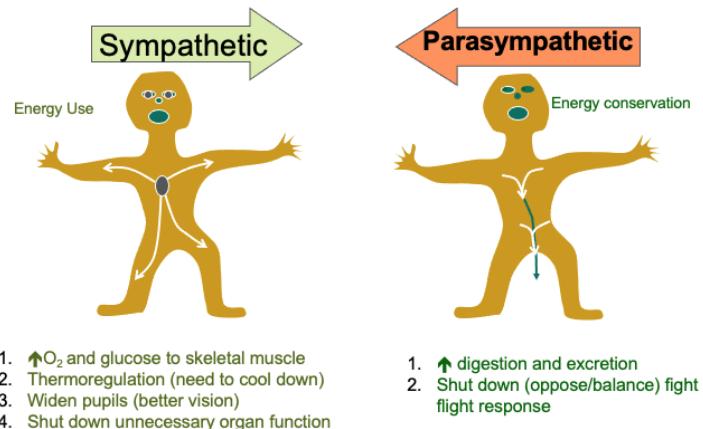
Signals flow through the **brainstem and spinal cord**, shaping cardiovascular, GI, GU, metabolic, and energy functions. Fast adjustments occur through autonomic reflexes; longer-term regulation involves hormonal feedback — all continuously monitored and adjusted.

In modern terms, this **mind-body-spirit connection** is the dynamic conversation between the senses, limbic memory, hypothalamic control, and the body's organs — all working together to protect survival and restore balance. Still's insight was that this integrated design is the foundation of **self-healing**, an idea that remains central to osteopathic practice today.

Learners are encouraged to reflect on the following:

1. What is the core difference between homeostasis and allostasis, and how does the autonomic nervous system contribute to both?
2. Why is the ANS able to produce rapid, immediate changes in organ function, while hormones provide longer-lasting effects? Give an example of each.
3. What does the term allostatic load mean, and how might chronic stress affect a patient's cardiovascular or metabolic health through this process?
4. How do the limbic structures and hypothalamus work together to link emotional experiences to physical body responses? Why is this clinically important?
5. Reflect on Dr. Still's concept of mind-body-spirit: How does modern neuroscience support the idea that emotional and sensory input shape physiologic balance and self-healing?

II. ANS Overview of Sympathetic and Parasympathetic Divisions



The autonomic nervous system (ANS) governs involuntary physiological processes critical to survival and homeostasis. It is divided into two main branches: the **sympathetic nervous system (S-ANS)** and the **parasympathetic nervous system (P-ANS)**. These systems often act in opposition but with coordinated balance, continuously adjusting organ function based on the body's internal needs and external environment.

Importantly, the ANS is not just a motor system — it also relies on **afferent sensory input** from the body's organs and tissues. Visceral sensory fibers constantly send information about stretch, pressure, chemical changes, and tissue damage to the central nervous system. This sensory feedback allows the brainstem and hypothalamus to monitor and adjust autonomic output in real time.

S-ANS: Fight or Flight

The sympathetic branch optimizes survival during times of physical or psychological challenge. Its main role is to prioritize the delivery of oxygen and glucose to the brain and skeletal muscles, ensuring these organs can meet increased demands during stress, activity, or danger.

Afferent role: Sensory input from baroreceptors, chemoreceptors, and visceral nociceptors informs the CNS about blood pressure, oxygen levels, and organ status, guiding appropriate sympathetic adjustments.

To optimize flow of oxygen and glucose, the S-ANS:

1. Increases cardiac output and respiratory efficiency (more oxygen and fuel flow).
2. Redirects blood flow away from non-essential organs like the GI and GU systems towards essential organs like muscle and brain.
3. Dilates alveoli in lungs to optimize oxygen absorption.
4. Stimulates the release of stored energy from the liver and fat.
5. Temporarily inhibits functions not critical for immediate survival (e.g., digestion, urination).

6. Integrates sensory feedback to fine-tune these responses rapidly.

P-ANS: Restoration and Conservation

The parasympathetic branch promotes restorative and energy-conserving functions during periods of calm. It helps maintain long-term health by slowing systems elevated during stress and by enhancing growth, repair, and digestion.

Afferent role: Continuous sensory input from stretch and chemoreceptors in the gut, bladder, and other organs informs the CNS when to activate parasympathetic pathways to support digestion, elimination, and rest.

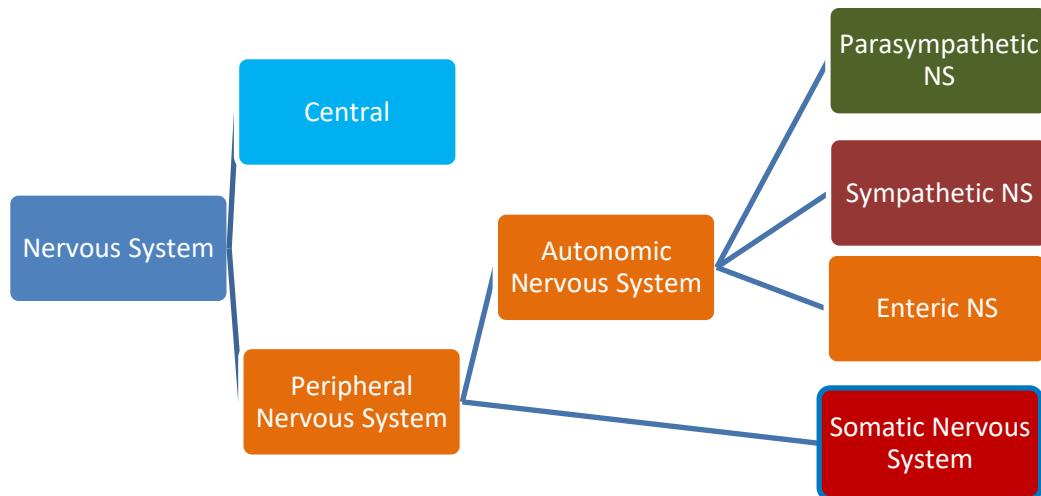
To optimize restoration and conservation, the P-ANS:

1. Slows heart rate and lowers metabolic output.
2. Enhances digestive secretion and motility.
3. Facilitates urination and defecation.
4. Protects airways during relaxation.
5. Supports nutrient absorption and storage.
6. Supports immune system regulation and tissue repair by promoting a physiologic state that favors recovery and balanced inflammatory responses.

Key point: The ANS works as a dynamic loop — **afferent sensory signals** gather real-time information, and **efferent ANS pathways** adjust organ function to maintain homeostasis and adapt to changing demands that promotes survival.

B. Anatomy

I. Anatomy: Nervous System Nomenclature



The **nervous system (NS)** is comprised of neurons inside the brain cavity and spinal cord (**Central NS**) and neurons that exit and enter the spinal cord from the body (**Peripheral NS**). The PNS, therefore, represents neurons that **exit** the spinal cord (**efferent pathways**) that control body function and sensory neurons that send signals from the body that **arrive** in the brain (**afferent pathways**). The CNS provides higher order processing of internal and external information and the organization of subsequent responses. The peripheral NS has two main branches. 1) The **somatic nervous system**, which is the conscious, voluntary, control of skeletal muscle activity and 2) the autonomic nervous system (ANS) or involuntary nervous system responsible for a dynamic balance between priming the body for fight or flight and creating a homeostatic maintenance of function to optimize survival. The ANS, in turn, is comprised of two main outputs: **Sympathetic** and **Parasympathetic** branches. The sympathetic side is associated with the fight or flight response that primes the body for action by increasing oxygen and glucose supply to muscle and brain when needed. When movement is unnecessary the parasympathetic side predominates. This side is associated with rest and digestion or perhaps energy acquisition states (decrease heart rate, lung alveolar diameter, protect eh retina from excess light via pupillary constriction, and increased digestion and micturition). The parasympathetic and sympathetic systems often provide opposing control on organ function (heart, lungs, and GI) allowing for rapid switching between rest and action and then back and forth. The enteric nervous system controls local gut function and is also influenced by the ANS.

[Chapter Reference \(5\)](#)

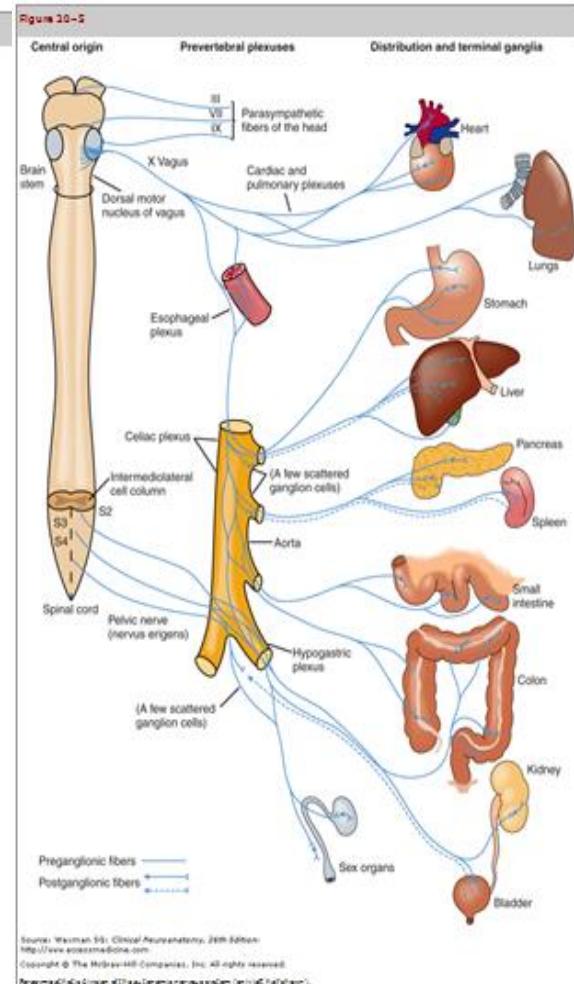
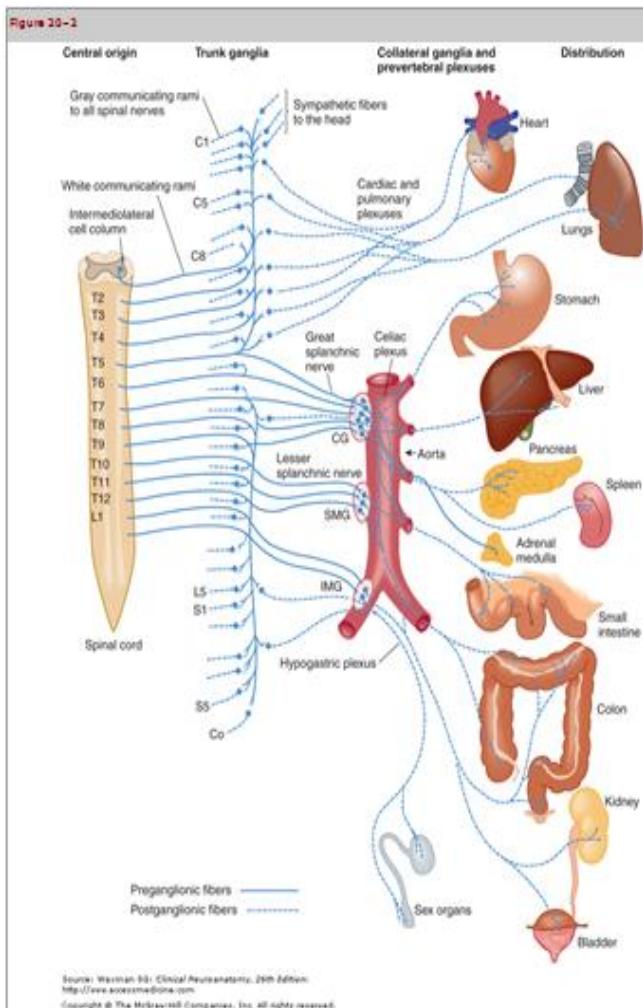
II. Anatomical Overview.

Sympathetic Nervous System (Anatomy)

Parasympathetic Nervous System (Anatomy)

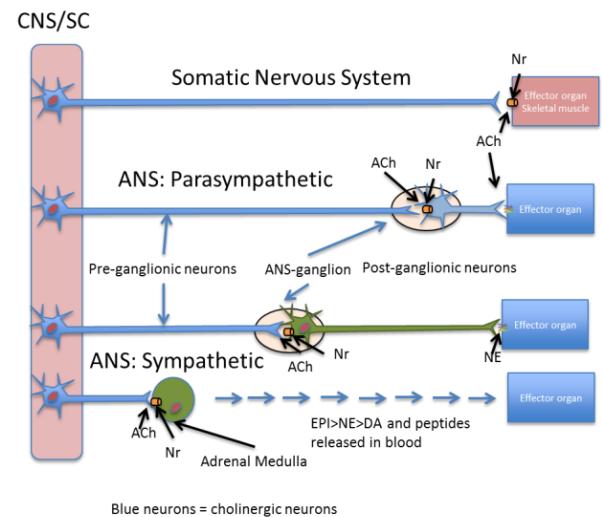
Future

Believe it or not you will become an expert about these figures shown below on your learning path journey to be ready for your clinical years. So—let's get started.



Chapter Reference (5)

The autonomic nervous system (ANS) has two main efferent pathways, the **parasympathetic** and sympathetic systems, that connect the CNS to the body. Both involve **pre-ganglionic** neurons, which originate in the CNS and synapse in peripheral ganglia, and **post-ganglionic** neurons, which extend to target tissues. Peripheral ganglia are clusters of neuron cell bodies outside the CNS where these synapses occur. Both systems use acetylcholine as the neurotransmitter at the pre-ganglionic synapse. Note: neurons are specialized to release only one type of classic neurotransmitter at all its terminals. This handout will focus on the nerves and organs innervated by the ANS, their functional control, and the cellular effects.



Blue neurons = cholinergic neurons

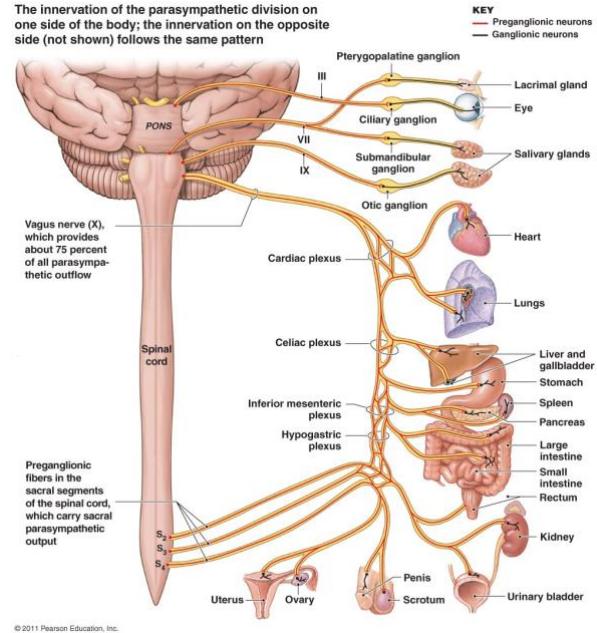
Adapted from—Barrett, Barman, Boitano, Brooks: Ganong's Review of Med. Phys.

Parasympathetic (PNS) efferent fibers exit the CNS via cranial nerves III, VII, IX, X, and sacral nerve roots S2-4. The long preganglionic fibers synapse with short postganglionic fibers in mural ganglia, which are flat, "painted-on" structures adhered to the organ wall. In both the parasympathetic and sympathetic systems, the junction between the preganglionic neuron and the postganglionic neuron is called a ganglion. (Ganglion names will be covered later; they are shown for reference in the diagram below.)

Components of the Parasympathetic Nervous System

- CN III - Oculomotor - Pupil constriction (Miosis), lens accommodation
- CN VII Facial - Lacrimal, sublingual and submandibular glands/nasal mucosa
- CN IX Glossopharyngeal - Parotid gland
- CN X Vagus - Heart, lungs, pancreas, liver, GB, upper GI, small intestine, large intestine to the splenic flexure.

[Chapter Reference \(5\)](#)



Anatomy of the Vagus Nerve (Parasympathetic neuron)

Think of the vagus nerve as a powerful communication network that controls many vital functions in the body, including heart rate, lung function, and digestion. Originating from the medulla oblongata in the brainstem, the vagus nerve exits the cranial cavity through the jugular foramen and travels downward within the carotid sheath alongside the common carotid artery and jugular vein.

As it enters the thoracic cavity, the vagus nerve branches out to the pharynx and larynx, as well as to the cardiac and respiratory plexuses. It then wraps around the esophagus as the right and left vagal trunks, forming the esophageal plexus. Before passing through the diaphragm at the esophageal hiatus (T10), the nerve rotates—the left vagus nerve moving anteriorly and the right moving posteriorly.

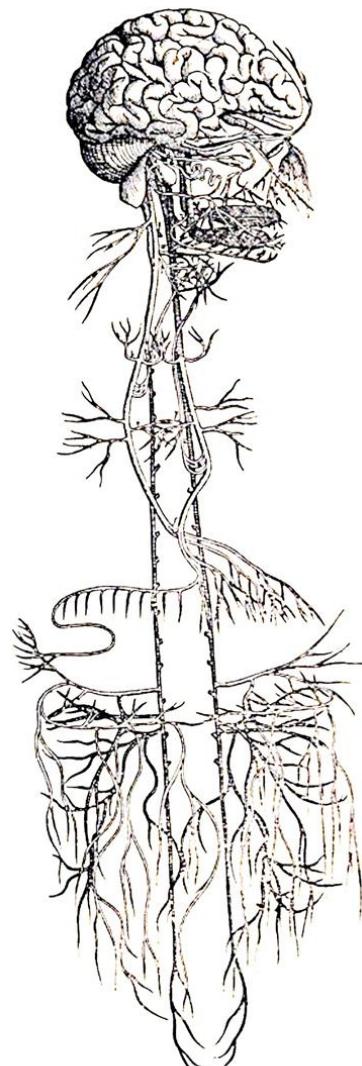
Once in the abdominal cavity, the vagus nerve integrates with the prevertebral ganglia, blending into the surrounding nerves as it follows the blood vessels to its target organs, where it plays a crucial role in parasympathetic innervation.

Pelvic Splanchnics - large intestine, urinary bladder, reproductive organs

The lower segments of the spinal cord S2-4 have intrinsic parasympathetic neurons that innervate the large intestine from the splenic flexure to the rectum and all the pelvic organs. These nerves begin in the lateral horn of the S2-4 spinal cord and travel with the ventral rami and branch off to become the pelvic splanchnic nerves. These nerves follow the endopelvic fascia to join the hypogastric plexus and synapse at the organ wall.

The various organs that these parasympathetic efferents innervate are:

- 1 Cranial roots:
 - a. Vagus (X) =lung, heart, stomach, pancreas, small intestine, large intestine to the splenic flexure.
 - b. IX and VII tear and salivary glands
 - c. III pupil constriction (Miosis), lens accommodation
- 2 Sacral roots S2-4: Pelvic splanchnic nerves
 - a. Large intestine beginning from splenic flexure
 - b. Rectum
 - c. Bladder
 - d. Reproductive organs.



Sympathetic Nervous System (SNS) Anatomy and Pathways

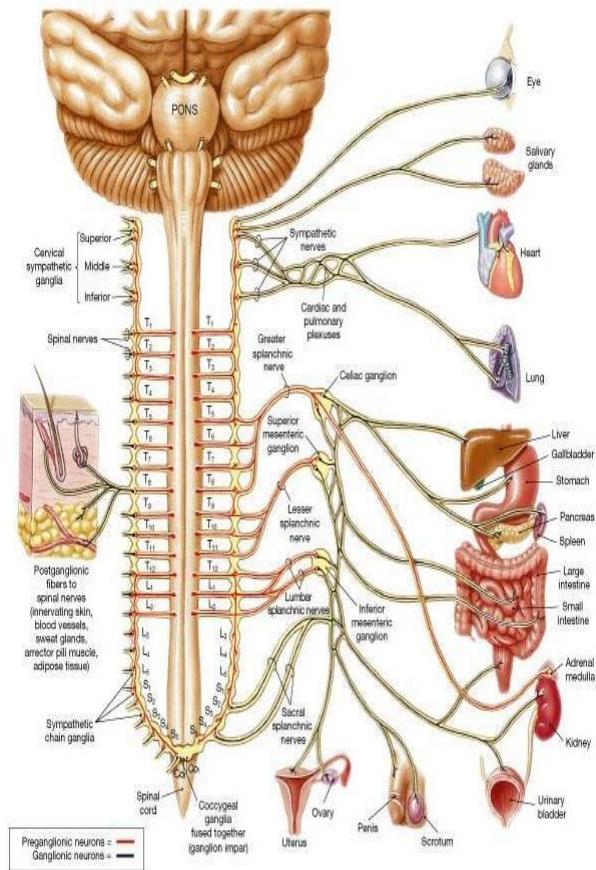
The sympathetic nervous system can be divided into two categories. The first is the vascular or peripheral component which innervates the vasculature (vasomotor), the sweat glands (secretomotor) and smooth muscle of the hair follicles (pilomotor) in the periphery of the body (skin, extremities face, etc.) The second category is that of the visceral region. This component innervates the vasculature and smooth muscle of the thoracic and abdominal organs, cardiac muscle of the heart and glands of the visceral organs.

The anatomy of the sympathetic nervous system includes the two sympathetic trunks that extend from the cervical region to the sacrum where they converge at the ganglion impar. The sympathetic trunks contain paravertebral ganglion which are organized as follows:

- 3 cervical - Superior, middle and inferior/stellate ganglion
- 12 thoracic
- 4 lumbar
- 4 sacral

The SNS is also associated with prevertebral ganglion which reside on the median axis of the body close to the vertebral bodies of the spinal column. These include:

- Celiac ganglion
- Superior mesenteric ganglion
- Inferior mesenteric ganglion
- Hypogastric plexus



Chapter Reference (5)

III. Osteopathy, ANS, Viscerosomatic Reflex

The autonomic nervous system (ANS) does not work in isolation — it's deeply integrated with the spinal cord's local circuitry, where sensory (afferent) input and motor (efferent) output can interact directly. This co-localization of visceral, somatic, and autonomic pathways within the spinal cord segments provides a neurobiological basis for *viscerosomatic reflexes*: patterns in which visceral organ dysfunction can produce palpable changes in segmentally related somatic tissues — or vice versa.

How does this happen?

Each spinal segment has a dorsal horn (where sensory information arrives) and a ventral horn (where motor and preganglionic autonomic neurons originate). Visceral afferents (sensory input from internal organs) travel back to the spinal cord and converge onto the same dorsal horn neurons that receive input from somatic tissues (like skin and muscle). This overlap means that abnormal or persistent visceral input — such as inflammation or organ irritation — can “spill over,” leading to increased excitability (facilitation) of local interneurons and motor neurons.

This facilitation can result in:

- **Altered sympathetic outflow:** Sustained visceral irritation can upregulate sympathetic activity to the affected region, contributing to increased tone in blood vessels, glands, or smooth muscle.
- **Somatic tissue changes:** The same segment may show palpable tissue texture changes, muscle hypertonicity, or tenderness — a hallmark of the viscerosomatic reflex recognized in osteopathic practice.
- **Bidirectional effects:** The reflex can go the other way too — persistent somatic dysfunction (e.g., muscle spasm) can send afferent signals that influence visceral organ function, contributing to a *somatovisceral reflex*.

Why does this matter clinically?

Understanding these connections helps explain why a patient with chronic gastritis, for example, may develop increased tension and tenderness in the mid-thoracic paraspinal muscles (T5–T9) — the same levels that supply sympathetic innervation to the stomach. Treating the somatic dysfunction can help modulate autonomic tone, improving visceral function — an important osteopathic principle.

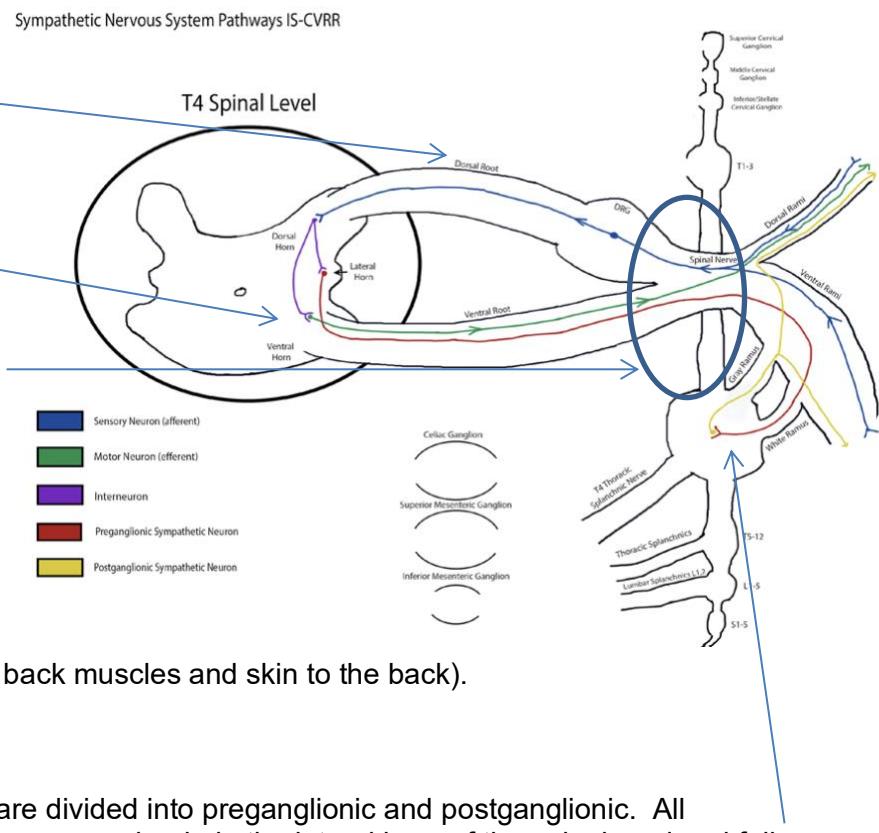
The example you gave — a patient with chronic GERD and new mid-thoracic back pain — illustrates this perfectly: the ongoing visceral irritation generates afferent signals that keep the corresponding spinal segments “primed,” producing muscle hypertonicity, restricted motion, and tenderness that can be palpated during an osteopathic exam.

Note: the co-localization of neuronal connections in the spinal cord and ganglia is likely to involve many types of pathology and is central to viscerosomatic reflexes [\(8\)](#).

The Section below will first describe the connections involved and then discuss the concept of facilitation and viscerosomatic reflexes.

Spinal segment overview

Each spinal segment (e.g. T4 shown) contains a dorsal horn and root which are afferent sensory pathways and a ventral horn and root containing efferent neurons. Those two roots converge to form a mixed spinal nerve and diverge to form the ventral and dorsal rami. The ventral ramus will innervate the hypaxial part of the body (limbs, trunk, head and neck) while the dorsal ramus innervates the epaxial part of the body (intrinsic back muscles and skin to the back).



The neurons in the SNS are divided into preganglionic and postganglionic. All preganglionic sympathetic neurons begin in the lateral horn of the spinal cord and follow the ventral root through the spinal nerve and into the ventral ramus. From here, the neuron courses through the white rami communicans into the sympathetic (paravertebral) ganglion.

The outflow from the spinal cord only happens from spinal segments T1-L2, meaning there are only white rami at these segments.

From the sympathetic ganglion, there are three options:

1. Exit on the same spinal level (yellow neurons shown)

As the preganglionic neuron reaches the sympathetic ganglion it will synapse in that ganglion and course through the gray rami communicans and diverge into the ventral rami and dorsal rami. These postganglionic neurons will only travel to the periphery on the body to innervate fascia, blood vessels, sweat glands and erector pilae muscles.

2. Travel up or down the sympathetic trunk (shown in red below)

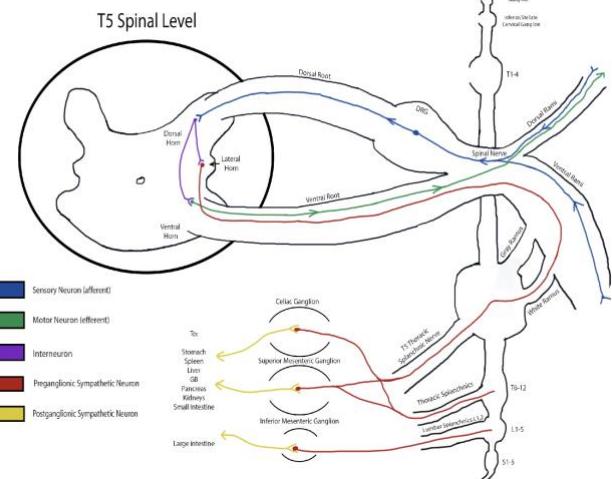
In this scenario, the preganglionic neuron enters the sympathetic ganglion, but instead of synapsing, the neuron can travel up or down the sympathetic trunk. For our purposes here, we will focus on the heart and lung which only require an ascending pathway. For the innervation to the heart (T1-4) and lungs (T2-6), the preganglionic neuron will travel all the way up to the three cervical ganglion and synapse in those ganglion. The postganglionic fibers will exit the ganglia and combine with fibers from the vagus nerve forming the cardio-respiratory plexus. Some fibers will exit the T1-6 ganglia directly to innervate parts of the heart and lungs.

3. Travel through splanchnic nerves to the viscera (shown in red below)

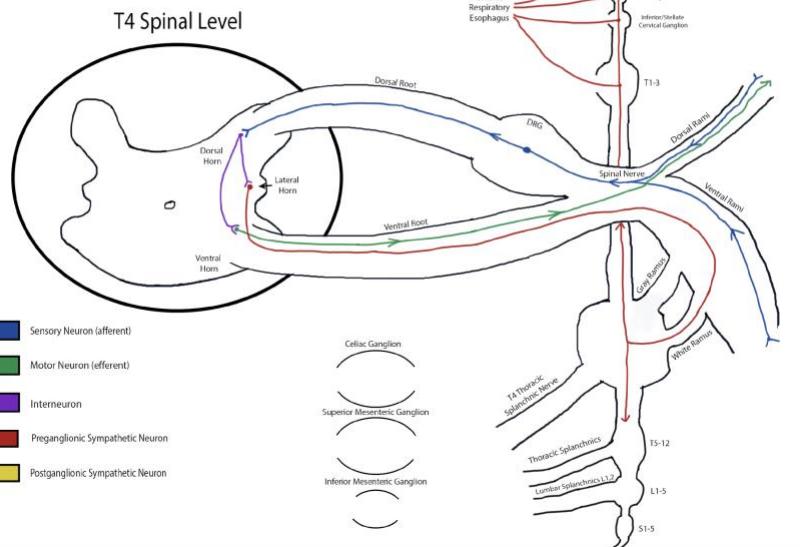
This last option again has the preganglionic neuron traveling through the white rami, into the sympathetic ganglion where it does not synapse. This neuron will not travel up or down the trunk, but exit through one of the splanchnic nerves. Splanchnic is Greek for “inward parts” or in our case, viscera. The neurons can pass through a number of splanchnic nerves including:

- Greater splanchnic nerve
T5-9
- Lesser splanchnic nerve
T10-11
- Least splanchnic nerve
T12
- Lumbar splanchnic nerve L1-2

Sympathetic Nervous System Pathways IS-CVRR



Sympathetic Nervous System Pathways IS-CVRR



The splanchnic nerves will course through the endothoracic and endoabdominal fascia to reach the prevertebral ganglia where they synapse with a postganglionic neuron. In these ganglia, the postganglionic sympathetic neurons combine with the preganglionic parasympathetic neurons to form a single autonomic plexus. This large, combined plexus will then follow the vasculature to the target organs. The prevertebral ganglion and associated organ systems are listed as follows:

- Celiac ganglion - foregut
- Superior mesenteric ganglion - midgut
- Inferior mesenteric ganglion - hindgut

Sacral Sympathetic

The sympathetic innervation to parts of the large intestine (splenic flexure to rectum) and pelvic organs have a different pathways to their target organ. The preganglionic neurons originate in the lateral horn of L1-2 and descend to the S2-4 sympathetic ganglion. From there they synapse on a postganglionic neuron and exit the ganglion to either directly innervate the target organ or connect with the hypogastric plexus and travel back up into the abdomen to innervate that part of the large intestine.

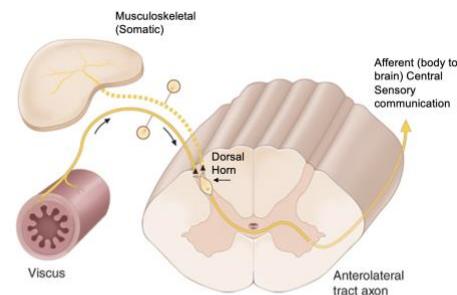
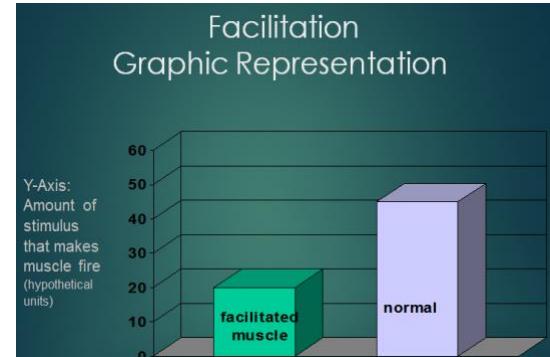
C. Facilitation and Central Sensitization

In osteopathic medicine, **facilitation** — also called **central sensitization**, **segmental sensitization**, or **spinal cord hyperexcitability** — describes a state in which certain spinal cord neurons (like interneurons and second-order neurons) become partially depolarized and more responsive than normal.

Once a segment is facilitated, those neurons require less input to fire, meaning that *even minor or routine signals* from the body can trigger exaggerated responses. This heightened excitability explains how *chronic pain, persistent somatic dysfunction, or altered autonomic output* can continue long after the initial cause (like local irritation or injury) is resolved.

Facilitation is a core mechanism behind **viscerosomatic reflexes**. When ongoing visceral afferent signals — such as from an inflamed organ — converge on spinal cord segments that also receive input from somatic tissues, they can maintain those segments in a facilitated state. This explains why:

- **Visceral dysfunction can produce predictable patterns of somatic changes.** For example, chronic gallbladder inflammation can lead to palpable muscle tension or tenderness at spinal levels T5–T9 — the same segments supplying sympathetic innervation to the gallbladder.
- **The reflex becomes self-sustaining.** Once neurons are facilitated, normal background input is enough to perpetuate the loop, amplifying both local muscle tension and altered sympathetic tone.
- **Somatic dysfunction can persist or recur until the cycle is interrupted.** Osteopathic manipulative treatment (OMT) seeks to identify and treat these facilitated segments, restoring normal motion, breaking the abnormal feedback loop, and supporting balanced autonomic regulation.

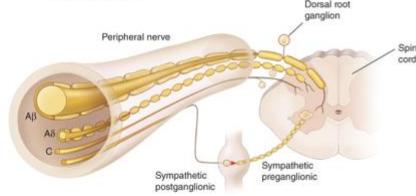


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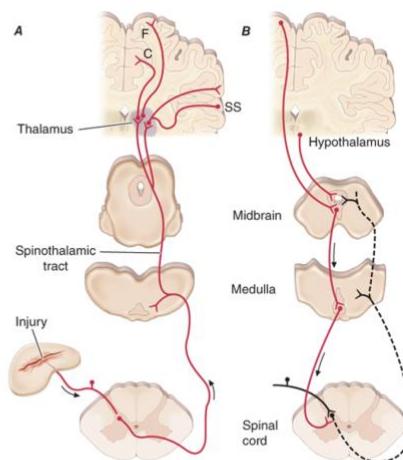
Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo; Harrison's Principles of Internal Medicine, 20th Edition
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In summary, **facilitation provides the neurophysiologic explanation for why visceral problems can manifest as somatic findings — and why treating the somatic component can help normalize autonomic function and promote healing of the underlying visceral issue.** [\(9\)](#)

- “**Nociception**”: Unconscious detection of tissue injury, a function of first order (nociceptors) and second order neurons
 - Mechanical and neurochemical process
 - Nociceptor (heat, cold, mechanical distortion, pH)
 - A β , A δ , C sensory neurons
 - Localized somatic sensation that can discern different types of painful stimuli via sending signals up the spinal column (nociception)
 - Similar in physiology and intensity in all individuals



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser; D.L. Longo, J. Loscalzo. Harrison's Principles of Internal Medicine, 20th Edition
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Now lets take a closer look on how facilitation or central sensitization might occur.

The key sensory inputs that converge in the dorsal horn are shown below.

Nociceptive input: Pain signals carried by A-delta and C fibers from nociceptors (mechanical, thermal, polymodal).

Proprioceptive input: Position and stretch information from muscles and joints via Ia, Ib, and II fibers.

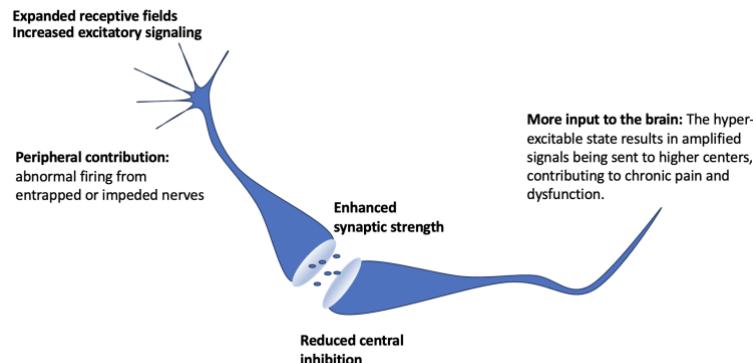
Mechanoreceptive input: Touch, pressure, and vibration signals via A-beta fibers.

Visceral afferents: Internal organ input that overlaps with these pathways.

Note: Viscero-visceral reflexes are the hardest clinically to detect but do occur. Any viscera that is irritated could feedback and upregulate the efferent input to a viscera of the same segmental innervation (like liver and stomach).

Primary Afferent Nociceptors (PAN's) are nociceptors that respond to injurious or potentially injurious stimuli. These are small caliber, unmyelinated or lightly myelinated nerves. They are widely distributed throughout the body, but are conspicuously ABSENT from the following tissues:

- Articular and other hyaline cartilage
- Nucleus pulposus of intervertebral discs
- Central nervous system parenchyma



When these signals overlap in the same spinal segments, abnormal or repetitive input can keep neurons in a hyper-exitable state (more neuronal depolarization, increased excitatory transmitter release, less central efferent inhibition). This overlap explains referred pain and viscerosomatic reflexes — key reasons why dysfunction can persist or spread to seemingly unrelated structures.

Axonal Conditions Can Alter Communication

Facilitation is not just about the spinal cord. The axons carrying sensory input play an important role in maintaining or amplifying this state.

What conditions can alter axonal functioning?

- Mechanical stress and entrapment: Compression within anatomical tunnels or fascial restrictions can deform the axon, causing local depolarization and spontaneous discharges — like the shooting pain when you hit your “funny bone” (ulnar nerve).
- Inflammation: Local chemicals lower ion channel thresholds, making nerves fire more easily.
- Axoplasmic flow: Healthy bidirectional transport within the axon is vital for neuron health. Even mild mechanical restrictions can disrupt this flow and sustain abnormal firing.

Osteopathic manipulative treatment (OMT) addresses these peripheral factors by restoring tissue motion, relieving nerve entrapment, and improving local circulation. This can help break the cycle of excessive input that feeds facilitation. Facilitation shows how overlapping input in the dorsal horn lets visceral, somatic, and autonomic pathways interact — creating referred pain and viscerosomatic reflexes. When visceral and somatic afferents converge on spinal interneurons, neurons can become hyperexcitable, needing less input to fire. This helps explain why chronic visceral issues, like GERD, can cause related back pain or tissue changes: the affected spinal segments are “facilitated.”

Types of viscerosomatic reflexes produced by facilitation.

THE NERVOUS SYSTEM

CENTRAL NERVOUS SYSTEM Body's coordinator & decision maker	BRAIN Directs & coordinates more complex innate reflexes and learned reflexive responses.						
	SPINAL CORD Directs & coordinates less complex innate reflexes.						
PERIPHERAL NERVOUS SYSTEM Network of peripheral nerves connecting the Central Nervous System to the body.	<table border="1"> <tbody> <tr> <td>SOMATIC NERVOUS SYSTEM Manages somatic reflexive responses:<ul style="list-style-type: none">• Triggered thru skeletal muscles• Innate, involuntary & non-directed• Learned, voluntary & directed</td><td>AUTONOMIC NERVOUS SYSTEM Manages autonomic reflexive responses:<ul style="list-style-type: none">• Triggered thru smooth muscles of the organs, glands & blood vessels• Innate, involuntary & non-directed• Can be learned and directed thru conditional association</td><td>PARASYMPATHETIC NERVOUS SYSTEM Engages & moderates non-alarm state reflexes, maintaining vital functions, fostering calm, & optimizing growth through:<ul style="list-style-type: none">• Restoration• Social Engagement</td><td>SYMPATHETIC NERVOUS SYSTEM Engages & moderates mobilization state reflexes, readying the body for action through:<ul style="list-style-type: none">• Focus & Advance, or• Fight & Flight</td><td>NON-MYELINATED VAGUS NERVE Engages & moderates immobilization state reflexes, stilling the body's vital functions to a minimum to ensure preservation through:<ul style="list-style-type: none">• Pause, or• Freeze</td><td>ENTERIC NERVOUS SYSTEM Manages the gastrointestinal system</td></tr> </tbody> </table>	SOMATIC NERVOUS SYSTEM Manages somatic reflexive responses: <ul style="list-style-type: none">• Triggered thru skeletal muscles• Innate, involuntary & non-directed• Learned, voluntary & directed	AUTONOMIC NERVOUS SYSTEM Manages autonomic reflexive responses: <ul style="list-style-type: none">• Triggered thru smooth muscles of the organs, glands & blood vessels• Innate, involuntary & non-directed• Can be learned and directed thru conditional association	PARASYMPATHETIC NERVOUS SYSTEM Engages & moderates non-alarm state reflexes, maintaining vital functions, fostering calm, & optimizing growth through: <ul style="list-style-type: none">• Restoration• Social Engagement	SYMPATHETIC NERVOUS SYSTEM Engages & moderates mobilization state reflexes, readying the body for action through: <ul style="list-style-type: none">• Focus & Advance, or• Fight & Flight	NON-MYELINATED VAGUS NERVE Engages & moderates immobilization state reflexes, stilling the body's vital functions to a minimum to ensure preservation through: <ul style="list-style-type: none">• Pause, or• Freeze	ENTERIC NERVOUS SYSTEM Manages the gastrointestinal system
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PARASYMPATHETIC NERVOUS SYSTEM

Predominant when in the Non-Alarm State

Normative Action:

- ↑ Slows heartbeat – *normalizes blood flow*
- ↑ Lowers blood pressure -- *slows pulse/stroke volume decrease*
- ↑ Constricts pupils – *returns to normal focus*
- ↑ Normalizes trachea and bronchia – *returns to normal respiration*
- ↑ Normalizes blood flow to all areas of the body – *returns to normal skin color, energy normalized for all organs*
- ↑ Normalizes peristalsis in gastrointestinal tract – *returns to normal digestion*

SYMPATHETIC NERVOUS SYSTEM

Predominant when in the Mobilization State

Excitatory Action:

- ↑ Stimulates heartbeat -- *increases blood flow to brain/muscles*
- ↑ Raises blood pressure – *increases pulse/stroke volume*
- ↑ Dilates pupils – *heightens focus*
- ↑ Dilates trachea & bronchia – *increases respiration*
- ↑ Shunts blood from skin & viscera to skeletal muscles, brain, & heart – *pales skin, conserves energy for necessary organs*
- ↑ Inhibits peristalsis in gastrointestinal tract – *slows digestion*

<https://masgutovamethod.com/the-method/the-role-of-autonomic-reflexes>

Due to the complexity of the nervous system, there are overlapping spinal reflex pathway. Somatic, visceral, and autonomic nerves can cross in the spinal cord. This “cross-wiring” can lead to increased tone in a visceral efferent nerve it was synapsed upon by a somatic afferent nerve.

There are 4 main types of spinal reflexes we talk about:

- Viscero-somatic
 - Visceral sensory input produces a reflex response in a segmentally related somatic structure
- Somato-visceral
 - Somatic sensory input produces a reflex response in a segmentally related visceral structure
- Somato-somatic
 - Somatic sensory input produces a reflex response in a segmentally related somatic structure
- Viscero-visceral
 - Visceral sensory input produces a reflex response in a segmentally related visceral structure

When naming these reflexes, it is important to remember that the cause of the effect comes first, then the effect. In a viscero-somatic reflex, the cause is visceral and the effect is somatic.

Clinical Correlates:

- 1) What often deadly cardiac condition is a clear demonstration of a viscero-somatic reflex?

A **heart attack (myocardial infarction, MI)** is a classic real-world example of how **facilitation** and **referred pain** arise through the autonomic nervous system.

Sensory side:

- Pain signals from the ischemic heart travel through **visceral afferent fibers** that run with **sympathetic cardiac nerves** back to spinal cord segments **T1–T5**.
- These segments also receive **somatic sensory input** from the chest wall, left shoulder, arm, and jaw.
- Because both inputs **converge in the same dorsal horn neurons**, the brain can misinterpret the pain's true source. This explains why cardiac pain is often **felt in the shoulder, inner arm, or jaw** — a classic case of **referred pain**.

Autonomic motor side:

- The same segments contain **preganglionic sympathetic neurons** that become **facilitated** when this input is strong or repetitive.
- This increased sympathetic activity can:
 - **Raise heart rate and contractility**, which may further strain the ischemic myocardium.
 - Cause **segmental tissue texture changes**, such as tight or boggy muscles in the upper thoracic spine.
 - Contribute to **sweating, pallor, or vasoconstriction** in areas linked to the same spinal levels.

This pattern is a classic **viscero-somatic reflex** driven by the **ANS**: the visceral input (heart) alters the excitability of spinal neurons, which affects both somatic tissues and autonomic outflow. Osteopathic physicians can use palpation to detect these changes (e.g., paraspinal hypertonicity at T1–T5) as clues to underlying visceral disease.

- 2) 33-year-old male with GERD (Gut acid reflux disease) who now complains of upper thoracic back pain. Put your osteopathic thinking cap on and think of how the two conditions are related. The visceral primary afferents from the stomach and esophagus come from the region of T5-T10, which is where the pathology of GERD exists.
- 3) A 9-year-old female with asthma is experiencing an acute bout of coughing and shortness of breath and upon osteopathic structural examination has warm, boggy soft tissue findings in thoracic segments T2-T6 is likely experiencing a viscero-somatic reflex.
- 4) A 2-week-old infant male that always sleeps with his head turned to the right presents with extreme abdominal distension, decreased food intake, and poor sleep. Osteopathic structural examination reveals a compressed right occipital condyle (and likely right vagus nerve). This likely represents a somato-visceral reflex.
- 5) A 25-year-old male avid soccer player presents with mild, chronic low back pain for the last 3 months. He admits to experiencing several ankle sprains playing soccer in the years prior. This likely represents a somato-somatic reflex.
- 6) A 43-year-old male presented to your clinic with acute onset of low back pain radiating down his right leg. He has never had these symptoms before and they began suddenly after lifting a heavy box. You diagnose him with a herniated nucleus pulposus of the lumbar spine.

True/False: It is the nucleus pulposus of the intervertebral disc that senses the nociceptive input that you perceive as pain.

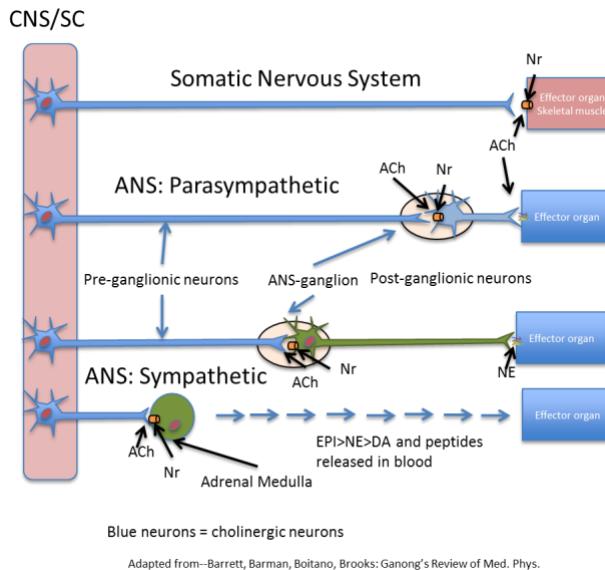
PAN's are stimulated primarily by mechanical, thermal, and chemical signals. They synapse in the spinal gray matter and project to the arousal centers of the brainstem. Through repetitive stimulation, they become MORE sensitive to lower-level stimuli.

Note: The concept above explains why sitting or typing with poor ergonomics becomes more and more difficult, eventually leading to pain and disability in some. Through the repetitive stimulation of the mechanoreceptors, they become more sensitive to the stimulus and can therefore more readily transmit nociceptive input to the brain where it is perceived as pain.

[Reviewed in 9,10](#)

D. ANS neurotransmitters, receptor, intracellular responses

I. Neurotransmitters



A simple rule of thumb for understanding autonomic neurotransmission is this:
All neurons that exit the spinal cord are cholinergic, meaning they synthesize and release **acetylcholine (ACh)** as their primary neurotransmitter.

This includes:

- **All preganglionic autonomic neurons** (both sympathetic and parasympathetic)
- **Somatic motor neurons** (which innervate skeletal muscle)
- **Preganglionic sympathetic neurons** that directly stimulate the adrenal medulla, which then releases **epinephrine (and some norepinephrine)** into the bloodstream as hormones. At the ganglionic synapse, **acetylcholine** is always released and binds to **nicotinic receptors** on postganglionic neurons or adrenal chromaffin cells.

Autonomic Neurotransmitters

Norepinephrine

Released from sympathetic post-ganglionic neurons only. Mediates most sympathetic control of organ function except secretion and adrenal hormone release

Acetylcholine

Utilized by both parasympathetic & sympathetic systems

- 1) Acetylcholine that is secreted by preganglionic nerves and binds to post-synaptic nicotinic acetylcholine receptors—mediates both parasympathetic and sympathetic effects at the ANS ganglion, sympathetic response at adrenal medulla, and Non-ANS somatic muscles.
- 2) Acetylcholine binding to muscarinic ACh receptors mediates parasympathetic response on organ and sympathetic response on thermoregulatory sweating

Postganglionic neurons then differ:

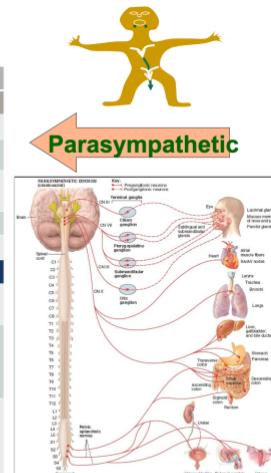
- **Parasympathetic postganglionic neurons** remain **cholinergic**, releasing acetylcholine onto **muscarinic receptors** at the target organ.
- **Most sympathetic postganglionic neurons** are **adrenergic**, releasing **norepinephrine (NE)** onto **adrenergic receptors (α and β)** in target tissues.
- An important exception is that **sympathetic postganglionic neurons** innervating **thermoregulatory sweat glands** are **cholinergic** — they release acetylcholine onto **muscarinic receptors** to trigger sweating.

Additionally, **dopamine** serves as a neurotransmitter in some specialized sympathetic pathways (e.g., renal vasculature) and as a precursor for norepinephrine and epinephrine synthesis in the adrenal medulla and sympathetic nerves.

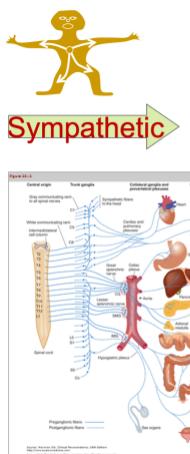
A summary of the NT location and receptors involved for norepinephrine and acetylcholine is provided below. More details will be provided in the next section.

PANS: NT and Receptors

Effect Produced	Physiologic effect	NT, R	ISM
↑ digestion and excretion			
↑ urinary outflow	Contract bladder walls	Ach, M3	IP3
	Dilate bladder sphincters	ACh, M3/NO	cGMP, K+ outflow
↑ digestion			
↑ gastric acid and salivary secretion	Ach, M3	IP3	
Contract gut walls	Ach, M3	IP3	
Relax gut sphincters	ACh, M3/NO	cGMP, K+ outflow	
Shut down unnecessary organ function			
Decrease Cardiac output	Slow heart	ACh, M2	Dec cAMP, K+ outflow
Constrict lung alveoli and increase secretions	Optimize lung protection	Ach, M3	IP3
Constrict pupils, lacrimation	Protect retina from excessive light, inc. corneal and conjunctival moisture	ACh, M3	IP3



The parasympathetic nervous system promotes energy storage and conservation by using acetylcholine to activate muscarinic receptors. This supports digestion, nutrient absorption, and reduced cardiac output during rest and recovery.



SANS: NT and Receptors

Effect Produced	Physiologic effect	NT, R	ISM
↑O₂ and glucose to skeletal muscle and brain:			
relax bronchi	↑ Surface area = more O ₂ exchange	NE, β2	cAMP
Shunt blood from organs to muscle	Vasoconstrict organ blood flow Vasodilate skeletal muscle flow	NE, α1 NE, β2	IP3 cAMP
↑ glucose production (liver)	Stimulate gluconeogenesis and promote glycolysis	NE, β2 (mix)	cAMP
↑ Heart rate and contractile force	Increases blood supply	NE, β1	cAMP
↑ water volume through hormones	Increases kidney renin release	NE, β1	cAMP
Shut down unnecessary organ function			
Relax bladder walls	Reduces urgency	NE, β3>2	cAMP
Constrict bladder sphincters	Reduces urgency	NE, α1	IP3
Relax gut walls	Reduces gut muscle activity	NE, β2>3	cAMP
Constrict gut sphincters	Reduces defecation	NE, α1	IP3

The sympathetic nervous system primarily uses norepinephrine to activate alpha and beta receptors, triggering cAMP or IP₃ signaling based on tissue needs. An exception is thermoregulatory sweating, where acetylcholine stimulates muscarinic receptors to promote heat loss during activity.

Key takeaway:

- **Acetylcholine** is the dominant neurotransmitter for all somatic and preganglionic autonomic pathways and for parasympathetic targets.
- **Norepinephrine** is the primary neurotransmitter for most sympathetic postganglionic neurons.
- **Epinephrine**, mainly secreted by the adrenal medulla, acts as a hormone to reinforce sympathetic responses systemically.
- **Dopamine** plays a role in some sympathetic targets and in catecholamine synthesis.

Together, these neurotransmitters and their receptors provide the precise, tissue-specific control that is essential for balanced autonomic function.

The two main transmitters of the autonomic nervous system are _____ and _____.

Which neurotransmitter is used by both the S-ANS and P-ANS?

_____.

Which neurotransmitter stimulates secretions?

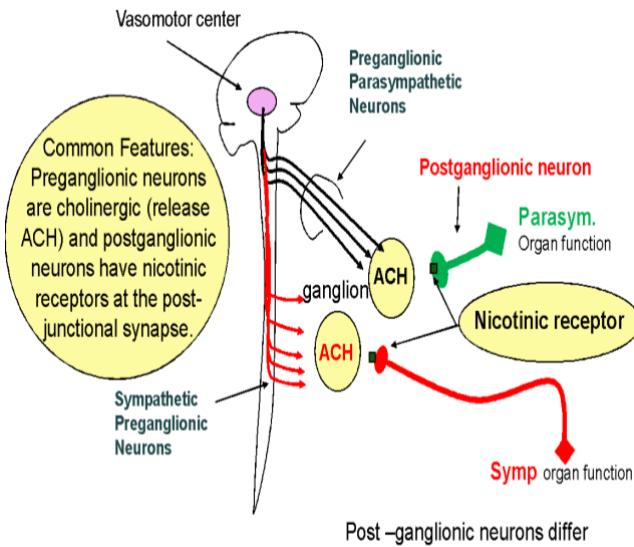
_____.

Which neurotransmitter is released by pre-ganglionic neurons in both S-ANS and P-ANS ganglia? _____

All neurons that exit the spinal cord synthesize and release _____

[Chapter reference \(7\)](#)

II. Receptors and Locations



Nicotinic Receptors (ANS Ganglionic and Neuromuscular Junction):

Both the **parasympathetic** and **sympathetic** divisions of the autonomic nervous system (ANS) share **acetylcholine (ACh)** as the neurotransmitter released by their **preganglionic neurons**. At the ganglionic synapse, acetylcholine binds to **nicotinic cholinergic receptors** on the **postganglionic neurons**.

These **nicotinic acetylcholine receptors (nAChRs)** are **ligand-gated ion channels**: when ACh binds, they open and allow positive ions — mainly sodium (Na^+) and some calcium (Ca^{2+}) — to flow into the postsynaptic cell. This causes a **rapid depolarization**, bringing the postganglionic neuron closer to threshold so it can fire its own action potential.

Key point: Nicotinic receptors at ganglia are sometimes called **Nn receptors** (neuronal type). These differ structurally from the nicotinic receptors found on skeletal muscle.

Acetylcholine is also the neurotransmitter used by somatic motor neurons, which innervate skeletal muscle for voluntary movement. These neurons are also **cholinergic**, but the nicotinic receptors on muscle cells are a **muscle subtype (Nm)**. Although they function similarly as ion channels, they have a different **subunit composition**, which gives them slightly different properties suited for fast, strong muscle contraction.

Why this matters:

- Ganglionic nicotinic receptors (Nn) → found on postganglionic neurons in both S-ANS and P-ANS pathways.
- Muscle nicotinic receptors (Nm) → found at the neuromuscular junction.
- Both receptor types rapidly transmit signals but are pharmacologically distinct — an important point when learning about drugs that target one but not the other.

A more detailed discussion of receptor structure, subunits, and downstream effects will follow in later sections.

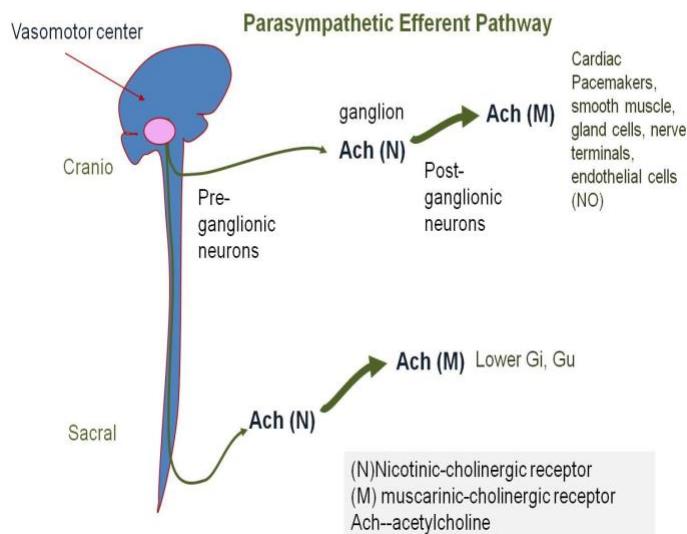
At this stage the parasympathetic and sympathetic neurons share common features. For example, both systems have preganglionic neurons that release _____, and both systems post-ganglionic neurons activated when the released acetylcholine binds to and opens _____-Ach-receptor channels.

Thus far the take home message regarding neurotransmitters and receptors involved in activation of post-synaptic ganglionic neurons is that both systems share the pre-synaptic-cholinergic-neuronal-type and post-synaptic nicotinic receptors. The systems differ in how they are regulated, their anatomy, and function. This will be discussed next.

Post-ganglionic effector organ receptors:

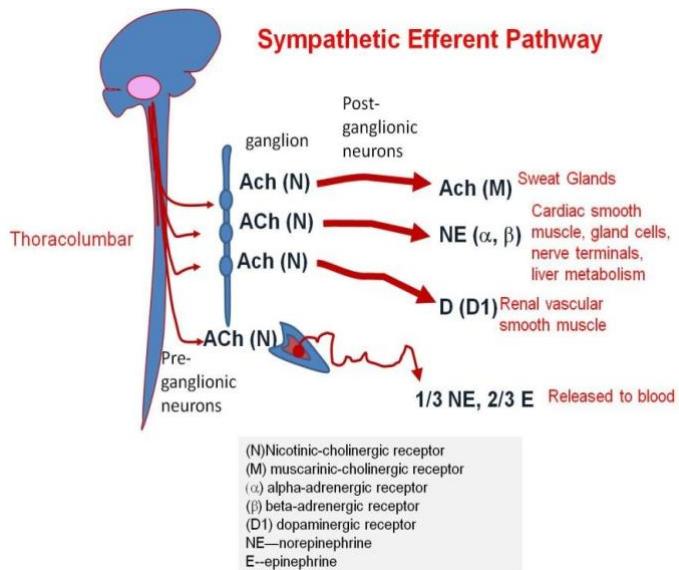
The **sympathetic** and **parasympathetic** systems differ in their **post-ganglionic** neurons.

ANS Anatomy; Receptors & Neurotransmitters



Parasympathetic post-synaptic-organ cell receptor (located on heart, smooth muscle, secretory glands) activated by released acetylcholine is always a muscarinic-acetylcholine-receptor type (more on muscarinic receptors later).

[Chapter reference \(7\)](#)



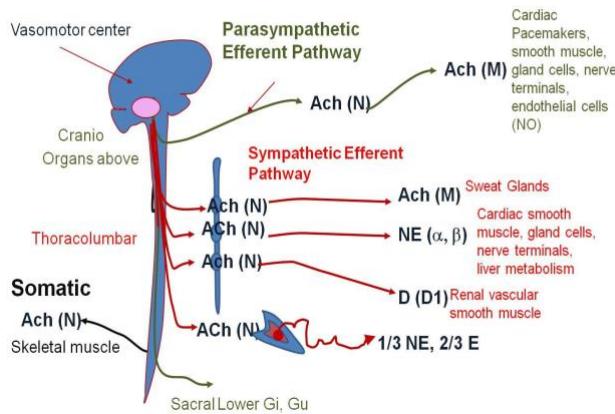
Sympathetic post-ganglionic neurons are either:

- 1) Cholinergic (nerves that make and release acetylcholine) when innervating sweat glands and adrenal medulla.
- 2) Noradrenergic (nerves that synthesize and release norepinephrine) Norepinephrine activates either alpha or beta adrenergic transmembrane receptors. The function of these receptors and how they regulate organ function will be discussed in the receptor section of this handout. Sympathetic neurons are mostly noradrenergic
- 3) Dopaminergic (nerves that synthesize and release dopamine). Dopaminergic neurons innervate the vasculature of the kidneys to produce vasodilation.

Sympathetic post-ganglionic neurons are either _____,
_____, or _____

Clinical Relevance: Nicotinic Receptors and ANS Balance

ANS Anatomy; Receptors and Neurotransmitters



Key point:

Drugs that block or enhance acetylcholine (ACh) signaling at **nicotinic receptors** affect both sympathetic (S-ANS) and parasympathetic (P-ANS) pathways because **all autonomic preganglionic neurons** use ACh to activate **nicotinic receptors** on postganglionic neurons.

- **Ganglionic blockers** (nicotinic receptor antagonists, also called ganglion-blockers) reduce both sympathetic and parasympathetic output by preventing signal transmission at autonomic ganglia.
- Conversely, drugs that **increase ACh levels at these synapses** (e.g., by blocking acetylcholinesterase) enhance transmission through both pathways. This is the basis for the toxic effects of **organophosphate insecticides and nerve gas**, which cause overstimulation of nicotinic and muscarinic receptors throughout the body.

Integration: Final Organ Effects

The **net effect on an organ** is the sum of inputs from both the S-ANS and P-ANS. Whether sympathetic or parasympathetic activity dominates depends on which system has more influence over that specific tissue.

Rule of thumb:

- **Parasympathetic effects** dominate most visceral organs that are co-innervated by PANS and SANS, at rest (heart rate, bronchial tone, digestion).
- **Sympathetic effects** dominate the vasculature, because blood vessels **lack parasympathetic innervation**; their resting tone is maintained by sympathetic vasoconstrictor fibers.

Clinical Correlates

Correlate 1:

Ganglionic blockers, once used in hypertensive crises, cause **profound vasodilation and hypotension**. This is because blocking sympathetic ganglia removes the basal sympathetic tone that normally keeps peripheral blood vessels constricted. The P-ANS has **minimal direct effect** on most blood vessels.

Correlate 2:

Nicotinic cholinergic receptors are named after **nicotine**, which binds and activates them. When a person smokes or uses nicotine products, nicotine stimulates autonomic ganglia, leading to **increased sympathetic outflow** — this causes **vasoconstriction**, which raises blood pressure and can contribute to **coronary ischemia** (reduced blood flow to the heart muscle). Chronic ischemia can damage tissue and increase the risk of heart attack.

Correlate 3:

Patients with **myasthenia gravis**, an autoimmune disease that targets nicotinic receptors at the neuromuscular junction, are often treated with **acetylcholinesterase inhibitors** to increase synaptic ACh levels at all synapses that release ACh. While this improves muscle contraction, it also increases ACh levels at ganglionic synapses and post-ganglionic organ synapses, boosting both parasympathetic and sympathetic signals. This can lead to **side effects of parasympathetic excess**, including:

- **Bradycardia (slow heart rate)**
- **Increased salivation and sweating**
- **Gastrointestinal cramps and diarrhea**
- **Bronchoconstriction**
- **Miosis (pupil constriction)**
- **Urinary urgency**

Correlate 4:

From an **osteopathic perspective**, treatments that restore balance between sympathetic and parasympathetic tone — such as **osteopathic manipulative treatment (OMT)** — may help reduce these excessive responses by modulating autonomic outflow.

Key takeaway:

Nicotinic receptors are a crucial common link in both ANS branches. Blocking or amplifying ACh at this level affects **all downstream autonomic pathways**, with widespread clinical implications.

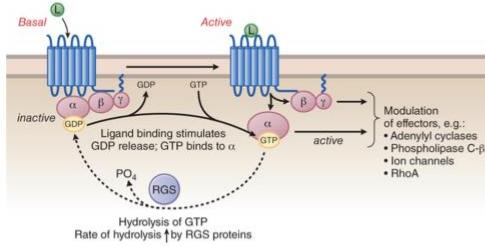
III. Autonomic Receptors Intracellular Signaling Cascades.

Autonomic Neurotransmitter Receptors

Specificity of neurotransmitter responses are mediated by binding to and activating specific transmembrane receptors that are distributed on organs depending on the function necessary.

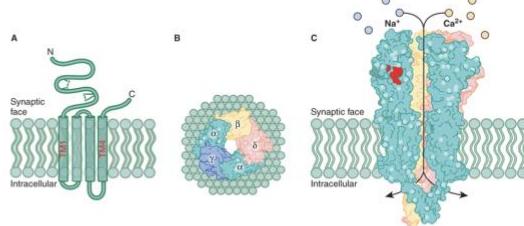
The ANS utilizes 2 main mechanism to produce an intracellular response from an external neurotransmitter.

- 1) Ionotropic Receptors: Activate an ion channel to produce a flow of ions
- 2) Metabotropic Receptors: Activate a transmembrane receptor that when activated stimulates an intracellular response via intracellular proteins.



Source: Laurence L. Brunton, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e; Copyright © McGraw-Hill. All rights reserved.

- 1) Autonomic metabotropic receptors couple to g-proteins
- 2) They are called g-proteins because when activated by receptors GTP binds and activates them.
- 3) When activated they in turn activate an "effector protein" that amplifies the intracellular response.
- 4) G proteins are comprised of three smaller proteins the active moiety is the alpha subunit. The beta and gamma help hold the alpha subunit next to the receptor.
- 5) There are three main g-proteins
 - a. Gs (stimulates the effector protein adenyl cyclase)
 - b. Gi (inhibits the effector protein adenyl cyclase)
 - c. Gq (activates the enzyme phospholipase C)



Source: Laurence L. Brunton, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e; Copyright © McGraw-Hill. All rights reserved.

- 1) Autonomic ionotropic receptor is nicotinic
- 2) When activated by acetylcholine positive charges flow into the cell causing intracellular depolarization
 - a. in neurons this response activates (depolarizes) neurons which initiates the propagation of signals down the axon.
 - b. in skeletal muscle cells this response produces depolarization, which results in more calcium entry and contraction

The autonomic nervous system (ANS) uses neurotransmitters like norepinephrine and acetylcholine to communicate with cells via specific receptors on their surfaces. These receptors are mainly of two types: metabotropic (G-protein coupled receptors, GPCRs) and ionotropic receptors. Typically, each receptor is activated by a single neurotransmitter or hormone, ensuring specificity of action.

Ionotropic Receptors: Ionotropic receptors are ligand-gated ion channels made up of five subunits forming a pore. When acetylcholine binds to a nicotinic ionotropic receptor, the receptor changes shape, opening the ion channel and allowing specific ions (such as sodium, potassium, or calcium) to flow in or out of the cell. This ion movement directly alters the cell's membrane potential, leading to rapid responses like muscle contraction or neurotransmitter release.

G-Protein Coupled Receptors (GPCRs): GPCRs are transmembrane proteins that undergo a conformational change upon binding to their specific neurotransmitter, such as norepinephrine or acetylcholine. This change activates an intracellular G-protein, which, depending on its subtype (Gs, Gi, Gq), initiates different intracellular signaling cascades that alter cell function. GPCRs are vital in regulating processes like heart rate, smooth muscle contraction, and glandular secretion.

Chapter Review 11

Together, these receptors enable the ANS to precisely control the activity of various tissues throughout the body.

G-protein-coupled receptors (GPCRs) initiate intracellular changes by linking an extracellular signal, such as a neurotransmitter or hormone, to a G protein. The specific type of G protein activated determines the intracellular cascade that follows. The nomenclature for these G proteins is straightforward:

- **Gs:** The "s" stands for "stimulate," as this G protein stimulates the production of the second messenger cAMP, which then triggers various cellular responses.
- **Gi:** The "i" stands for "inhibit," indicating that this G protein inhibits the production of cAMP, reducing the cell's response to the initial signal.
- **Gq:** The "q" represents "question." Researchers identified this G protein as being involved in the phosphatidylinositol (PI) turnover pathway but couldn't initially determine its exact function, hence the label "q." Functionally, the q causes a rise in intracellular calcium which in turn initiates smooth muscle "q"traction or glandular secretions.

Each type of G protein, by either promoting or inhibiting specific pathways, plays a crucial role in fine-tuning the cell's response to external signals.

ANS Receptor Signaling Cascades: Summary

G Protein	Effector Target	Second Messenger	PKA Target Phosphorylated	Response to Phosphorylation	cAMP direct effects
Gs (Cardiac)	↑ Adenylyl cyclase	↑ cAMP	L-type Ca ²⁺ channels, phospholamban, troponin I	↑ Ca ²⁺ influx (↑ contractility), ↑ SERCA activity (faster relaxation), ↓ myofilament Ca ²⁺ sensitivity (via troponin I)	Activation of funny (If) channels → ↑ pacemaker firing
Gs (Smooth Muscle)			Myosin light chain kinase (MLCK)	Inhibition of MLCK → ↓ myosin phosphorylation → smooth muscle relaxation	
Gi	↓ Adenylyl cyclase; βγ subunits → GIRK (↑ K ⁺ efflux) channels	↓ cAMP	None (↓ PKA activity)	↓ Ca ²⁺ influx, hyperpolarization, ↓ neurotransmitter release	
Gq	↑ Phospholipase C (PLC)	↑ IP ₃ , ↑ DAG		↑ MLCK activation (via Ca ²⁺ -calmodulin) → contraction	

Summary of G Protein-Mediated Intracellular Signaling in Autonomic Function

Autonomic signaling through G proteins—Gs, Gi, and Gq—produces tissue-specific effects via distinct second messenger pathways.

- Gs signaling, when activated in **cardiac tissue**, increases cAMP, which activates PKA. PKA phosphorylates L-type calcium channels, phospholamban, and troponin I, resulting in increased heart rate, **contractility**, and faster relaxation (lusitropy). Additionally, cAMP directly opens **funny (If)** channels in pacemaker cells, accelerating depolarization and firing rate.
- In **smooth muscle**, Gs-mediated PKA phosphorylates and inhibits myosin light chain kinase (MLCK), leading to **relaxation**—notably in bronchioles, vasculature, and bladder.
- Gi signaling reduces cAMP levels and **inhibits PKA**, while its **βγ subunits open GIRK potassium channels**, causing **hyperpolarization** in cardiac and neuronal cells. This slows heart rate and dampens neurotransmitter release (e.g., via M₂ and α₂ receptors).
- Gq signaling activates **PLC**, leading to increased IP₃ and DAG. IP₃ triggers intracellular Ca²⁺ release, and DAG activates PKC, together promoting **smooth muscle contraction** and glandular secretion, primarily via α₁ and M₃ receptors.

This diagram illustrates how **neurotransmitters like acetylcholine, norepinephrine and epinephrine** bind to their respective receptors on the cell surface and translate an external signal into precise changes inside the cell through **second messenger cascades**. Each receptor subtype couples with a specific **G protein (Gs, Gi, or Gq)** that activates a unique set of downstream enzymes, such as **adenylyl cyclase** or **phospholipase C (PLC)**.

These enzymes generate **second messengers** (like **cAMP** or **IP₃/DAG**) that then activate **protein kinases** — such as **protein kinase A (PKA)** — which phosphorylate

target proteins inside the cell. Importantly, the effect depends on the **cell type and which proteins or channels are present**.

- For example, in **cardiac muscle**, β_1 receptors (via Gs) raise cAMP and PKA activity, boosting **calcium channel** function and **SERCA pump** activity to increase **contractility and relaxation rate**.
- In **smooth muscle**, β_2 receptors also raise cAMP but instead inhibit **myosin light chain kinase (MLCK)**, leading to **smooth muscle relaxation** — the opposite effect, despite using the same second messenger!
- **Gi-coupled α_2 receptors** reduce cAMP and open **K⁺ channels**, which lowers neurotransmitter release at presynaptic sites.
- **Gq-coupled α_1 receptors** use IP₃ to release intracellular calcium and activate MLCK, resulting in **smooth muscle contraction**.

Clinically, this explains why the same neurotransmitter can produce **organ- and tissue-specific responses** — it's not just about the messenger, but about **which enzyme or channel is targeted and how phosphorylation changes its activity**. This elegant system of **cell-specific “wiring”** allows the autonomic nervous system to finely tune heart rate, blood pressure, bronchial tone, bladder function, and more — ensuring each tissue responds optimally to stress or rest.

Key takeaway: Neurotransmitters “speak the same chemical language” but produce diverse effects because **second messengers and kinases translate the signal differently in each cell type**, enabling precise physiologic control.

Autonomic Neurotransmitter Receptors

Norepinephrine

- Adrenergic receptors
- alpha adrenergic receptors
- Alpha 1 (α_1 R)
- Alpha 2 (α_2 R)
- Beta adrenergic receptors
- Beta 1 (β_1 R)
- Beta 2 (β_2 R)
- Beta 3 (β_3 R)

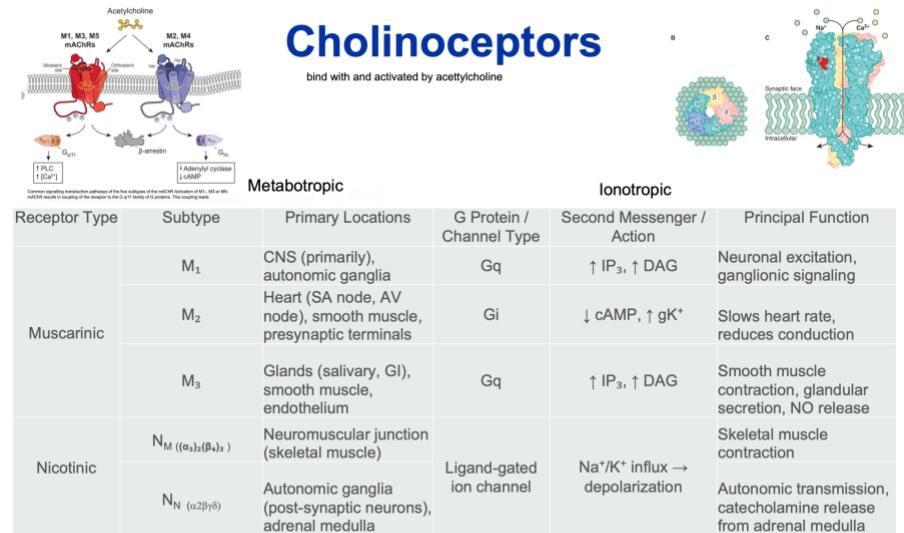
Acetylcholine

- Cholinergic Receptors
- Nicotinic (cation channels)
- Ganglionic (N_n or g)
- Neuromuscular junction (N_m)
- Muscarinic (M_{1-4})

Acetylcholine (ACh) is the primary neurotransmitter of all autonomic preganglionic neurons (both sympathetic and parasympathetic), acting on nicotinic receptors in autonomic ganglia. Postganglionic parasympathetic neurons also release ACh, which activates muscarinic receptors on target organs. Norepinephrine (NE) is the primary neurotransmitter of most sympathetic postganglionic neurons, activating alpha (α_1 , α_2) and beta (β_1 , β_2 , β_3) adrenergic receptors to modulate cardiovascular, respiratory, and metabolic functions.

Receptors that are activated when bound to by norepinephrine are called adrenergic receptors. There are two principal types of adrenergic receptors: alpha and beta. These are further subdivided into subtypes, 1 and 2, 3, etc. which differ significantly in function and the intracellular cascades that they activate. Similarly, receptors that bind acetylcholine are cholinergic receptors. There are also two main receptor subtypes that are activated by acetylcholine, nicotinic and muscarinic. Muscarinic receptors also have subtypes 1-4. With subtypes 2 and 3 being the most important for autonomic function.

Cholinergic Receptor Subtypes:



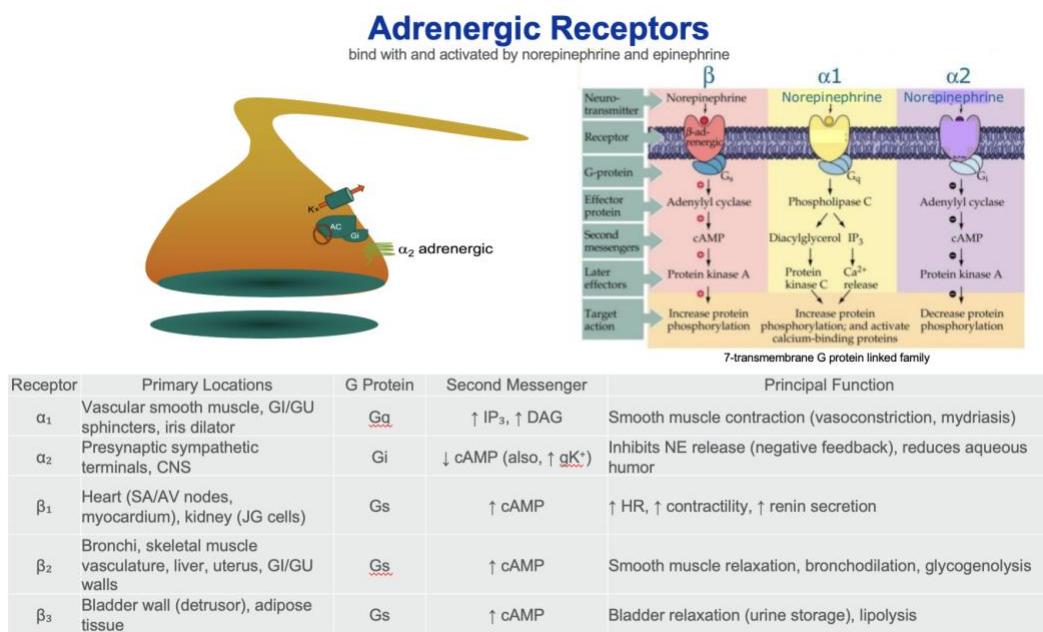
This diagram illustrates how **acetylcholine (ACh)** acts through two main classes of receptors — **muscarinic (M₁, M₂, M₃)** and **nicotinic (N_m, N_n)** — each with distinct

locations, signaling pathways, and physiologic roles. The muscarinic receptors use **G protein-coupled mechanisms** to modulate organ functions like **heart rate, glandular secretion, smooth muscle tone, and vasodilation**, showing how a single neurotransmitter can produce very different effects depending on the receptor subtype and its downstream messenger. In contrast, the nicotinic receptors function as **ligand-gated ion channels** that rapidly transmit signals across autonomic ganglia and the neuromuscular junction, highlighting their importance in both **autonomic reflexes and voluntary muscle contraction**. Clinically, understanding these pathways explains how drugs, toxins, or diseases can selectively disrupt normal function — for example, why ganglionic blockers lower blood pressure or how myasthenia gravis targets skeletal muscle-type nicotinic receptors but not neuronal ones. This integrated view reinforces the big picture: the **specific receptor, its location, and its intracellular messenger cascade together determine how the nervous system fine-tunes each organ's response**.

Tip for learners:

When you see “ACh,” always ask: *Which receptor? Where? And what’s the second messenger doing?* — that’s the key to connecting the diagram to real-life pharmacology and pathophysiology.

Adrenergic receptor Subtypes



This diagram shows how **norepinephrine (NE)** and **epinephrine (EPI)** interact with **adrenergic receptors** — grouped into **α (alpha) and β (beta) subtypes** — to produce diverse effects throughout the body. Each receptor type is coupled to a specific **G protein** that activates a unique **second messenger pathway**, which then shapes the final cellular response.

- **α_1 receptors** primarily use the **Gq pathway** to increase IP₃ (IP₃ = calcium = contraction) and DAG, leading to **smooth muscle contraction** — like **vasoconstriction, sphincter tightening**, or pupil dilation.
- **α_2 receptors** use the **Gi pathway** to **decrease cAMP**, providing **negative feedback** that inhibits further NE release, and they also reduce aqueous humor in the eye.
- **β_1 receptors** (in the heart and kidney) use the **Gs pathway** to raise cAMP, which **increases heart rate, contractility, and renin secretion**.
- **β_2 receptors**, found in the bronchi, skeletal muscle vasculature, liver, and GI/GU walls, also work through **Gs proteins** to increase cAMP — causing **smooth muscle relaxation, bronchodilation, and glycogen breakdown** for energy release.
- **β_3 receptors**, mainly in the bladder wall and adipose tissue, use the same **Gs mechanism** to promote **bladder relaxation (for urine storage)** and **lipolysis**.

Clinically, this helps explain why drugs that **block or stimulate specific adrenergic receptors** have widespread and predictable effects — like using β_1 blockers to slow the heart, or β_2 agonists to relax airways during asthma attacks.

Key takeaway: The same neurotransmitter — norepinephrine — can cause opposite effects (like contraction vs. relaxation) depending on **which receptor subtype is activated, where it's located, and which second messenger cascade it triggers**.

Big picture: Always match **receptor subtype + tissue location + G protein + messenger** to understand **how the sympathetic nervous system fine-tunes organ function under stress, activity, or rest**.

Below is useful mnemonics from 1st aide – use them as you see fit.

Autonomic Receptor mnemonic

- “Qiss (kiss) and qiq (kick) till you’re siq (sick) of sqs (sex)”

Or X1 = Gq

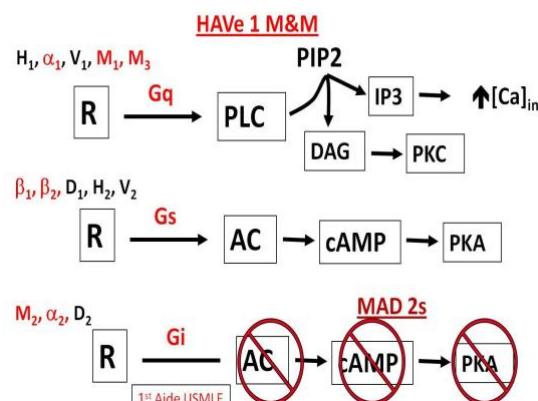
but betas (all Gs coupled) and the dumb Ds

X2 = Gi coupled but betas and V2

receptor	G-protein class
α_1	q
α_2	i
β_1	s
β_2	s
M1	q
M2	i
M3	q
D1	s
D2	i
H1	q
H2	s
V1	q
V2	s

1st Aide USMLE

Autonomic Receptor Mnemonic



Use the above diagrams to answer the following questions:

Acetylcholine activates both _____ and muscarinic cholinergic receptors.

Nicotinic cholinergic receptors are the principal receptors at both the neuromuscular junction (skeletal muscle contraction) and at autonomic _____, which is responsible for activating all autonomic post-synaptic neurons.

_____ activates both alpha adrenergic and beta adrenergic receptors.

Connecting the intracellular cascades with the receptor is the basis for autonomic control of heart, vascular, gut, secretory, urinary, and genital function. Connecting the drugs that activate or block the autonomic receptors is the basis for clinical management of several important cardiovascular, respiratory, gastrointestinal, and genital-urinary disease states.

Beta (1, 2, and 3) are all coupled to the G protein _____ which when activated increases the second messenger _____.

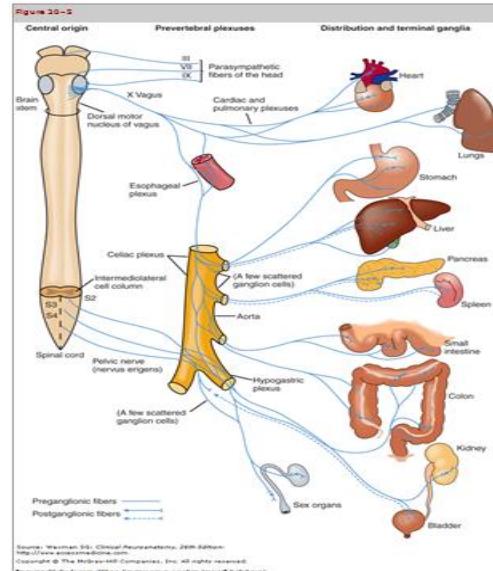
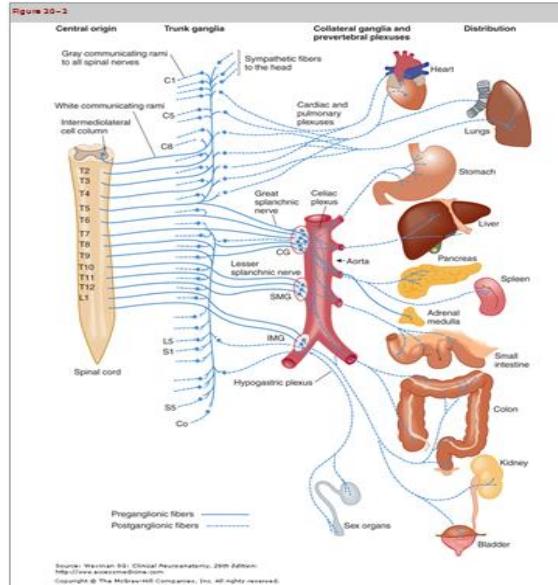
Alpha 1 receptors as well as the muscarinic receptor subtypes M1 and M3 are coupled to the g protein _____, which when activated leads to an increase in the second messenger _____ and the increase in intracellular _____ ions.

Chapter Review 11

Section 2-

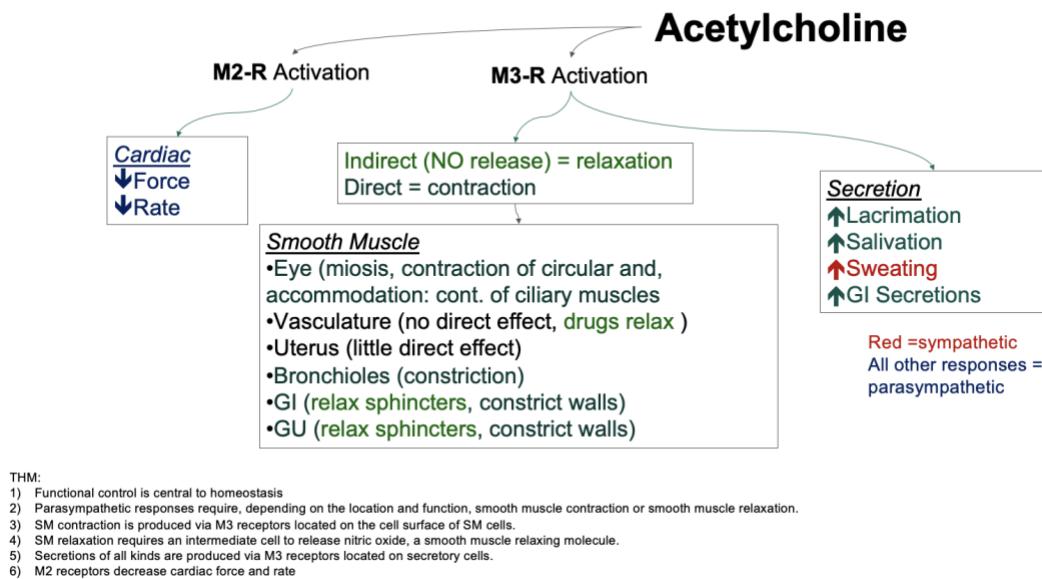
Control of Organ Function

A. General Concepts



Organ	Sympathetic Innervation	Parasympathetic Innervation
Head and Neck	T1- T5	Vagus (also CNIII, VII, IX)
Heart	T1- T5	Vagus
Lung	T2-T6	Vagus
Lower Esophagus / Stomach	T5-T10	Vagus
Liver and Gallbladder	T6-T9	Vagus
Small Intestine	T10-T11	Vagus
Ascending / Transverse Colon	T12-L1	Vagus
Descending and Sigmoid Colon / Rectum	L1-L2	S2-S4
Kidney	T10-L1	Vagus
Ureter	T10-L2	Vagus (proximal 2/3), S2-S4 (distal 1/3)
Ovary/Testes	T9-T11	S2-S4
Bladder	T10-L2	S2-S4
Uterus	T12-L1	S2-S4
Cervix	T10-L2	S2-S4

Note: Study of these figures and the anatomic location of the afferent and efferent neurons at the level of the spinal cord is crucial to your development as an osteopathic physician. Knowing this material is helpful, both for diagnosis when incorporating osteopathic principles and as a therapeutic approach that accounts for the integration of the entire body as a unified entity. For now, the understanding of basic organ function control is the focus.



Acetylcholine and Organ Muscarinic Receptor Control of Organ Function: The autonomic nervous system (ANS) finely tunes the function of secretory glands, cardiac muscle, and smooth muscle throughout the body by releasing neurotransmitters that bind to specific receptors on target tissues. The key neurotransmitter, **ACh**, plays diverse roles depending on the tissue type and receptor involved.

In the parasympathetic system, ACh is released by postganglionic neurons to act directly on muscarinic receptors — M2 on the heart and M3 on other organs. In the sympathetic system, Ach is released to promote thermoregulatory sweating.

ACh and Smooth Muscle Control

- **Contraction:** When smooth muscle contraction is needed (e.g., moving food through the GI tract), ACh binds to M3 receptors on smooth muscle cells. This activates a Gq–IP3 cascade, raising intracellular calcium and causing contraction.
- **Relaxation:** When relaxation is needed (e.g., relaxing gut sphincters), ACh binds to M3 receptors on neighboring cells, triggering nitric oxide (NO) release. NO diffuses into smooth muscle, activates cGMP pathways, and reduces intracellular calcium to produce relaxation.

ACh and Cardiac Muscle Control

In the heart, parasympathetic neurons release ACh, which binds mainly to M2 receptors on pacemaker cells.

- **Main effect:** Slows heart rate via Gi-protein pathways that lower cAMP, reduce calcium entry, and increase potassium efflux, hyperpolarizing the cell.

ACh and Secretory Function

ACh also promotes secretion in glands by binding to M3 muscarinic receptors on glandular cells. This activates pathways that increase intracellular calcium, stimulating secretion of saliva, mucus, digestive enzymes, sweating and other fluids needed for normal physiologic function.

This receptor-specific action of ACh illustrates a core principle: the effect depends not only on the neurotransmitter but also on the receptor subtype and the downstream signaling pathway in each tissue. This allows the ANS to precisely coordinate complex functions — for example, promoting gut motility while relaxing sphincters, or slowing the heart to conserve energy during rest.

Ach-induced activation of muscarinic receptors located on cardiac myocytes and pacemaker cells produce a _____ (type either increase or decrease) in some atrial myocyte contractile force and heart rate.

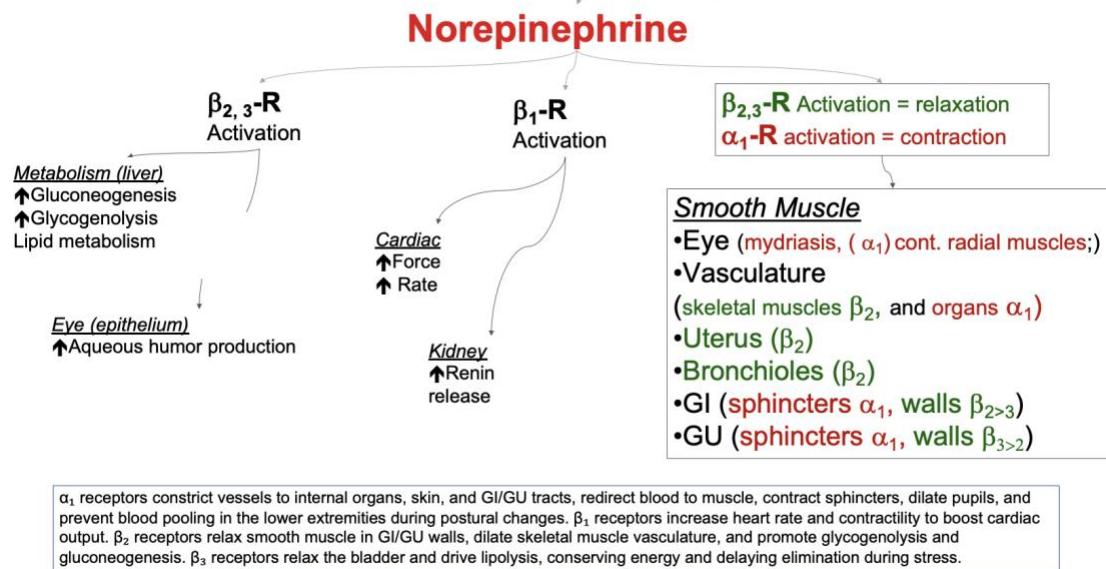
Ach-induced activation of muscarinic receptor whether on lacrimal, salivary, sweat gland cells or in the gut produces a(n) _____ (type either increase or decrease) in secretion.

Ach when acting directly on muscarinic receptors, without the intermediary step of nitrous oxide (NO) release, produces _____ (type either relaxation or contraction) of eye, gut and bladder wall smooth muscles.

Ach induced _____ (type either relaxation or contraction) of smooth muscle requires the intermediary step of nitrous oxide (NO) release.

Why would thermoregulatory sweating be a Sym-ANS controlled event?

[Chapter reference \(7\)](#)



Norepinephrine (epinephrine) and Control of Organ Function: Norepinephrine is the main neurotransmitter released by postganglionic sympathetic neurons. It binds to α and β adrenergic receptors to coordinate “fight or flight” responses that shift cardiac, smooth muscle, and metabolic function to meet acute demands.

Cardiac Control (β_1 Receptors)

- Heart:** Activation of β_1 receptors increases heart rate and contractility to boost cardiac output.

Kidney (JG cells)

- β_1 receptors stimulate renin release, which supports blood pressure regulation.

Smooth Muscle Control (α_1 , β_2 , β_3 Receptors)

- α_1 Receptors:** Promote smooth muscle contraction — vasoconstriction in visceral vessels, sphincter tightening (GI/GU tracts), and pupil dilation (mydriasis via radial muscle).
- β_2 Receptors:** Relax smooth muscle where dilation or relaxation is needed — bronchodilation (lungs), vasodilation in skeletal muscle to enhance blood flow, relaxation of the uterus and GI/GU walls to reduce motility during stress.
- β_3 Receptors:** Relax the bladder wall to delay urination during stress and stimulate lipolysis in adipose tissue to increase fuel availability.

Secretory and Metabolic Effects

- Metabolism:** β_2 and β_3 receptor activation in the liver enhances glycogenolysis and gluconeogenesis; β_3 receptors promote lipolysis in adipose tissue.
- Eye:** β_2 receptor activation increases aqueous humor production (ciliary epithelium).

Clinical Note: A helpful mnemonic is “one heart, two lungs”: β_1 receptors affect the heart (1), β_2 receptors affect the lungs (2).

General rule: α_1 activation = contraction; β_2/β_3 activation = relaxation.

Osteopathic Clinical Correlations

Sympatheticotonia - is a stimulated condition of the nervous system marked by:

- Vascular spasm
- Elevated blood pressure
- General dominance of sympathetic functions and increased sympathetic visceral efferent tone
 - Note: the sympathetic nervous system innervates the vasculature and the parasympathetic does not

Clinical Correlate: Elevated blood pressure that has no other identifiable cause is thought to be related hypersympathetic tone (sympatheticotonia).

Parasympatheticotonia - is a stimulated condition of the autonomic nervous system that is far less common than sympatheticotonia. The cardinal features are less obvious, but typically relate to excessive forms of its normal function including rest, salivation, urination, digestion, and defecation.

Clinical Correlate: A common clinical condition related to hypersympathetic tone is colic in infants. Colic is typically defined as crying for more than 3 hours a day for more than 1 week in an otherwise healthy child. Osteopathic manipulation has been postulated to help colic as techniques can decompress the vagus nerve thought to be associated with the pathogenesis of colic.

An increase in glucose production, which is required for energy expenditure, is produced by norepinephrine activation of beta_____ (type 1 or 2, we will ignore 3 at this time because of the lack of pharmacologic agents currently available) receptors located on which organ _____.

Norepinephrine-induced smooth muscle relaxation is mediated by activation of _____ receptors.

Norepinephrine-induced smooth muscle contraction is mediated by activation of _____ receptors.

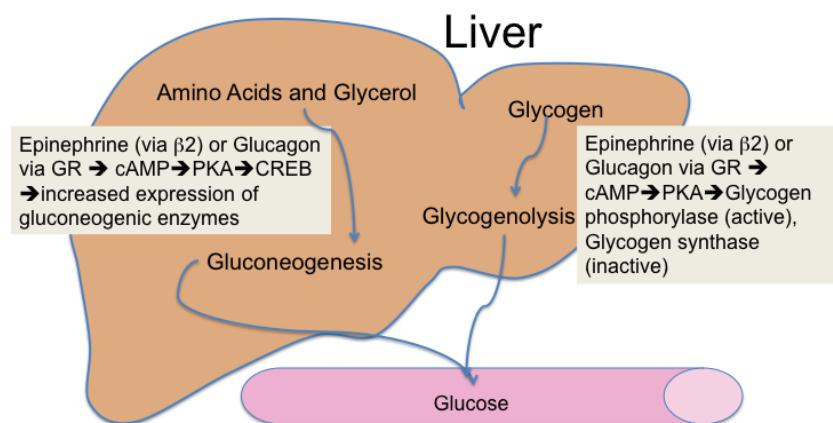
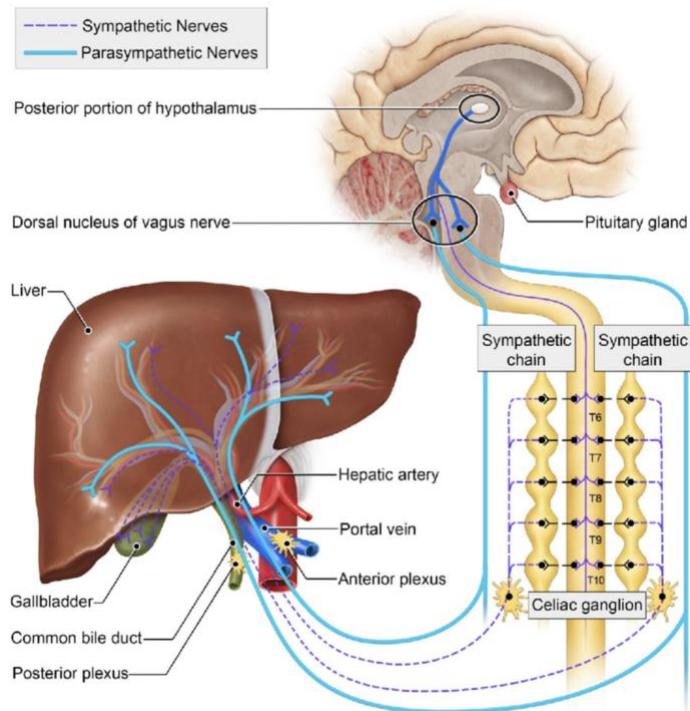
Sympathetic neuronal release of norepinephrine can oppose parasympathetic bowel evacuation effects because it places the smooth muscle contractile-inducing _____ adrenergic receptor on sphincters smooth muscle membranes, preventing outflow, and relaxation-inducing _____ adrenergic receptors on the membranes of smooth muscles of the gut walls. Same process applies to urination.

Which type of secretion is activated by the sympathetic system when energy is used and converted to heat? _____

B. ANS role in Liver Function

Control of glucose metabolism in the liver involves a complex interplay between blood glucose detection, circulating hormones, and autonomic nervous system (ANS) regulation. During fasting, glucagon and cortisol are the primary hormones that increase blood glucose levels by inducing gluconeogenic enzymes and suppressing glycolytic enzymes. In contrast, during feeding, insulin is released to promote glycolysis and inhibit gluconeogenesis. Insulin secretion can also be directly inhibited or increased by sympathetic and parasympathetic neurons innervating the pancreas, respectively.

The ANS also plays a critical role, with sympathetic efferents enhance gluconeogenesis and glycolysis. The parasympathetic system, which includes both sensory and motor components, detects changes in osmolarity and can reduce hepatic glucose output. When necessary, sympathetic activation increases blood glucose by promoting glycogen breakdown. Norepinephrine or circulating epinephrine activates beta-2 receptors, leading to cAMP-induced activation of protein kinase A (PKA). PKA phosphorylates and activates glycogen phosphorylase (which breaks down glycogen) while inhibiting glycogen synthase (which synthesizes glycogen). If further glucose is needed, sympathetic stimulation also enhances gluconeogenesis by upregulating gluconeogenic enzymes. This coordinated response via beta-2 receptor activation ensures an adequate supply of glucose, particularly during hypoglycemic conditions or when glucose reserves are depleted ([13](#))



Clinical Correlate: The sympathetic increase in plasma blood glucose is important during exercise. It is also important during hypoglycemic events produced when insulin is administered. It is part of the reason for the following excerpt from UpToDate regarding the use of the beta-receptor antagonist, propranolol.

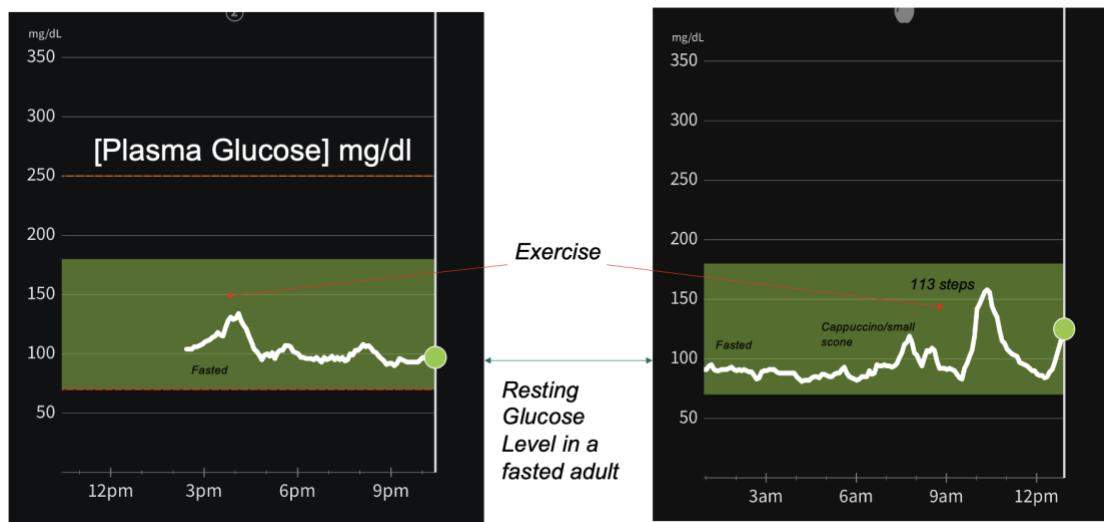
Beta-blockers may worsen, prolong, or cause **hypoglycemia**. **Mechanism:** Dose-related; related to the pharmacologic action. Beta-blockers inhibit hepatic gluconeogenesis and glycogenolysis. Beta-blockers also reduce activation of the sympathetic nervous system, therefore masking hypoglycemic symptoms that are catecholamine-mediated.

Onset: Varied; blood glucose recovery was significantly reduced following one dose or one day of therapy. In another study, episodes of severe hypoglycemia were reported over the course of 4 years.

Risk factors:

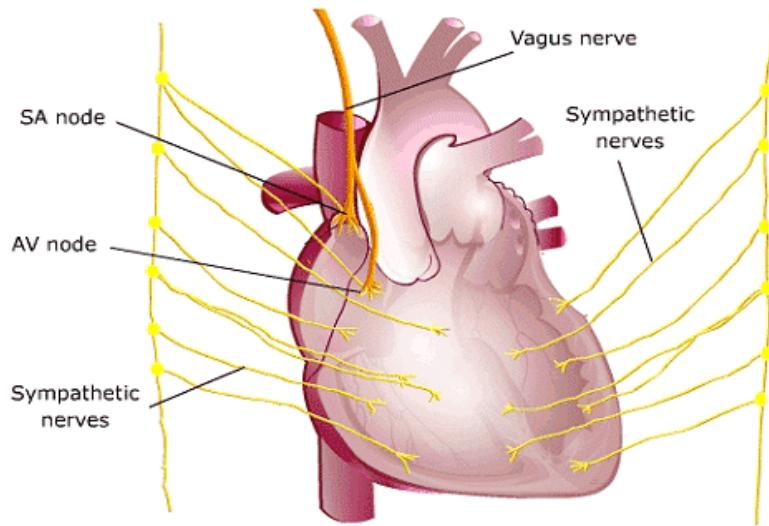
- Diabetes mellitus, especially insulin-dependent diabetes and type 2 diabetes
- Patients who are fasting (ie, surgery, not eating regularly, vomiting)
- Patients who are hospitalized and not requiring basal insulin

Clinical Correlate: The following recording demonstrates the rise in plasma glucose with exercise using a continuous glucose monitor. The image on the left was taken from an adult who had been fasting for over 16 hours. The rise in glucose was produced by exercise via the sympathetic response. On the right the same effect was observed while the same person walked up the 113 steps from LHA to the top for lunch. Note that the breakfast resulted in a small glucose rise from the cappuccino and small scone at 8:00 am compared to the rise observed after the steps.



Definition review: **Gluconeogenesis** = the synthesis of glucose from molecules that are not carbohydrates, such as amino and fatty acids. **Glycogenolysis** = the splitting up of glycogen in the liver, yielding glucose.

C. ANS role in Cardiac Function



<http://www.nuclearcardiologyseminars.net/autonomic.htm>

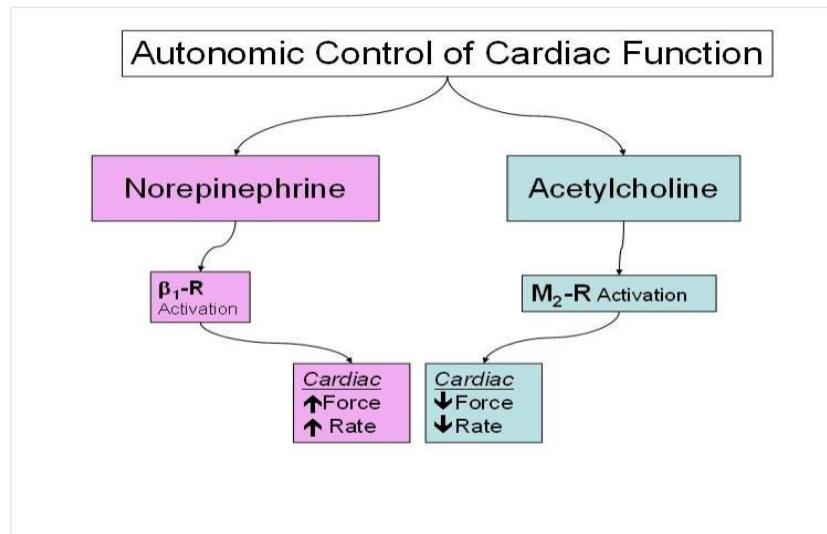
Note: There are three principal muscle types: Cardiac, Smooth, and Skeletal

- **Cardiac Muscle:** Found in the heart (cardiomyocytes)
- **Smooth Muscle:** Smooth muscle is found in the walls of hollow organs such as blood vessels, the gastrointestinal tract, and the bladder requires myosin light chain kinase for contraction.
- **Skeletal Muscle:**
Skeletal muscle is responsible for voluntary movements.

Cell Types in the Heart and Their Functions:

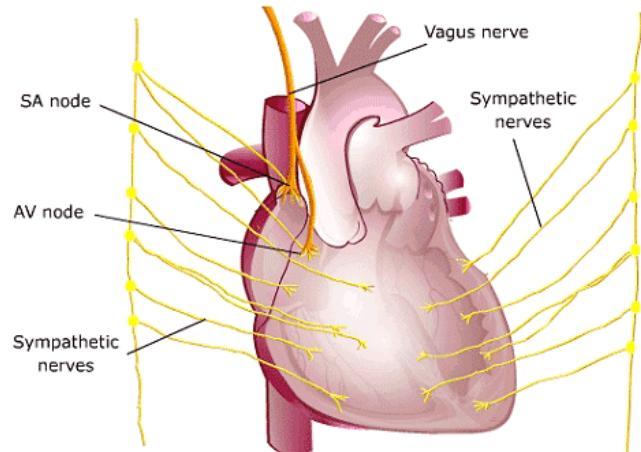
- **Cardiomyocytes:** Found in atria and ventricles are the contractile cells.
- **Pacemaker Cells:** Located in the sinoatrial (SA) node--specialized cells that generate spontaneous action potentials that set the heart's rhythm. They control the timing of cardiac contractions and regulate the heart rate.
- **Conducting Cells:** These cells, including those in the atrioventricular (AV) node, bundle of His, and Purkinje fibers, transmit electrical signals from the pacemaker cells to cardiomyocytes. They ensure the rapid and coordinated spread of impulses, allowing the heart to contract as a unit.

Sympathetic nerve fibers innervate both ventricular and atrial cardiomyocytes as well as pacemaker and conducting cells of the SA and AV node. Parasympathetic neurons mainly innervate pacemaker and conducting cells. Together, with blood vessels and fibroblast that provide structural components these diverse cell types ensure the heart's function as a highly efficient and regulated pump, maintaining blood circulation throughout the body.



Autonomic control of heart rate and contractile forces is an important avenue for opposing control.

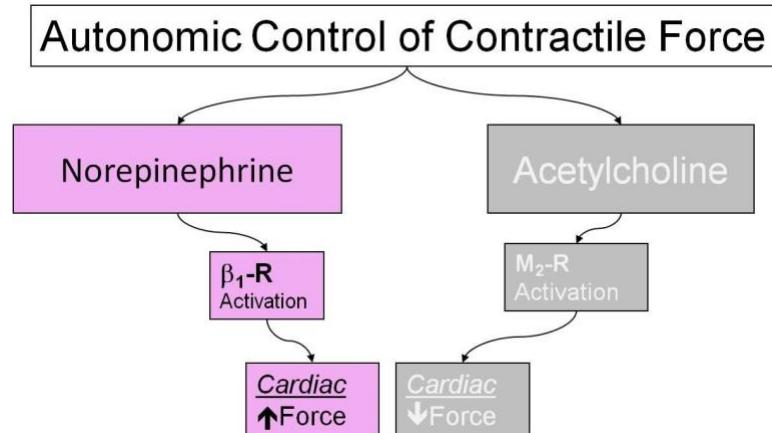
Sympathetic: The central role of the sympathetic nervous system is to increase supply of oxygen and glucose to the brain and skeletal muscle. Increasing heart rate and contractile force provides the needed increase in blood supply carrying oxygen and glucose to both tissues. This process occurs when sympathetic neurons release **norepinephrine** which then binds to **beta-1-adrenergic receptors** on the cardiac myocytes and pacemaker cells located at SA and AV nodes.



Parasympathetic: Sympathetic increased activity occurs on demand and cannot be maintained without damage to the heart. The parasympathetic provides the opposing influences to slow down the heart during rest. Parasympathetic-induced- **acetylcholine** –release at the heart and subsequent muscarinic receptors activation can dominate control of the heart rate (note predominate innervation of heart occurs at the SA and AV nodes). The heart muscarinic receptor types are **M2**, while the CNS, GU and GI tracts are M1 and M3. The opposite effects of these two neurotransmitters are produced because distinct intracellular cascades are activated in heart cells.

Osteopathic and anatomic considerations:

Sympathetic innervation to the heart originates in cord segments T1-T6. Pre/post-ganglionic synapse occurs either in the upper thoracic spine or cervical chain ganglia. Although crossover occurs, clinical implications primarily occur ipsilaterally (right sided fibers -> SA node, left sided fibers -> left cardiac plexus and AV node).



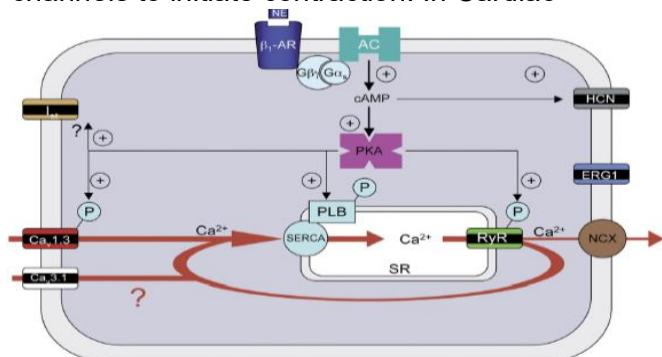
Cardiac Muscle Contractile Force:

Cardiac and smooth muscle cells differ in the requirement for phosphorylation of the myosin chain by the enzyme, myosin-light-chain-kinase (MLC-K). Smooth muscle cells require, and cardiac myocytes do not require this step. This is why norepinephrine-activated-beta adrenergic receptors can produce cardiac contraction and smooth muscle relaxation. Smooth muscle regulation will be covered later. Both muscle cell types require Ca^{++} entry through voltage-gated- Ca^{++} channels to initiate contraction. In Cardiac myocytes; Ca^{++} mediated-excitation-contraction coupling occurs when Ca^{++} binds to Troponin C allowing the troponin complex to move off the actin binding site—thus allowing myosin to bind to actin.

Sympathetic-induced increases in contraction:

Norepinephrine produces an ↑ in contractile force and rate by activating β 1-adrenergic receptors. All β -adrenergic receptors are coupled to the g-protein, Gs, which activates adenylyl cyclase (AC)--the enzyme that produces the intracellular 2nd messenger, cAMP (see diagram). The raise in intracellular cAMP increases both heart rate and contractile force by promoting an ↑ in intracellular calcium levels. Activated PKA produces an ↑ in intracellular Ca⁺⁺ by phosphorylating membrane bound voltage gated Ca⁺⁺ channels (Ca_v1,3) allowing more Ca⁺⁺ entry into the cell and by phosphorylation and subsequent opening of the ryanodine receptor (RYR) located on the sarcoplasmic reticulum (SR), which releases Ca⁺⁺ from this storage compartment.

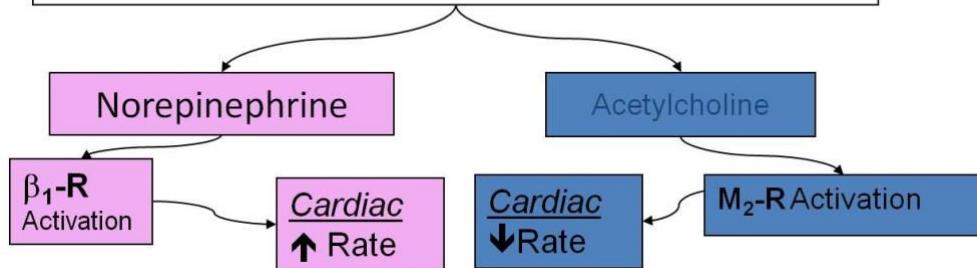
Note: At rest there is very little free calcium. Most of the calcium is stored in the SR.



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Ca_{1.3},¹ (voltage-gated calcium channel), **HCN**,² (Hyperpolarization-activated cyclic nucleotide-gated (HCN) sodium channels), or **iP3R**,³ (IP₃-activated receptor A, activated by cAMP), **SR SERA**,⁴ (Sarcoplasmic reticulum endoplasmic reticulum associated receptor A, located on the cell to the lumen of the SR), **RYR** (ryanodine receptors) release calcium in response to PKA phosphorylation or IP₃. **PLB** (the rate at which SERCA moves Ca²⁺ across the SR membrane during contraction) is reduced by PKA phosphorylation, and the rate of PLB by PKA reduces association with SERA allowing more calcium entry into the cell.

In pacemaker cells, high basal cAMP-mediated plasma membrane phosphoprotein stimulates a persistent Ca²⁺ current (Ca_{1.3}) through Ca_{1.3} channels. Ca_{1.3} is also stimulated by SERCs and Ca/CaM via RYR, PKA also stimulates Ca₂₊ entry through Ca_{1.3} mediated (Ca_{1.3}). The thick red line indicates the persistent spontaneous Ca₂₊ cycling. This possibility is supported by the fact that SERCs are linked to the direct depolarization of Ca_{1.3} channels by Ca₂₊ activation of INCH current. Direct cAMP-dependent activation of HCN channels or cAMP-mediated, PKA-dependent phosphorylation of Ca_{1.3} channels and/or (Ca_{1.3}/SERCA) strongly stimulates the pacemaker cycle driven by the hyperpolarizing change in membrane potential (M₀).

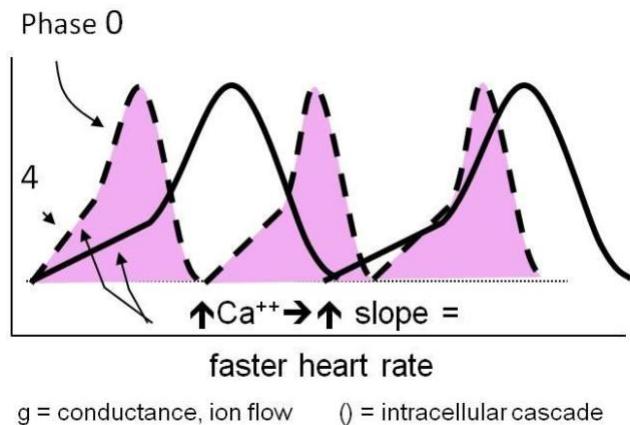
Autonomic Control of Cardiac Rate



Heart Rate:

Increases and decreases of heart rate are mediated by autonomic control of ion flow into SA-nodal cardiac pacemaker cells (figure above) which affects the (resting) phase 4 slope (see figure to right). The membrane potential drifts up (depolarizes) in phase 4 when Na^+ (flowing through the HCN channel) and Ca^{++} (flowing through the $\text{Ca}_{v1,3}$ channel) ions flow into SA nodal pacemaker cells (figure above).

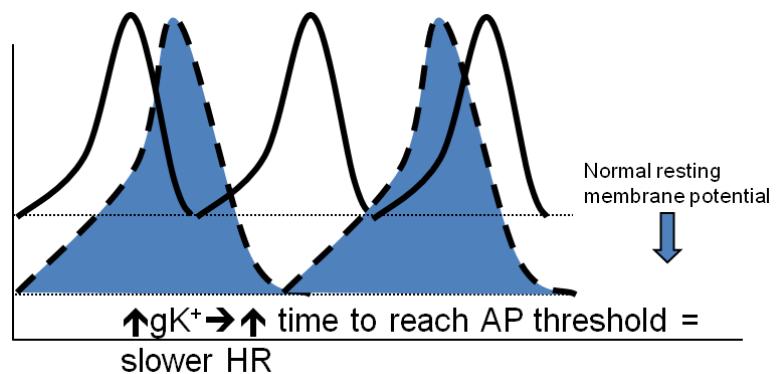
Sympathetic increases in HR: Influx of these ions depolarizes the cell bringing it closer to action potential threshold. In addition to increasing the phase 4 slope, Ca^{++} is the main cation flowing into the SA-N-PC during the action-potential-sharp-rise (phase 0). CAMP-PKA-mediated-increases in both Na^+ and Ca^{++} conductance increases the phase 4 depolarization rate, or phase 4 slope, which shortens the time to reach action potential threshold resulting in a faster rate—the mechanism underlying your racing heart when the lion is chasing or when studying for exams.



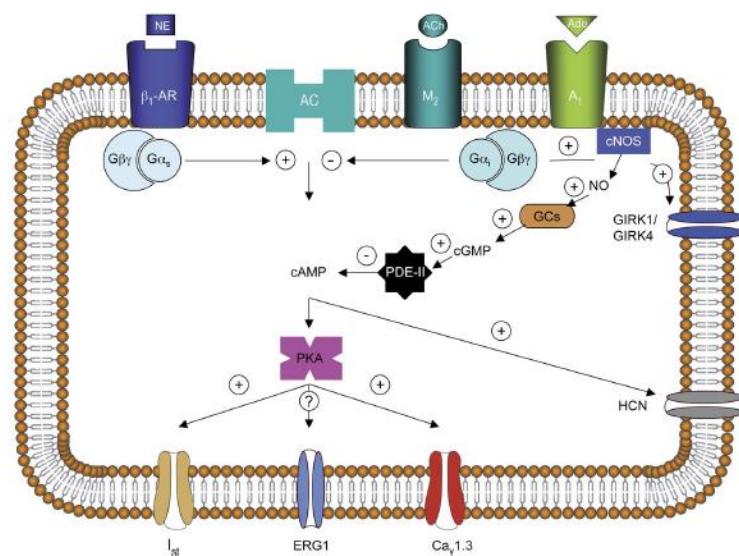
Parasympathetic decrease in HR

(M2 cholinergic receptor intracellular cascades):

Acetylcholine-induced-muscarinic-receptor-activation liberates the beta-gamma subunit from the alpha subunit of G_i . The free beta-gamma subunit activates voltage-gated-potassium channels (GIRK 1 and 4, shown on previous page) resulting in charged-ion outflow causing hyperpolarization (see figure to the right). Potassium ion outflow lowers the resting potential and requires more cation influx during the



action potential, which increases the time to reach action-potential-threshold. This results in a slower SA node pacemaker activity.



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Summary of the signaling pathways involved in the muscarinic regulation of pacemaker activity. In the SAN and AVN, ACh and Ado share the same pathways for signal transduction. ACh binds to the muscarinic M₂ receptor, which is coupled to a "direct" G protein-dependent pathway activating Kir3.1/Kir3.4 (GIRK1/GIRK4) channel complexes. Beside this direct pathway, two other "indirect" channel regulation pathways lead to downregulation of intracellular cAMP. In the first cascade of events, the G_i protein subunit inhibits AC activity, thereby reducing the synthesis of cAMP. Inhibition of AC synthesis is viewed as the predominant pathway by which ACh regulates the voltage dependence of f-channels (HCN). The second muscarinic pathway is initiated by the stimulation of the NOS activity and production of NO. NOS activates the enzyme guanylate cyclase (GC), which converts GTP to cGMP. Elevation of cGMP concentration stimulates PDE II-dependent hydrolysis of cAMP, thereby reducing PKA activity. This NOS-dependent pathway for regulation of PKA activity has been proposed to be the major pathway for the muscarinic regulation of $I_{Ca,L}$ during pacemaking. In the figure, negative NOS-dependent regulation of Cav1.3-mediated $I_{Ca,L}$ is suggested. It is not known if the SAN IKr can also be negatively regulated by the NOS-dependent pathway.

Norepinephrine released from sympathetic-post-ganglionic nerves activates _____ adrenergic receptors on cardiac myocytes and pacemaker cells resulting in an increase in the second messenger, cAMP.

Acetylcholine released from parasympathetic-post-ganglionic nerves activates _____ receptors on cardiac myocytes and pacemaker cells that results in hyperpolarization of cardiac pacemaker cells.

Beta-adrenergic-receptor-activation results in PKA-mediated voltage gated calcium channel phosphorylation, which leads to increased _____ entry into cells.

Muscarinic-receptor (M₂) activation results in opening of potassium channels that produces _____ in membrane potential.

Norepinephrine-induced-activation of calcium-channel-phosphorylation allows more calcium to enter and increases the _____ of the initial phase in SA nodal action potential.

Acetylcholine-induced-activation of _____ conductance hyperpolarizes SA-nodal pacemaker cells requiring more time to reach action potential threshold, which slows heart rate.

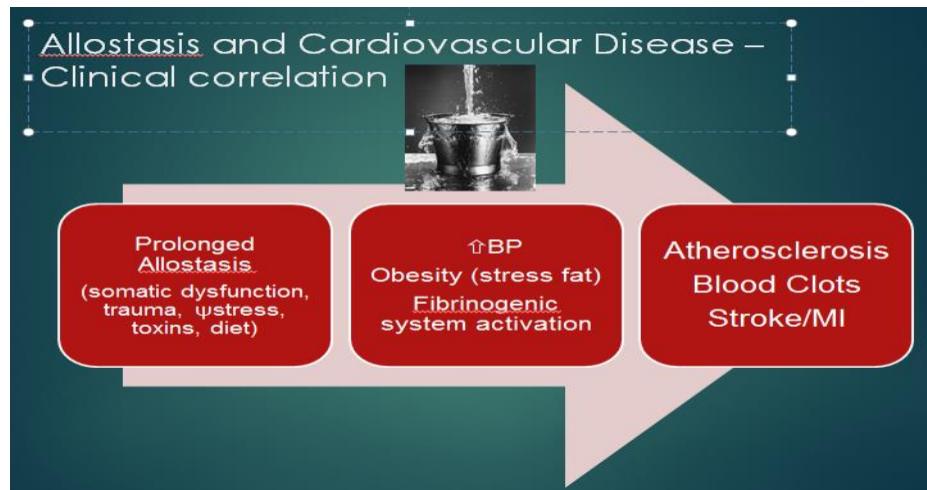
Beta receptor activation produces an increase in the second messenger _____ resulting in the activation of PKA. PKA then phosphorylates _____ channels resulting in increased intracellular calcium and contraction. The main difference between cardiac muscle cells and smooth muscle cells is that smooth muscle cell contraction requires the activation of _____ and in cardiac cells the entry of calcium is more important.

The vagal nerve (main cholinergic parasympathetic neuron) produces slowing of the heart and a decrease in contraction by releasing _____ and activating _____ receptors. Underlying both mechanism (slowing of the heart and a decrease in contractile force) is G_{αi} activation resulting in potassium efflux causing hyperpolarization and a decrease in calcium influx through voltage gated calcium channels.

Sympathetic neurons release norepinephrine which then stimulates _____ receptors on cardiac myocytes resulting in the phosphorylation of _____ by protein kinase A, allowing more calcium to enter the cell. Increased intracellular calcium produces more contractile strength.

Note: In smooth muscle cells, muscarinic receptors are the M3 type and these receptors coupled to G_{αq} resulting in the activation of the PIP2 cleavage pathway and an increase in intracellular calcium and subsequent smooth muscle contraction. More to come...

Osteopathic Considerations in Cardiovascular function



As Benjamin Franklin was fond of saying, “An ounce of prevention is worth a pound of cure.” There is no doubt that it is often easier to prevent clinical problems rather than waiting for them to become clinically relevant to treat them. In this manner, it is important to think about how we can optimize the cardiovascular system. The diagram above illustrates the continuum of dysfunction -> disease.

To help prevent cardiovascular disease, evaluation and treatment of somatic dysfunction should be a part of every routine health visit. It is especially important to look for viscerosomatic or somatovisceral reflexes that may be deleteriously affecting the heart and treating them (see section on reflexes).

Heart rate variability (HRV) is an independent marker of cardiac function and is used to monitor health status. HRV exhibits the heart's response to both internal and external stimuli. The more variability = better cardiac function. HRV is also used as an indirect

marker of the autonomic nervous system (ANS).



Osteopathic manipulative treatment (OMT) has been shown to increase HRV in several studies ([links in reference 16](#))

- A framework for the interpretation of heart rate variability applied to transcutaneous auricular vagus nerve stimulation and osteopathic manipulation. Kania A et al. *Physiology Rep*, 2024.
- Does Osteopathic Heart-Focused Palpation Modify Heart Rate Variability in Stressed Participants with Musculoskeletal Pain? A Randomised Controlled Pilot Study. Liem T et al. *Healthcare (Basel)*, 2024.
- Effectiveness of spinal manipulation in influencing the autonomic nervous system - a systematic review and meta-analysis. Kovanur K et al. *J Man Manip. Ther.*, 2024.
- Short-term effects on heart rate variability of occipito-mastoid suture normalization in healthy subjects. Besson C et al. *Front Neursci*, 2023.
- Effectiveness of Osteopathic Manipulative Treatment in Adults with Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis. Buffone F et al. *Healthcare (Basel)*, 2023.
- Osteopathic Manipulative Treatment Regulates Autonomic Markers in Preterm Infants: A Randomized Clinical Trial. Manzotti A et al. *Healthcare (Basel)*, 2022.
- Acute and Time-Course Effects of Osteopathic Manipulative Treatment on Vascular and Autonomic Function in patients with Heart Failure: A Randomized Trial. Amatuzzi F et al. *J Manipulative Physiol. Therapy*, 2021.
- Variations of high frequency parameter of heart rate variability following osteopathic manipulative treatment in healthy subjects compared to control group and sham therapy: randomized controlled trial. Ruffini N et al. *Frontiers in Neuroscience*, 2015.
- Suboccipital decompression enhances heart rate variability indices of cardiac control in healthy subjects. Giles P et al. *Journal of Alternative and Complementary Medicine*, 2013.
- Osteopathic manipulative treatment and its relationship to autonomic nervous system activity as demonstrated by heart rate variability: a repeated measures study. Henley C et al. *Osteopathic Medicine Primary Care*, 2008.

Clinical Correlate: A 26-year-old male with irritable bowel syndrome presents with bloating and cramping of the abdomen. Structural evaluation reveals warm, red, and boggy tissue texture changes in the region of T8-T12. There is also significant restriction of motion in these segments with a preference for the segments being neutral, side bent right, rotated left. You perform OMT as soft tissue technique and muscle energy technique to the T8-T12 region of the spine. Upon leaving the patient remarks that his abdominal symptoms are less severe.

D. ANS overview of Smooth Muscle Function

Why Smooth Muscle Tone Matters

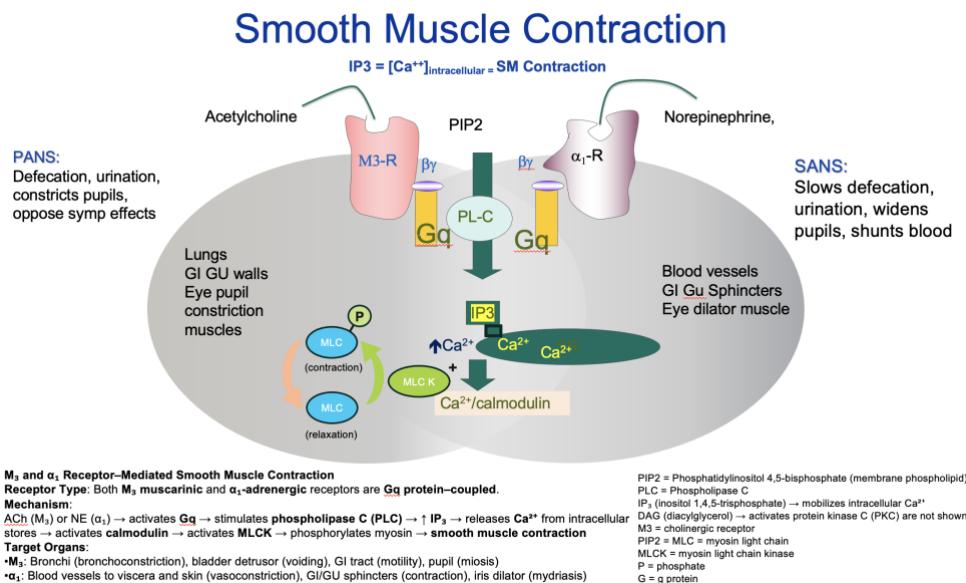
The autonomic nervous system (ANS) plays a vital role in regulating smooth muscle tone throughout the body. This balance between contraction and relaxation is central to maintaining homeostasis — directing blood flow, moving contents through the gastrointestinal (GI) and genitourinary (GU) tracts, adjusting airway diameter, and controlling organ sphincters. Local and hormonal mediators such as angiotensin II, prostaglandins, nitric oxide, and histamine also modulate smooth muscle tone and will be covered separately. This section focuses on how neurotransmitters released by the ANS — mainly acetylcholine (ACh) and norepinephrine (NE) — coordinate smooth muscle function.

Smooth muscle contraction and relaxation allow the body to adjust organ function according to immediate needs. For example:

- During **fight-or-flight**, the sympathetic nervous system (S-ANS) shifts resources by relaxing airways and skeletal muscle vasculature, while constricting blood flow to non-essential areas.
- During **rest-and-digest**, the parasympathetic nervous system (P-ANS) supports digestion, urination, and defecation by contracting GI walls and relaxing sphincters.

How the ANS Controls Smooth Muscle

1) Smooth Muscle Contraction



- **Mechanism:** Both ACh (via M₃ receptors) and NE (via α₁ receptors) trigger smooth muscle contraction through the G_q-PLC-IP₃ pathway. IP₃ increases

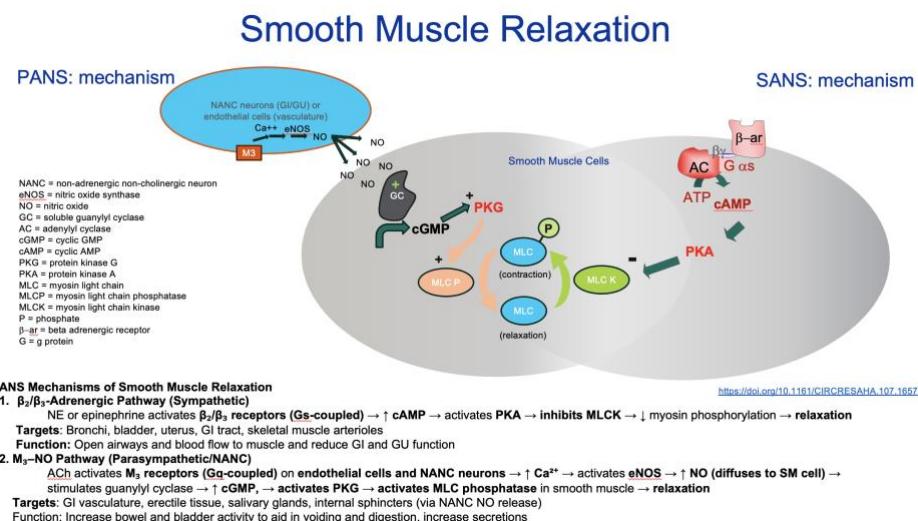
intracellular calcium, promoting along with calmodulin the activation of myosin light chain kinase (MLCK), which phosphorylates myosin light chain (MLC) to initiate contraction. The phosphorylation of MLC by MLCK is required for smooth muscle contraction.

- **Examples:**

- **Parasympathetic:** Contraction of gut and bladder walls to propel contents.
- **Sympathetic:** Constriction of blood vessels in the viscera and GU sphincters to limit elimination during stress.

2. Smooth Muscle Relaxation

- **Parasympathetic-Induced Relaxation:** ACh indirectly relaxes smooth muscle by activating M3 receptors on nearby endothelial or non-adrenergic neurons,

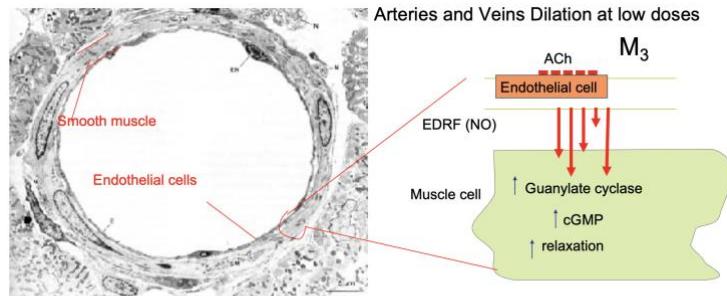


triggering NO release. NO diffuses into smooth muscle, activates guanylate cyclase, raises cGMP, and activates MLCP, which removes the phosphate from myosin light chain to reduce contraction. Example: relaxation of sphincters to facilitate urination or defecation.

- **Sympathetic-Induced Relaxation:** NE binds to β_2 or β_3 adrenergic receptors on smooth muscle cells.
 - **β_2 Receptors:** Commonly found in bronchioles, gut/bladder walls, and skeletal muscle vasculature. Activation increases cAMP, which activates PKA, inhibits MLCK, and leads to relaxation.
 - **β_3 Receptors:** Primarily located in the bladder wall and adipose tissue. In the bladder, β_3 activation promotes detrusor muscle relaxation, aiding urine storage during stress. In adipose tissue, β_3 activation enhances lipolysis to mobilize energy.

Key Note on Nitric Oxide (NO)

Note: Nitric Oxide (NO) or endothelium derived relaxing factor is a gas signaling molecule that earned Dr.'s Furchtgott, Ignarro, and Murad the Nobel prize in medicine in 1998 for their discovery of its action on smooth muscle cells. It is different from the inhaled anesthetic nitrous oxide (NO_2).



Note: No direct innervation of parasympathetic to blood vessels. Sympathetic system dominates = vasoconstriction. However, muscarinic agonist injected into vasculature can produce vasodilation at low doses.

Summary of Receptor Roles

Receptor	Effect	Example
M3 (P-ANS)	Contraction	Gut/bladder walls
M3 (via NO)	Relaxation	GI/GU sphincters
α_1 (S-ANS)	Contraction	Blood vessels, sphincters, radial eye muscle
β_2 (S-ANS)	Relaxation	Bronchioles, gut/bladder walls, skeletal muscle vasculature
β_3 (S-ANS)	Relaxation	Bladder detrusor muscle (urine storage), adipose tissue (lipolysis)

This section focused on ANS regulation of smooth muscle. Local and hormonal mediators such as angiotensin II, adenosine, metabolites, prostaglandins, histamine are also important and will be discussed elsewhere. These local mediators are equally as important in the combined regulation of organ function as compared to the neurotransmitters released by the ANS.

Control of smooth muscle tone (contraction and relaxation) is a key function of the autonomic nervous system (ANS), directly linked to the body's fight-or-flight (sympathetic) and rest-and-digest (parasympathetic) responses.

Nitrous oxide in smooth muscle cells activates guanylate cyclase increasing the production of _____

The sympathetic ANS gains functional difference, relaxation vs. contraction, by placing _____ receptors on smooth muscle cells that when activated by norepinephrine produce relaxation and alpha-1 receptors when it is functionally important for the smooth muscle to contract.

The fight-or-flight-sympathetic-response shuts down unnecessary functions for immediate survival. For example, sympathetic release of norepinephrine **relaxes** gut

_____ by activating beta-2 receptors located on the smooth muscle cells of the gut and bladder walls to prevent bowel evacuation.

The opposite is true when excretion or defecation is necessary. In this case, gut _____ are relaxed, when nitrous oxide is produced or diffuses into the smooth muscle cells allowing waste release.

Parasympathetic-induced smooth muscle relaxation is dependent on the indirect release of _____ by either endothelial cells or non-adrenergic non-cholinergic neurons, which diffuses across and into smooth muscle cells.

Sympathetic-induced smooth muscle relaxation is dependent on the presence of beta-2 adrenergic receptors on smooth muscles. When beta-2 receptors are activated the second messenger _____, activates protein kinase A, that in turn, inhibits, myosin light chain kinase.

Receptor location is central to autonomic functional control. The fight-or-flight-sympathetic-response requires constriction of gut _____ to prevent bowel evacuation and increased pupil diameter opening by contracting eye radial muscles to allow more light detection.

Muscarinic receptors are used in the gut by the parasympathetic ANS. The goal of the parasympathetic system is to aid in digestion, bowel evacuation, and urination. Therefore, it is logical that to evacuate the bowels the gut walls containing muscarinic receptors should produce _____ of the smooth muscle.

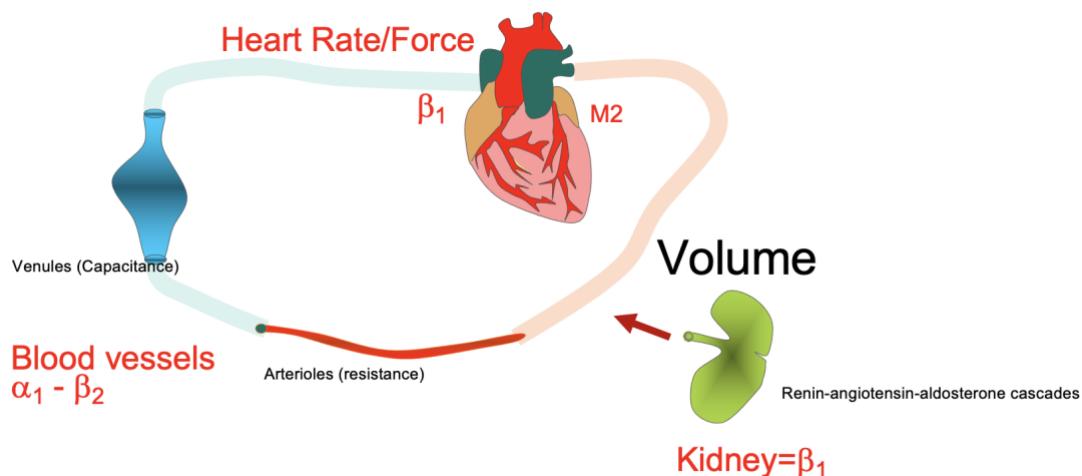
Muscarinic receptors located on circular eye muscles (pupillary constrictor muscles) cause _____ of this muscle resulting in decreased pupil diameter, which acts to protect the retina from excess light.

The molecular mechanism that underlies smooth muscle contraction will be the focus of the next section

Sympathetic-induced smooth muscle contraction is produced by activation of _____ receptors while parasympathetic-induced smooth muscle contraction is produced by activation of muscarinic (M3) cholinergic receptors. Both receptor types share the common intracellular cascade resulting in the activation of _____ and an increase in intracellular _____.

E. ANS control of Vascular Function and Blood Pressure.

Vascular Loop and Blood Pressure Regulation:

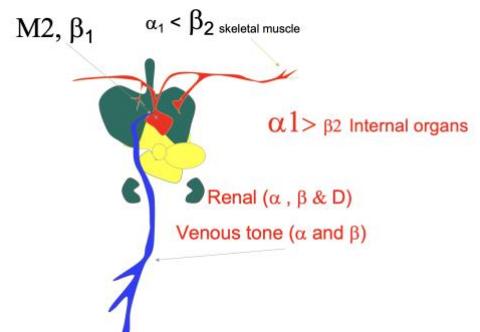
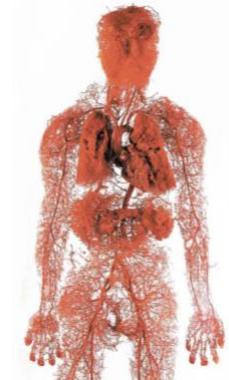


The vascular loop is a closed circulatory system that plays a critical role in maintaining blood pressure, which is regulated through the coordinated actions of the heart, blood vessels, and kidney function, all influenced by the autonomic nervous system (ANS).

Autonomic Nervous System Regulation:

1. Sympathetic Response:

- **Function:** The primary goal of the sympathetic nervous system (SNS) is to increase oxygen and glucose delivery to muscles and the brain, especially during stress or physical activity. It achieves this by constricting blood flow to less essential organs, such as the gastrointestinal tract while increasing blood flow to muscles while increasing heart rate and contractile force (pumping action)
- **Mechanism:** SNS activation increases heart rate and contractility through beta-1 adrenergic receptors, enhancing cardiac output. It also causes vasoconstriction via α_1 adrenergic receptors, reducing the diameter of blood vessels, particularly in non-essential areas, and redirecting blood flow to vital organs. Beta-2 receptors cause skeletal muscle blood vessels to dilate, ensuring adequate blood supply during activity. Note: α_1 effect dominate blood pressure as there is vastly more vasculature directed toward organ function (see blood vessels in figure). The ratio of α_1 to β_2 is



greater in the blood vessels of the viscera, conversely, the ratio of β_2 to α_1 is greater on muscle blood vessels.

2. Parasympathetic Response:

- **Function:** The parasympathetic nervous system (PNS) provides balance by reducing cardiovascular activity when high output is not needed, promoting energy conservation and facilitating digestive processes.
- **Mechanism:** PNS activation decreases heart rate through muscarinic (M2) receptors, which reduces cardiac output and, subsequently, blood pressure. It has minimal direct effect on blood vessel tone but counterbalances the SNS to prevent excessive cardiovascular stimulation.

Blood Pressure Regulation Mechanisms:

1. Heart Force and Rate:

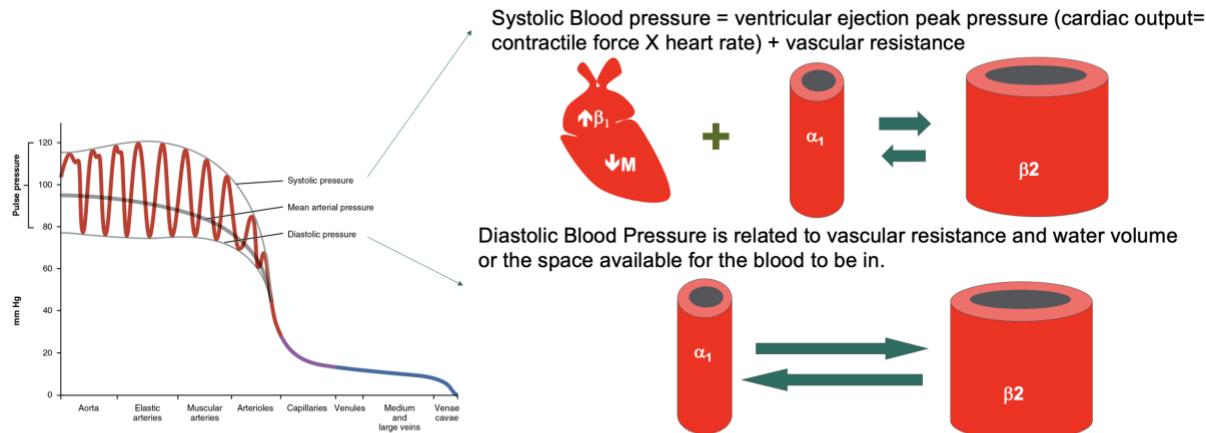
- Blood pressure is directly influenced by the heart's pumping action, which fills the vascular loop. The SNS increases heart rate and the force of contraction (positive inotropy) via beta-1 receptors, elevating blood pressure. The PNS, via M2 receptors, slows the heart rate, reducing blood pressure.

2. Vascular Tone:

- The amount of space inside the vascular loop is regulated by the balance of vasoconstriction and vasodilation. SNS-induced alpha-1 receptor activation causes vasoconstriction, reducing the diameter of blood vessels and increasing resistance and blood pressure. Conversely, beta-2 receptor activation in certain tissues (like skeletal muscles) leads to vasodilation, increasing space within the vascular loop and reducing resistance.

3. Fluid Volume:

- Blood pressure is also determined by the volume of fluid within the vascular loop. This is regulated by kidney function, which is influenced by the SNS. The SNS stimulates renin release from the kidneys via beta-1 receptors, leading to the activation of the renin-angiotensin-aldosterone system (RAAS), which increases sodium and water retention, thereby increasing blood volume and pressure.



Autonomic Regulation of Systolic and Diastolic Blood Pressure
Systolic blood pressure (SBP) reflects the pressure generated during **ventricular systole** and is determined by a combination of **cardiac output (CO)** and **total peripheral resistance (TPR)**. CO is modulated by autonomic input to the heart: β_1 -adrenergic receptor activation increases heart rate and contractility, while M_2 muscarinic receptor activation opposes this by reducing both. Sympathetic tone predominates during activity or stress, enhancing SBP through increased cardiac performance.
Diastolic blood pressure (DBP), measured during **ventricular diastole**, is primarily dependent on **TPR alone**, as the heart is not actively ejecting blood. Autonomic regulation of TPR is mediated by α_1 -adrenergic receptors, which cause **vasoconstriction** and raise DBP, and β_2 -adrenergic receptors, which promote **vasodilation** in select vascular beds (e.g., skeletal muscle), reducing localized resistance and DBP.
Together, the **balance of sympathetic and parasympathetic tone** and the differential activation of adrenergic and muscarinic receptors allow for **precise regulation of arterial pressure** across the cardiac cycle.

Note: Systolic BP: Systolic blood pressure is a balance of receptor activated by the autonomic nervous system. *Blood pressure is increased by:* Beta-one receptor (\uparrow Cardiac output = $HR \times$ contractile force) and alpha-1 receptors (constrict vasculature). See figure above and remember that during systole the heart is contracting.

minus

Factors that decrease blood pressure—muscarinic (\downarrow Cardiac output) and beta 2-receptors (dilate skeletal muscle vasculature)

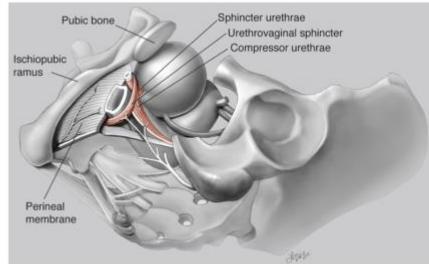
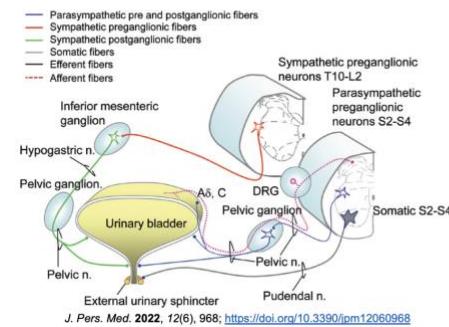
Diastolic BP: Diastolic blood pressure is not influenced by CO since it is the blood pressure after contraction and is; therefore, influenced by the vascular blood volume and space only, which equals alpha-one receptor constricting influences minus beta-2 receptor. Note: Beta-one receptor effects are not important in controlling diastolic BP.

Overall Regulation: As a closed system, the vascular loop's pressure is managed by adjusting heart output, vessel diameter, and fluid volume. The SNS primarily drives increases in blood pressure by enhancing heart function, constricting blood vessels, and increasing blood volume. The PNS provides the necessary counterbalance, reducing heart rate and promoting relaxation of the cardiovascular system when high pressure is not needed.

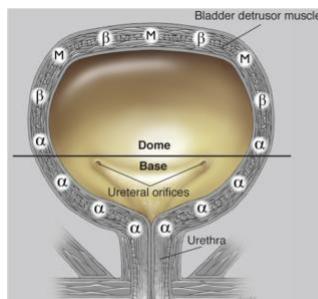
This integrated regulation ensures that blood pressure is maintained at optimal levels, supporting effective oxygen and nutrient delivery to vital organs while preventing excessive strain on the cardiovascular system.

F. Effects on Genito-Urinary Function

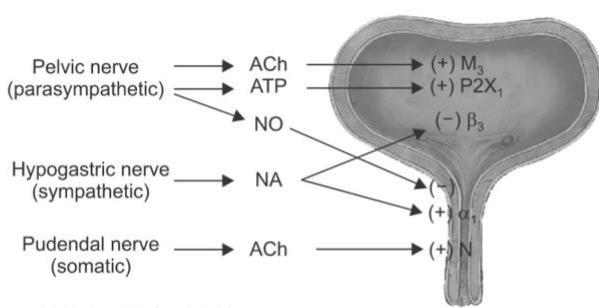
ANS control points for GU function



Source: Barbara L. Hoffman, John O. Schorge, Lisa M. Halvorson, Cherine A. Hamid, Marlene M. Corton, Joseph I. Schaffner: Williams Gynecology, 4th Edition
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Overview

Bladder function relies on an intricate balance between **involuntary autonomic control** (parasympathetic and sympathetic systems) and **voluntary somatic control** (pudendal nerve). This integrated system coordinates the detrusor muscle (bladder dome) and both the internal and external sphincters to maintain continence during storage and enable controlled voiding.

Involuntary (Autonomic) Control

Parasympathetic System (Pelvic Nerve, S2–S4)

Promotion of urination (voiding) is produced when the bladder dome contracts via the release of Ach and ATP from parasympathetic fibers, and the activation of M3 muscarinic and P2X1 purinergic receptors on the detrusor muscle → contraction to expel urine. In addition the internal sphincter relax when parasympathetic nerves stimulate non-adrenergic, non-cholinergic (NANC) neurons to release nitric oxide (NO), which relaxes the smooth muscle of the internal sphincter, aiding urine flow.

Sympathetic System (Hypogastric Nerve, T10–L2)

Sympathetic activations promotes storage by relaxing the bladder dome and tightening the internal sphincter. The bladder dome: is innervated by sympathetic fibers that release norepinephrine, which binds to β3 adrenergic receptors → relaxation of the detrusor muscle to increase storage capacity. Conversely, the internal sphincter contract

when norepinephrine binds to α_1 adrenergic receptors → contraction of the internal sphincter and bladder neck to prevent leakage.

Voluntary (Somatic) Control (Pudendal Nerve, S2–S4)

The somatic system provides conscious control of urination via the External Sphincter Complex: The external urethral sphincter, compressor urethrae, and urethrovaginal sphincter are skeletal muscles controlled by the pudendal nerve. ACh binds to nicotinic receptors, maintaining contraction of these muscles to prevent unwanted urine flow. During voiding, voluntary relaxation of these muscles allows urine to pass.

How Storage and Voiding Are Coordinated

During Storage:

- Sympathetic input dominates:
- β_3 receptors keep the bladder dome relaxed so it can fill.
- α_1 receptors contract the internal sphincter to keep urine in.
- Somatic input keeps the external sphincter tightly closed to maintain continence.

During Voiding:

- Parasympathetic input takes over:
- M3/P2X1 activation contracts the bladder dome to generate pressure for expulsion.
- NO release relaxes the internal sphincter for flow.
- Somatic control: Voluntary relaxation of the external sphincter muscles completes urination.

Clinical Pearl: Receptors and Treatment

- **Overactive bladder: β_3 agonists** (like mirabegron) relax the detrusor dome to reduce urgency and frequency.
- **Urinary retention: α_1 blockers** can relax the internal sphincter, improving urine flow in conditions like BPH.

Understanding how **M3, P2X1, β_3 , α_1 , and nicotinic receptors** contribute to storage and voiding guides pharmacologic treatment.

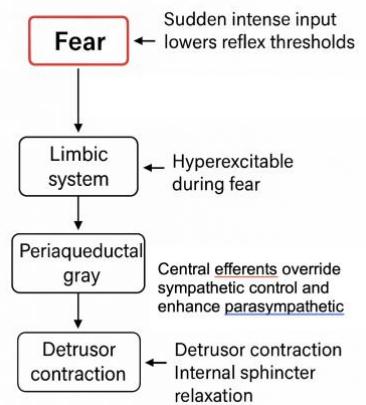
Key Takeaway

The bladder's detrusor muscle and sphincters require constant coordination between the **parasympathetic**, **sympathetic**, and **somatic** systems to store urine when needed and allow complete emptying when appropriate. Osteopathic care and targeted drug therapy can support this balance by influencing nerve pathways and receptor function.

FYI only: Why do animals void their bladder during extreme stress?

When someone becomes extremely nervous or frightened, the “**fight-or-flight**” sympathetic response is strongly activated. You’d expect this to suppress voiding — because sympathetic tone **relaxes the detrusor** and **contracts the internal sphincter**, promoting urine storage. However, under sudden extreme fear, there’s also a **surge in parasympathetic activation**, plus a **central override** of normal reflex loops — especially through the **pontine micturition center (PMC)** and higher cortical centers (e.g., prefrontal cortex, limbic system). In some species, sudden urination or defecation in fear is thought to lighten body weight for faster escape or to mark territory. In humans, the same primitive reflex can occur.

- **The PMC** coordinates detrusor contraction and urethral sphincter relaxation; sudden intense limbic input (from amygdala, hypothalamus) can trigger an inappropriate “void now” signal, overriding sympathetic inhibition.
- Emotional stress can lower the threshold for this reflex arc.
- The **periaqueductal gray (PAG)**, which integrates sensory bladder filling information, can become hyperexcitable during fear.
- Additionally, sympathetic overactivation can lead to transient sphincter fatigue — making it harder to maintain continence when there is sudden bladder pressure.



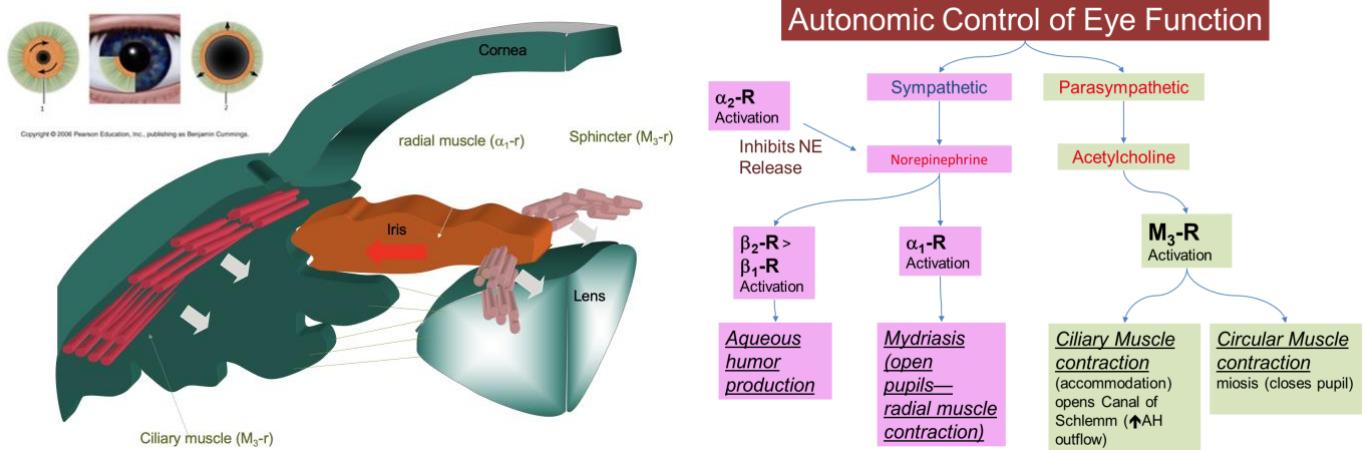
Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. *Nat Rev Neurosci*. 2008;9(6):453–66. PMCID:

[PMC2897743](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2897743/) DOI: [10.1038/nrn2401](https://doi.org/10.1038/nrn2401)

Holstege G. The emotional motor system and micturition. *Neurourology and Urodynamics* 29:42–48 (2010)

<https://doi.org/10.1002/nau.20789>

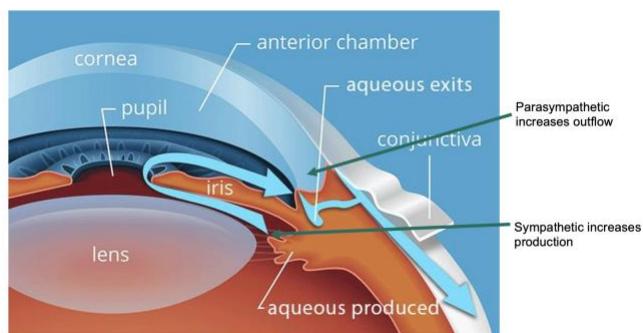
G. Autonomic Control of Eye Function



The eye relies on precise autonomic regulation to adapt to changing light levels, focus demands, and behavioral states. This balance is achieved through parasympathetic and sympathetic pathways acting on smooth muscle structures in the iris, ciliary body, and eyelids.

Parasympathetic Effects (M3 Receptors)

- Pupillary Constriction (Miosis):** Parasympathetic fibers release acetylcholine (ACh), which binds to M3 receptors on the sphincter pupillae (constrictor) muscle. This causes the pupil to constrict, protecting the retina from excessive light and enhancing near vision focus.
- Lens Accommodation:** ACh also stimulates M3 receptors on the ciliary muscle, reducing tension on the zonular fibers as it contracts towards the lens. This allows the lens to thicken, improving near vision for tasks like reading. Ciliary muscle contraction also helps maintain aqueous humor (AH) drainage by moving tissue away from the AH outflow trabecular meshwork pathway and the canal of Schlemm (the major AH outflow pathway), supporting drainage.



Sympathetic Effects (α_1 , β_1 , β_2 Receptors)

- **Pupillary Dilation (Mydriasis):** Sympathetic fibers release norepinephrine (NE) which activates α_1 receptors on the radial dilator pupillae muscle, pulling the pupil open. This enhances light capture in low-light settings and expands the visual field for situational awareness — part of the fight-or-flight response.
 - **Aqueous Humor Production:** β_1 and β_2 receptors on the ciliary body epithelium stimulate aqueous humor production, maintaining intraocular pressure (IOP) and providing nutrients to avascular eye structures.
 - **Eyelid Elevation:** Sympathetic tone to Müller's muscle lifts the upper eyelid slightly, enhancing alertness and the visual field.
-

Why This Matters Functionally:

This dynamic ANS balance optimizes vision for both bright and low-light environments, adjusts focus for near and far objects, and aligns vision with behavioral arousal. Proper aqueous humor production and outflow are vital for maintaining stable IOP and clear optics. Blockage of drainage pathways (e.g., trabecular meshwork dysfunction) can elevate IOP, leading to optic nerve damage — a key factor in glaucoma.

Clinical Relevance:

- **Diagnostic Clues:** Changes in pupil size or reaction (e.g., Horner's syndrome with miosis and mild ptosis) can signal lesions in sympathetic or parasympathetic pathways.
 - **Glaucoma Management:** Treatment often targets ANS pathways:
 - **β -blockers** (e.g., timolol) inhibit β -receptors on the ciliary epithelium to decrease aqueous humor production.
 - **α_2 -adrenergic agonists** (e.g., brimonidine) further reduce aqueous humor production by inhibiting NE release.
 - **Muscarinic agonists** (e.g., pilocarpine) contract the ciliary muscle, opening the trabecular meshwork and enhancing aqueous humor outflow.
 - **Clinical Significance:** Continuous production of aqueous humor nourishes the lens and cornea. Maintaining a balance between production and outflow prevents IOP buildup. Understanding these mechanisms is essential for preventing and treating conditions like open-angle glaucoma, which can cause irreversible vision loss if unchecked.
-

Note: **Miosis** is the constriction of the pupil

Mydriasis is the **d**ilation of the pupil.



Mnemonic—d in mydriasis = d for dilation

This section reinforces how autonomic pathways integrate local muscle control, fluid dynamics, and environmental responsiveness — a classic example of how the ANS maintains ocular homeostasis and adjusts vision to meet the body's needs.

During the fight-or-flight sympathetic response more light is required to increase visual acuity. This effect is mediated by sympathetic neurons releasing norepinephrine that causes mydriasis (pupil opening—contraction of the M. dilatator pupillae or radial muscle) via activation of _____ - _____ adrenoceptors located on eye radial muscles.

During rest the need for more light is reduced. The parasympathetic release of acetylcholine can close the pupil diameter (miosis) by constricting the _____ muscles around the pupil.

Radial muscles contract when Alpha-1 receptors are activated, which _____ the pupils.

Beta-adrenergic receptor activation increases _____ production

Note: Alpha-2 adrenergic receptor activation decreases aqueous humor production by preventing norepinephrine release.

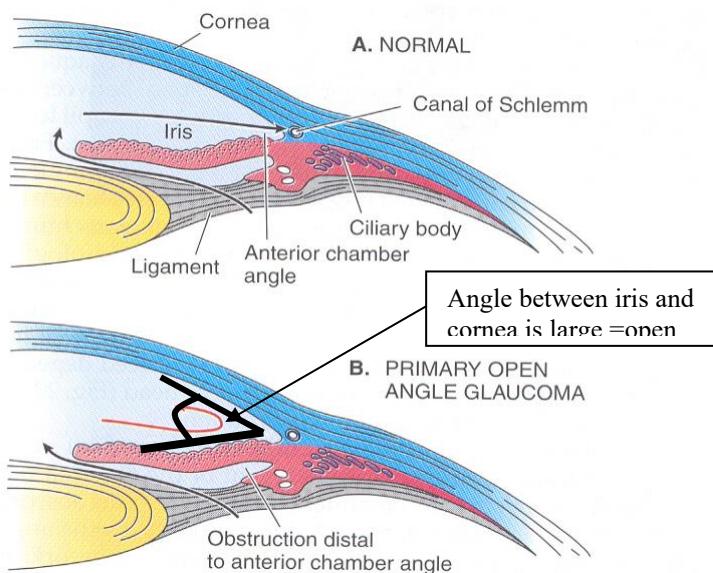
Acetylcholine has two main effects on the eye. One is to close the pupil diameter by causing muscarinic-receptor-mediated contraction of the _____ muscle (correct anatomical name is M. sphincter pupillae). The second is to cause contraction of ciliary muscle which is necessary for accommodation and for opening the canal of Schlemm allowing _____ to flow out.

Muscarinic-receptor-induced increases in aqueous-humor outflow are an important therapeutic management for patients with glaucoma.

Clinical Correlate: Therapy of open angle vs closed angle glaucoma

Observe the anatomy of the eye shown below, particularly the angle between the iris and cornea and the location of the Canal of Schlemm. When the Canal of Schlemm is

open and unobstructed, aqueous humor can flow out, effectively reducing intraocular pressure—a critical factor for patients with glaucoma. In open-angle glaucoma, the angle between the iris and cornea remains wide, allowing the Canal of Schlemm to stay accessible even when the iris contracts. This prevents blockage of the outflow pathway, which is essential for managing intraocular pressure in these patients.



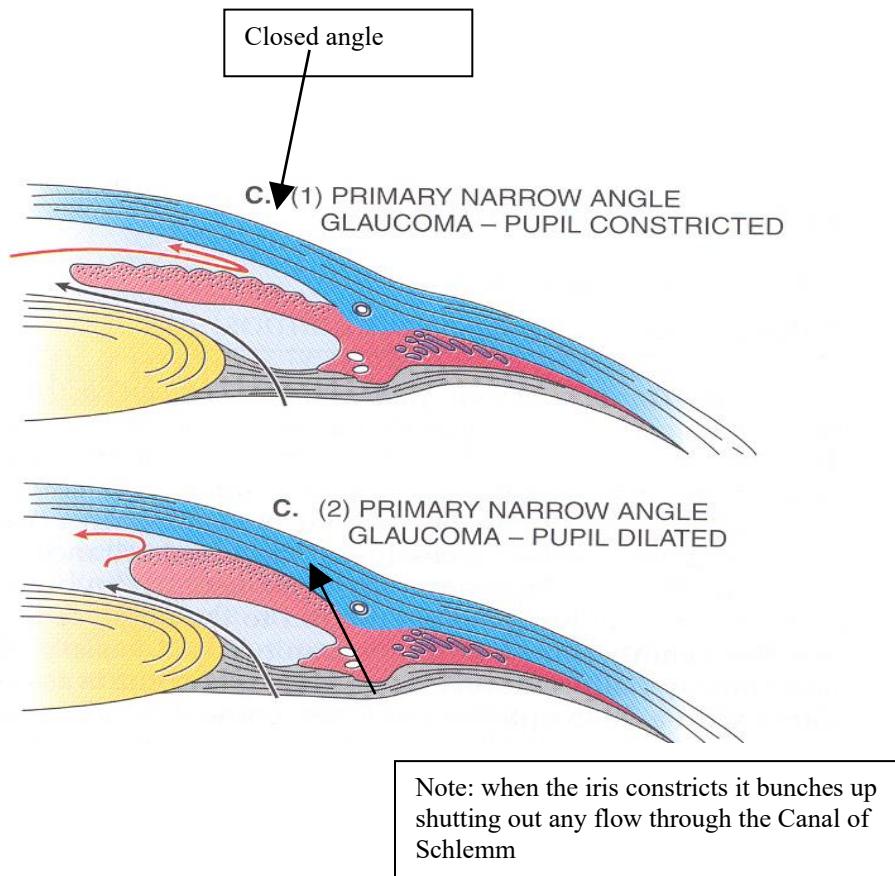
Rubin's Pathology

Clinicopathologic Foundations of Medicine 4th ed. Lippincott Williams & Wilkins

Pharmacology of Glaucoma: There are two pharmaceutical methods to reduce intraocular pressure.

- 1) Increase outflow:
 - a. Through the Canal of Schlemm = Cholinomimetics. Constriction of the ciliary muscle mediated by muscarinic receptor activation pulls tissue away from the Canal of Schlemm thus increasing patency and outflow
 - b. Through the uveoscleral pathway = alpha 1 adrenergic agonist (uncommon) and prostaglandins like latanoprost (very common) Note: using alpha agonist would be bad in a patient with closed angle glaucoma. See explanation to follow.
- 2) Decrease production or secretion
 - a. Preventing beta-adrenergic receptor induced aqueous humor secretion
 - i. Beta-receptor-blockers
 - ii. Diuretics (carbonic anhydrase inhibitors)

Closed Angle Glaucoma

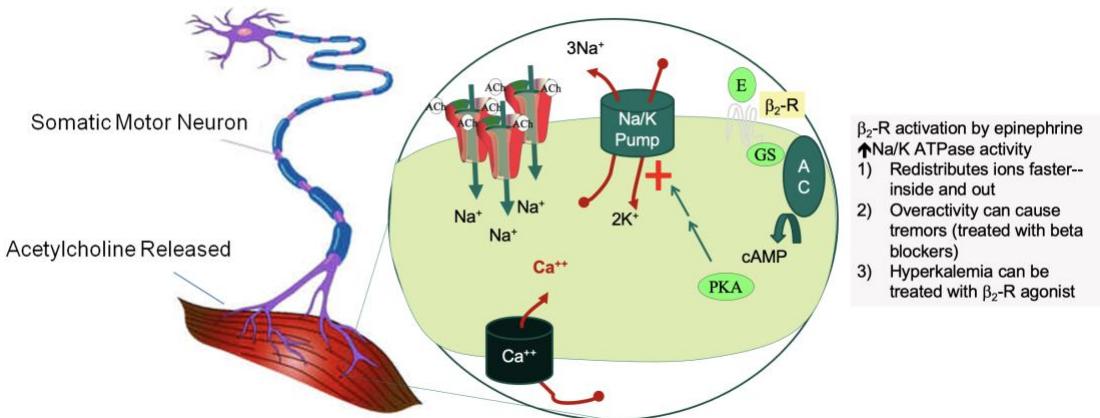


Rubin's Pathology

Clinicopathologic Foundations of Medicine 4th ed. Lippincott Williams & Wilkins

Observe the angle between the iris and the cornea when the iris muscle is closed. There is still access to the Canal of Schlemm. Now note what happens in the lower panel when the iris constricts (bunches up). There is no access or ability of the aqueous humor to flow out of the Canal of Schlemm. This is a medical emergency and usually requires surgery to remove part of the iris (iridectomy). However, while waiting for surgery the same drugs used to treat open angle glaucoma can be used EXCEPT for alpha agonist that cause the radial muscle of the iris to constrict resulting of the bunching up of the iris and the subsequent prevention of aqueous humor outflow through the Canal of Schlemm.

H. Autonomic Effects on Skeletal muscle



While voluntary skeletal muscle contraction is under somatic motor control, the **sympathetic nervous system (SNS)** plays an important supportive role during times of heightened demand, such as fight-or-flight responses.

Voluntary Contraction:

Motor neurons release acetylcholine at the neuromuscular junction, which binds to nicotinic receptors on muscle fibers. This opens ion channels, leading to membrane depolarization, activation of voltage-gated calcium channels, and calcium release from the sarcoplasmic reticulum — all steps that trigger muscle fiber contraction.

SNS Modulation via Beta-2 Receptors:

Epinephrine, released from the adrenal medulla during stress, binds to **beta-2 adrenergic receptors** on skeletal muscle cells. This activates a **cAMP-PKA pathway**, which increases **Na⁺/K⁺-ATPase (sodium pump) activity**. By accelerating sodium efflux and potassium influx, this process stabilizes the membrane potential and helps muscle fibers **repolarize more rapidly** after each contraction. This mechanism supports sustained, high-frequency firing during strenuous activity — aligning with the body's survival needs.

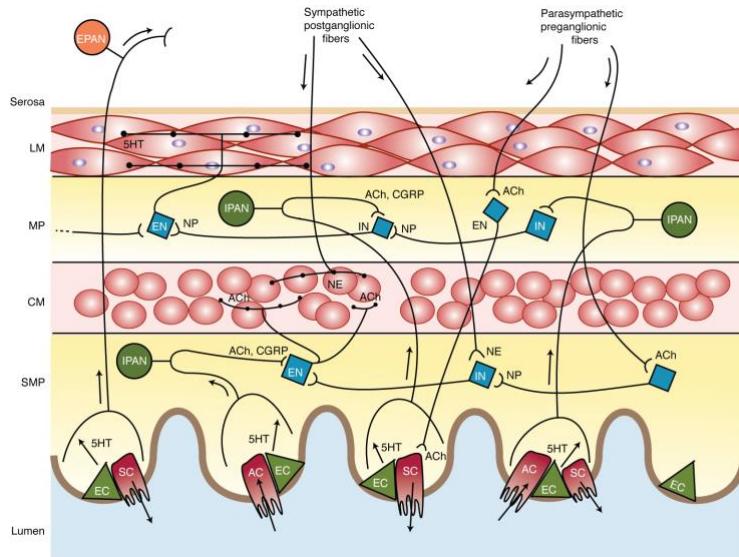
Clinical Relevance:

- **Skeletal Muscle Tremor:** Excessive beta-2 stimulation (e.g., high doses of beta-2 agonists for asthma or stage fright) can overstimulate sodium pump activity and ion fluxes in muscle fibers, leading to fine skeletal muscle tremors. **Beta-blockers** can reduce these tremors by dampening beta-2 receptor activity.
- **Hyperkalemia Management:** Beta-2 agonists (such as albuterol) can be used in acute hyperkalemia. By stimulating beta-2 receptors in skeletal muscle, they enhance Na⁺/K⁺-ATPase activity, driving **potassium into muscle cells** and lowering serum potassium levels. This use relies on skeletal muscle's large mass as a potassium reservoir.

Key Takeaway:

The SNS does not directly trigger skeletal muscle contraction, but **beta-2 receptor activation enhances the muscle's readiness** for rapid, repeated contractions by boosting ion transport and membrane recovery. This subtle yet vital effect explains how the body can meet the intense metabolic and neuromuscular demands of stress, and why beta-2 effects have clear **therapeutic and side effect implications**.

I. Autonomic Effects on Gastrointestinal System



The **enteric nervous system (ENS)** — often called the “second brain” — is a complex neuron network embedded in the gastrointestinal (GI) tract walls that coordinates digestion through local reflexes and ANS regulation. It independently coordinates **motility**, **secretion**, and **local blood flow**. In addition, its activity is also modulated by the **ANS** to match gut activity to the body’s overall state. The **parasympathetic nervous system** promotes “rest-and-digest” activity — increasing peristalsis, secretion, and nutrient absorption. The **sympathetic nervous system**, in contrast, suppresses gut motility and secretion during “fight-or-flight” states, conserving energy and redirecting blood flow to muscles and the brain.

How the ANS Modulates the ENS:

- **Parasympathetic Influence:** Parasympathetic fibers synapse within the ENS and release **acetylcholine (ACh)**, which binds mainly to **muscarinic (M3) receptors**. This promotes **smooth muscle contraction**, enhances **peristalsis**, and stimulates secretions that aid digestion and absorption.
- **Sympathetic Influence:** Sympathetic fibers release **norepinephrine (NE)**, which binds to **alpha and beta-2 adrenergic receptors**, typically reducing gut motility (relaxing the walls) and constricting splanchnic blood vessels, conserving blood flow for vital organs in “fight-or-flight” states.

Clinical Relevance for Osteopathic Medicine:

Postoperative patients — especially after abdominal or pelvic surgery — can develop **constipation** or **postoperative ileus** due to increased sympathetic tone and reduced parasympathetic input to the gut. Osteopathic manipulative treatment (OMT) can help restore **autonomic balance**, reduce sympathetic overactivity, and promote the return of normal bowel function. J Am Osteopath Assoc. 2013 Apr;113(4):271. PMID: 23485980.

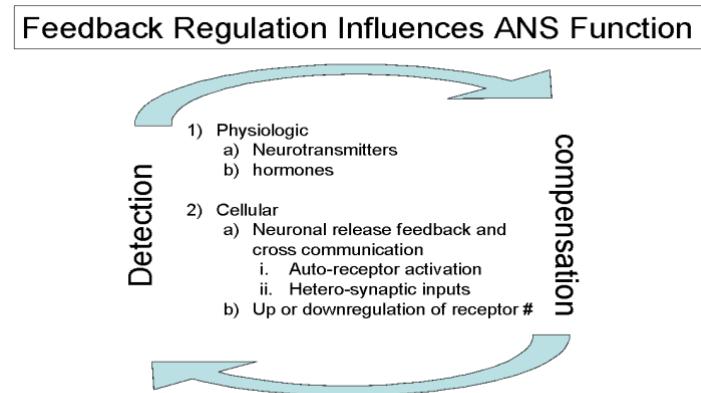
J. Summary of ANS, neurotransmitter and receptors

Also see table 6-3, page 86 of Basic & Clinical Pharmacology, B. Katzung, 11th ed.
McGraw Hill

Organ	Sympathetic	Parasympathetic
	Effect	Effect
Heart	↑ rate, contractile force, conduction velocity	β1 (1 heart)
Kidney	Renin release	β1
Bronchiolar SM	Relax (opens airways)	β2
GI SM walls	Relax (↓ motility)	β2
Bladder walls	Relax (↓ voiding)	β3 > β2
Uterus	Relax (slows delivery)	β2
Liver	Gluconeogenesis, glycogenolysis	β2
Skeletal muscle	↑ sodium pump activity	β2
Skeletal and coronary vasculature	Relax (↓ resistance)	β2
Arterioles, veins	Contract (↑ pressure)	α1
Penis (seminal vesicles)	Contracts (ejaculation) Shoot	α1
GI Sphincters	Contracts (↓ defecation)	α1
Bladder sphincters	Contracts (↓ micturition)	α1
Eye (Radial dilator muscle)	Contracts (mydriasis)	α1
Eye (sphincter muscle)		
Eye (ciliary muscle)		
Eye	Ciliary epithelium AH production	β2 > β1
Glandular secretions, gastric secretions	↑ Eccrine sweat glands ↑ Apocrine (stress)	M α
		Increases
		M3 (glandular) M1 (gastric)

Memorize this table: it represents a concise summation of the previous material.

Section 3 – ANS Feedback Regulatory Control

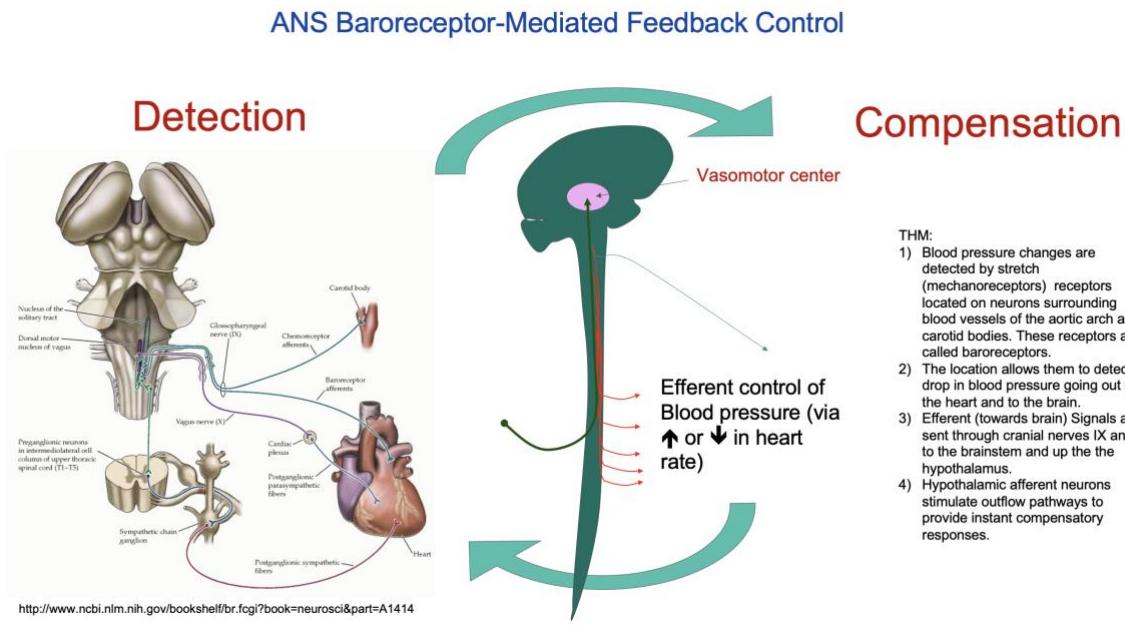


A core principle of the autonomic nervous system (ANS) is that it operates as a dynamic feedback system — continuously detecting internal and external changes and compensating through rapid adjustments to maintain homeostasis. The baroreceptor and chemoreceptor reflexes, stretch reflexes, and other visceral afferent pathways detect changes and send sensory input to the central nervous system, which integrates this information and coordinates the appropriate sympathetic and parasympathetic responses.

How It Works: Detection and Compensation

- **Detection:** Specialized receptors — such as baroreceptors (for blood pressure), chemoreceptors (for oxygen, CO₂, pH), stretch receptors (in the bladder, rectum, gut), and nociceptors (pain) — constantly monitor the body's internal environment.
- **Integration:** This sensory input travels to integrative centers in the brainstem (like the nucleus tractus solitarius), hypothalamus, or higher cortical-limbic areas, depending on the type of input.
- **Compensation:** The CNS integrates sensory input and sends efferent signals through autonomic pathways to adjust target organ function — modulating heart rate, vascular tone, smooth muscle contraction or relaxation, glandular secretions, and other vital processes to maintain homeostasis. In addition to this global feedback regulation, local adjustments also occur at the synaptic or cellular level. For example, presynaptic auto-receptors can fine-tune neurotransmitter release, heterosynaptic inputs can modulate neighboring synapses, and target tissues can up- or down-regulate receptor numbers in response to sustained stimulation or inhibition. Together, these central and local mechanisms ensure precise, adaptive control of autonomic function in response to changing internal and external demands.

A. ANS Feedback Regulatory Control of Blood Pressure



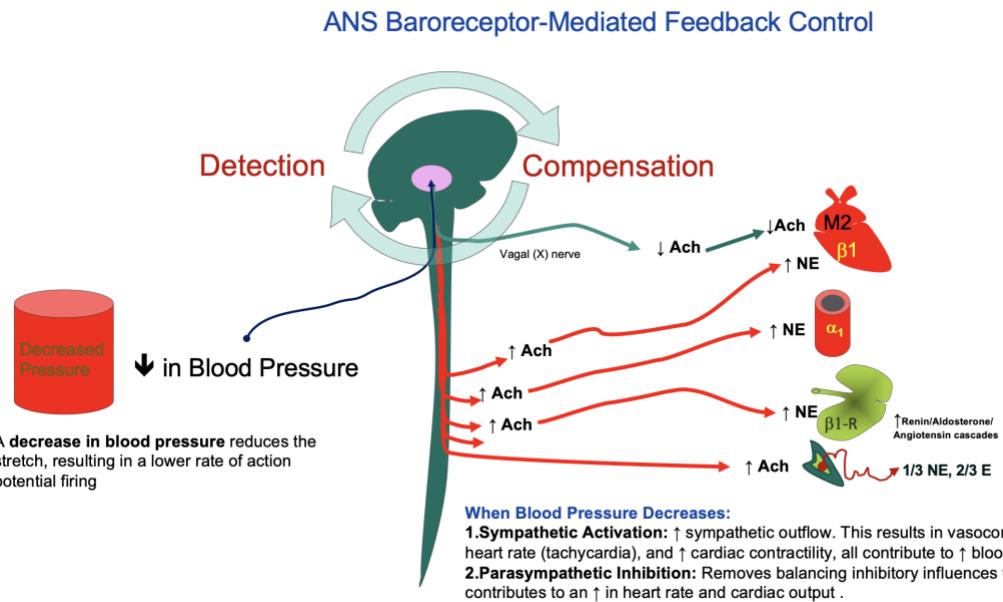
Autonomic Regulation of Blood Pressure: Blood pressure regulation is a crucial function of the autonomic nervous system (ANS), ensuring that adequate blood flow is maintained throughout the body, particularly to vital organs like the brain. The regulation is primarily mediated through the baroreceptor reflex, a feedback mechanism that detects and responds to changes in blood pressure.

Detection of Blood Pressure Changes: Blood pressure changes are detected by stretch-sensitive mechanoreceptors known as baroreceptors. These receptors are strategically located in the walls of the aortic arch and the carotid sinuses, which are part of the carotid bodies. Their location allows them to sense fluctuations in blood pressure, particularly drops in pressure as blood exits the heart and flows towards the brain.

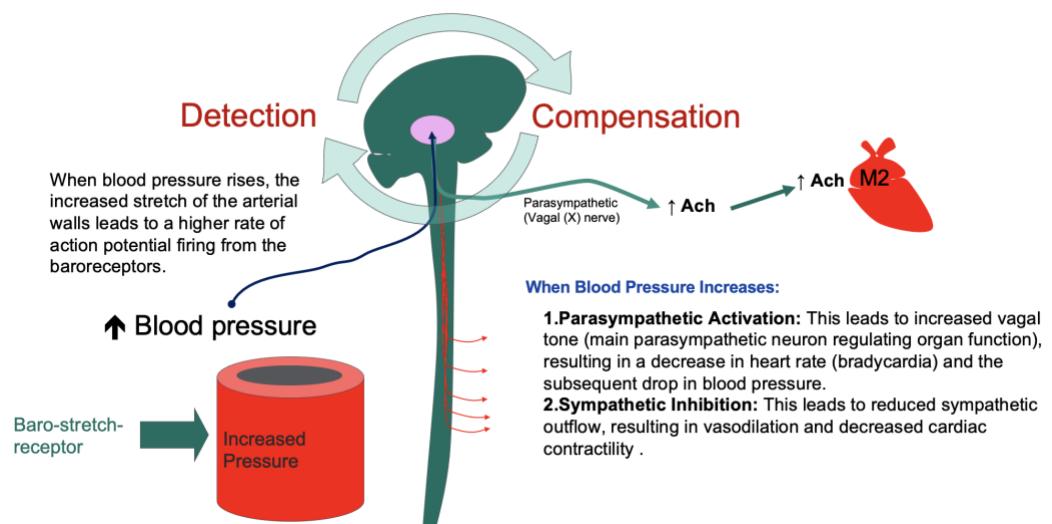
Afferent Signal Transmission: When baroreceptors detect a change in blood pressure, they generate afferent signals that are transmitted to the brain. These signals travel along cranial nerves IX (the glossopharyngeal nerve) and X (the vagus nerve) to the nucleus tractus solitarius (NTS) in the brainstem. The NTS serves as a critical integration center for cardiovascular reflexes.

From the NTS, signals are relayed to higher centers, including the hypothalamus, which plays a key role in coordinating autonomic responses. The hypothalamus processes this information and, depending on the need to either raise or lower blood pressure, modulates the output through efferent pathways.

Efferent Compensatory Responses: The hypothalamus and brainstem send efferent signals to the heart and vasculature to initiate compensatory responses. If a drop in blood pressure is detected, the hypothalamus may increase sympathetic outflow, leading to vasoconstriction and an increase in heart rate (positive chronotropy) and contractility (positive inotropy). These actions work together to elevate blood pressure back to normal levels.



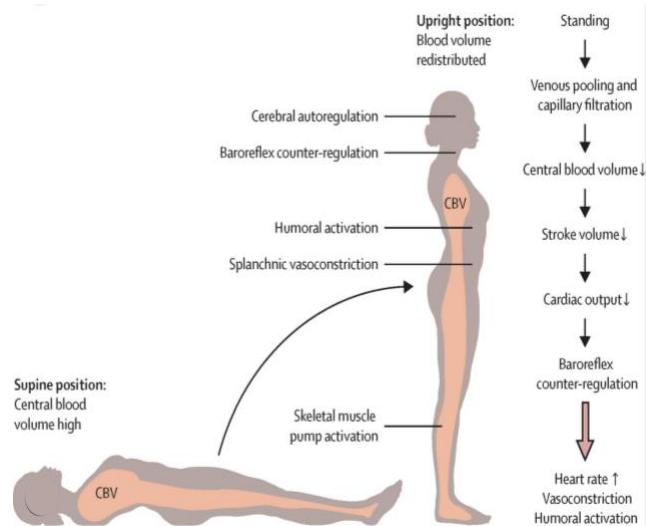
Conversely, if blood pressure is elevated, the hypothalamus may enhance parasympathetic output while reducing sympathetic tone. This leads to a decrease in heart rate, and a reduction in cardiac output, thereby lowering blood pressure.



Through these coordinated efforts, the autonomic nervous system ensures that blood pressure is constantly monitored and adjusted to meet the body's demands, maintaining homeostasis and preventing harmful fluctuations. Understanding these pathways is essential for medical students as it provides a foundation for managing cardiovascular disorders that involve dysregulation of blood pressure.

Continual adjustments in vascular tone, heart rate, and hormonal release are essential for maintaining optimal blood pressure both at rest and during activity. Additionally, local adjustments ensure adequate blood flow to vital organs like the brain.

Clinical Correlate: The use of the hypertensive medication, Prazosin, an alpha 1 receptor antagonist is associated with orthostatic hypotension. Drugs that interfere with any part of this output pathway can disrupt these regulatory mechanisms, leading to unwanted side effects including postural hypotension. Postural or orthostatic hypotension is a sudden drop in blood pressure upon standing. When you move from a lying or sitting position to standing, gravity causes blood to pool in the lower extremities, temporarily reducing venous return to the heart and thus decreasing cardiac output and blood pressure.



Baroreceptors located in the carotid sinuses and aortic arch detect this drop in blood pressure as reduced stretch in the arterial walls. The increased sympathetic tone causes vasoconstriction in the peripheral blood vessels including the large capacity leg veins, increases heart rate (tachycardia), and enhances myocardial contractility, all of which work together to restore blood pressure and maintain adequate cerebral perfusion as you stand. This rapid, autonomic adjustment prevents the symptoms of postural hypotension, such as dizziness or fainting, by ensuring a stable blood pressure during changes in posture.

Physiologic feedback peripheral function is very important in both the instantaneous as well as stable long-term control. _____ provide instantaneous control while hormones provide a slower-onset longer lasting control over peripheral tissue function.

A form of rapid neuronal control is demonstrated by the baroreceptor feedback mechanism. Changes in blood pressure are detected by _____ receptors located on the walls of some blood vessels, which when activated send a signal to the vasomotor center (VMC) in the brain. The VMC then sends a compensatory signal to the heart and vasculature.

Clinical Correlate: A drug induced drop in BP (in addition to alpha antagonist other clinically relevant drugs that reduce BP include direct acting vasodilators, calcium channel blockers, compounds that release NO).

A closer look at the events that occur when the blood pressure drops is described in this next section.

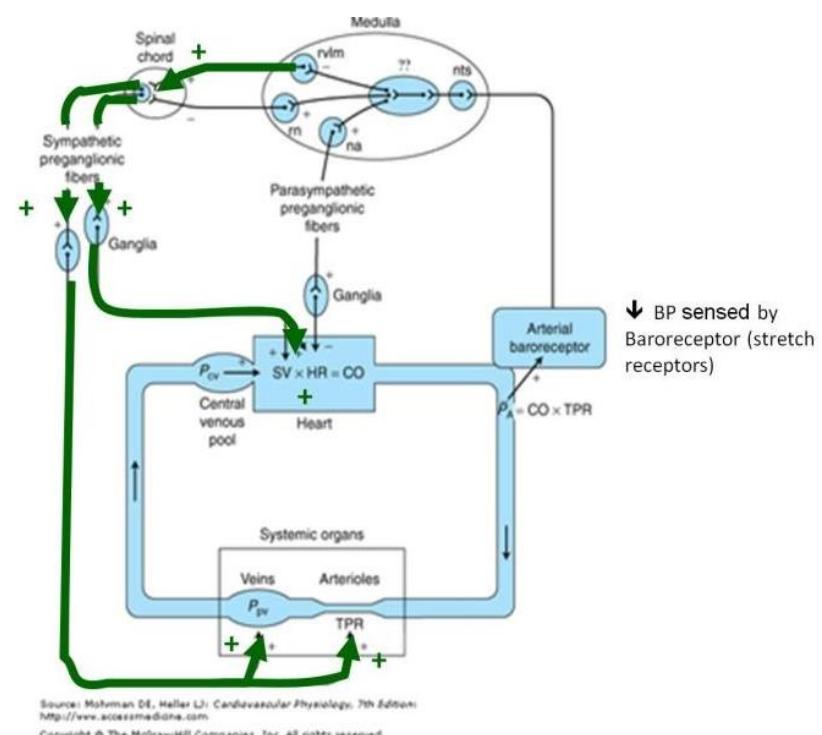
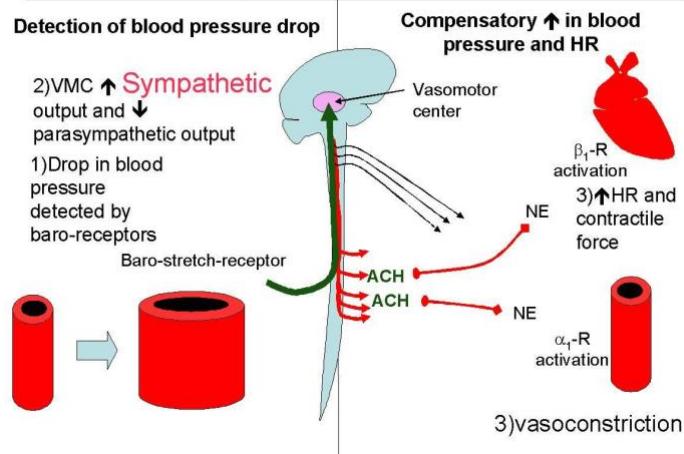
A decrease in blood pressure removes the stimulation of sensory (baroreceptor/stretch receptors) afferent inputs from the body to the vasomotor centers in the brain. Under these conditions the inhibitory influences that reduce sympathetic outflow are removed in the medullary vasomotor centers. The increased activity of sympathetic efferents produces and increases in heart rate and contractility as well as vasoconstriction (see figures). At the same time, loss of baroreceptor stimuli due to a drop of blood pressure decreases activation of medullary centers responsible for increasing parasympathetic output activity. The net result is an increase in sympathetic outflow and a decrease in parasympathetic outflow.

A drop in blood pressure is detected by _____ receptors. Afferent signals to the vasomotor center in the brain are reduced which results in an _____ in sympathetic output and a _____ in parasympathetic output.

Increased sympathetic efferent neurotransmission then results in a reflex increase in heart rate and contractile force (CO) and an increase in total vascular resistance.

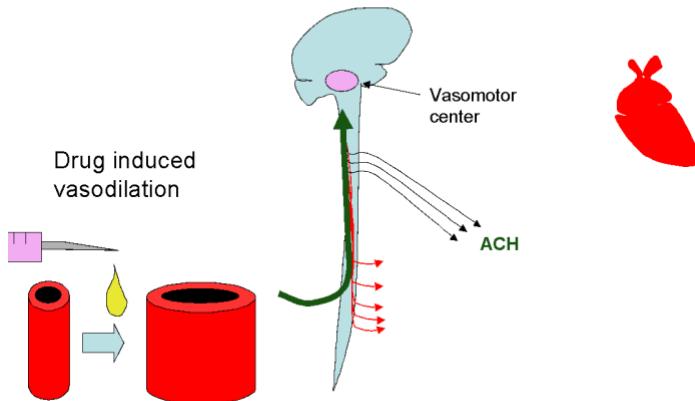
A drop in blood pressure results in a compensatory increase in _____ outflow and produces the subsequent increase in heart rate and contractile force.

ANS Baroreceptor-Mediated Feedback Control



Case Study: Angina treatment with vasodilator

Detection of blood pressure ↑



Clinical Perl (Stable Angina)

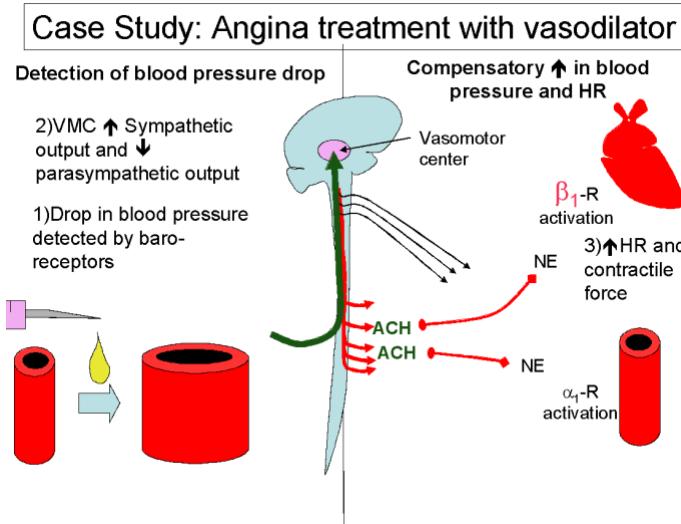
Case: A 65-year-old patient with a history of atherosclerosis complains of crushing substernal chest pain after exercise that goes away with rest. He is diagnosed with ischemic heart disease (Stable Angina)—a disease produced by constricted coronary blood vessels preventing oxygen from reaching heart tissue. Exercise increases oxygen demand past the ability of the occluded vessels to supply the tissue. Treatment of this patient involves decreasing the amount of work the heart has to do by opening up peripheral blood vessels with vasodilators. Less vascular resistance = Less work = less oxygen requirement = less anginal pain symptoms.

Angina treatment requires reducing the amount of work (heart rate or contractile strength) ↑ oxygen is required if heart rate or contractile force goes up to generate enough energy (ATP) to meet demand.

Will a direct acting vasodilator produce reflex increases in the work the heart has to do?

Is this a potential problem in the therapeutic management of anginal symptoms?

Please answer yes to the above questions.



Reflex increases in sympathetic-induced heart rate can be blocked by drugs that prevent norepinephrine from binding to _____-one adrenergic receptors on the heart. See example below.

Case: A 65-year-old patient with a history of atherosclerosis complains of crushing substernal chest pain after exercise that goes away with rest. He is diagnosed with ischemic heart disease (Stable Angina)—a disease produced by constricted coronary blood vessels preventing oxygen from reaching heart tissue. Exercise increases oxygen demand past the ability of the occluded vessels to supply the tissue. Treatment of this patient involves decreasing the amount of work the heart has to do by opening up peripheral blood vessels with vasodilators. Less vascular resistance= Less work = less oxygen requirement.

- Reflex tachycardia is a problem with this type of therapy because it can actually result in increased heart work and anginal symptoms.
- In practice this type of reflex tachycardia is avoided by using a combination of a vasodilator and a beta-receptor blocker

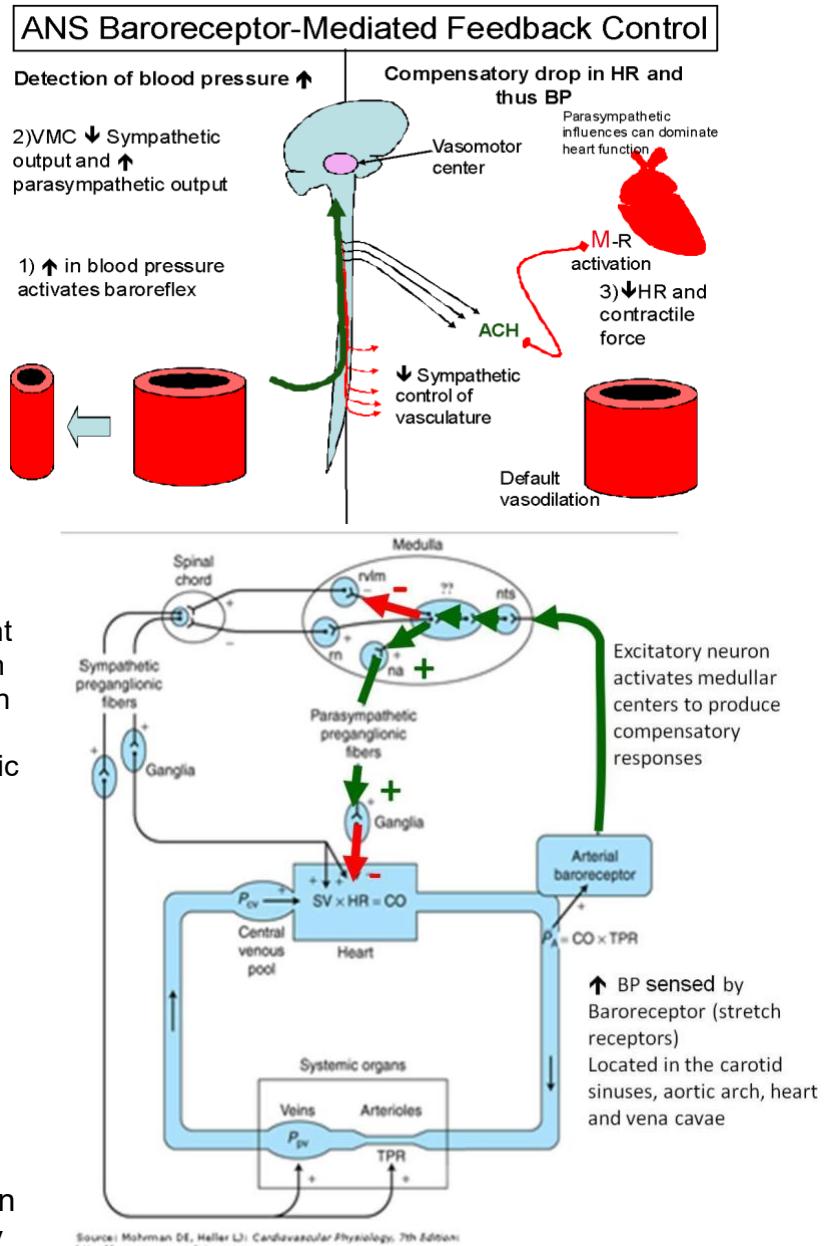
Increases in BP influences on Heart and Vascular tone

Look at the diagrams and review the effects on increased blood pressure on the compensatory increase in parasympathetic output to the heart. In a normal individual this type of regulation helps slow heart when energy expenditure is not needed. The net result when sensory baroreceptors are stretched is a signal to the CNS-medullary-vasomotor-centers is to shut down sympathetic and increase parasympathetic outflow to the body.

An increase in blood pressure is detected by _____ receptors. An afferent signal is sent to the vasomotor center in the brain that results in a _____ in sympathetic output and an _____ in parasympathetic output.

Drugs can slow down heart rate and contractile force without binding to heart receptors. For example, drugs that increase vascular resistance (alpha-1 agonist) have no direct effect on the heart but produce a marked slowing of the heart rate and contractile force because the baro-reflex causes an increase in parasympathetic efferent activity that results in acetylcholine release from post-ganglionic parasympathetic neurons and the activation of cardiac _____ receptors.

Remember the parasympathetic effects on the heart can dominate heart response.

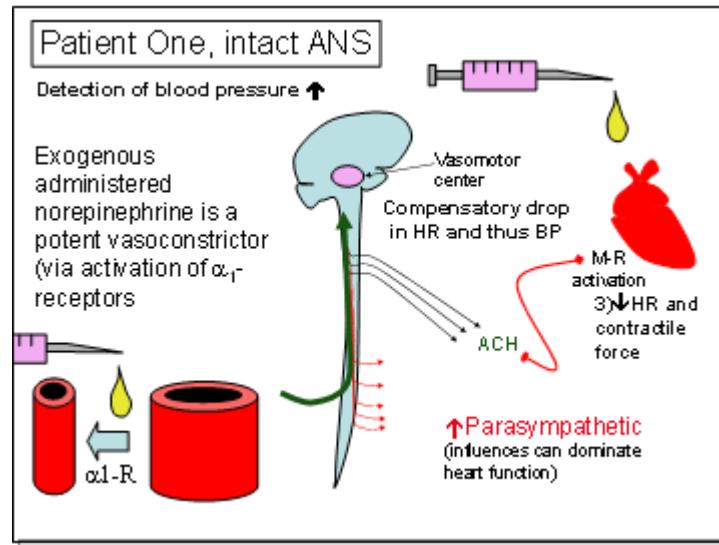


Clinical Pearl (CV Shock—huge drop in blood pressure)

Patient 1: A 54-year-old patient has an MI and goes into heart failure. Norepinephrine is administered to stimulate beta-1 receptors on the heart with the hopes of increasing contractile force and rate. This should cause the blood pressure to go up. In addition, norepinephrine activation of vasculature alpha-1 receptors should also result in an increase in blood pressure. Unfortunately, his heart or contractile force does not increase in this patient.

Unfortunately, this norepinephrine effect is common and is probably why its trade name of Levophed is transformed into the nickname leave-em-dead. Even though norepinephrine should constrict the vasculature by direct activation of alpha-one-receptors and increase cardiac output by directly stimulating cardiac beta-1 receptors, the heart rate can decrease via compensatory increases in

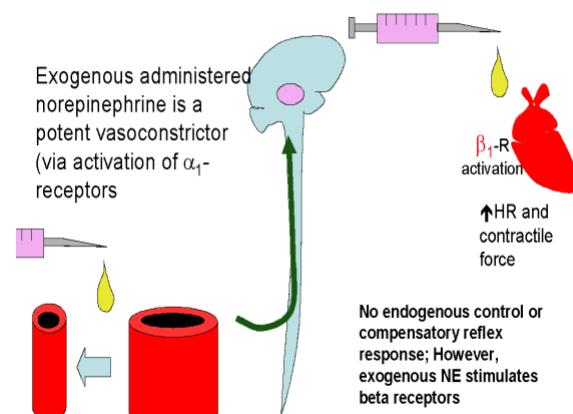
_____ efferent activity that will decrease heart rate.



In an actual ACLS situation epinephrine would be given in alternate combination with a muscarinic antagonist (atropine) to avoid this type of compensatory reflex.

Patient 2: A 54-year-old heart transplant recipient has heart failure. Norepinephrine is administered and his blood pressure and heart rate go up. Would compensatory reflexes occur without neuronal innervation? In patient two, all nerves leading to the heart are cut, and therefore there are no parasympathetic or sympathetic influences on the heart. When norepinephrine causes vasoconstriction there are no compensatory neural inputs to the heart to compete for the direct effect of exogenous norepinephrine. Therefore, in patient two, administered norepinephrine increases heart rate.

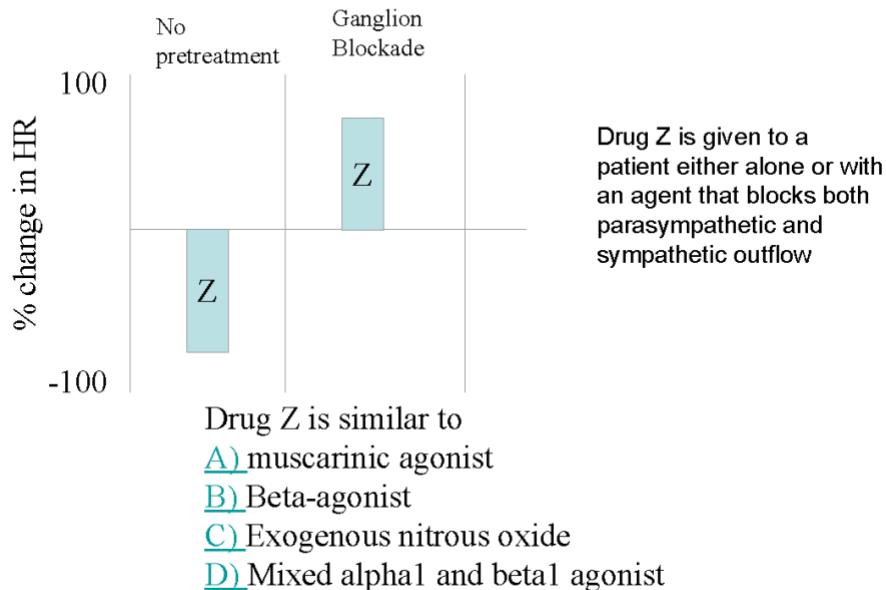
Patient Two, ANS nerves cut during transplantation



Direct (unopposed) effect of norepinephrine on the heart is to activate beta-one adrenergic receptors resulting in _____ in HR and contractile force.

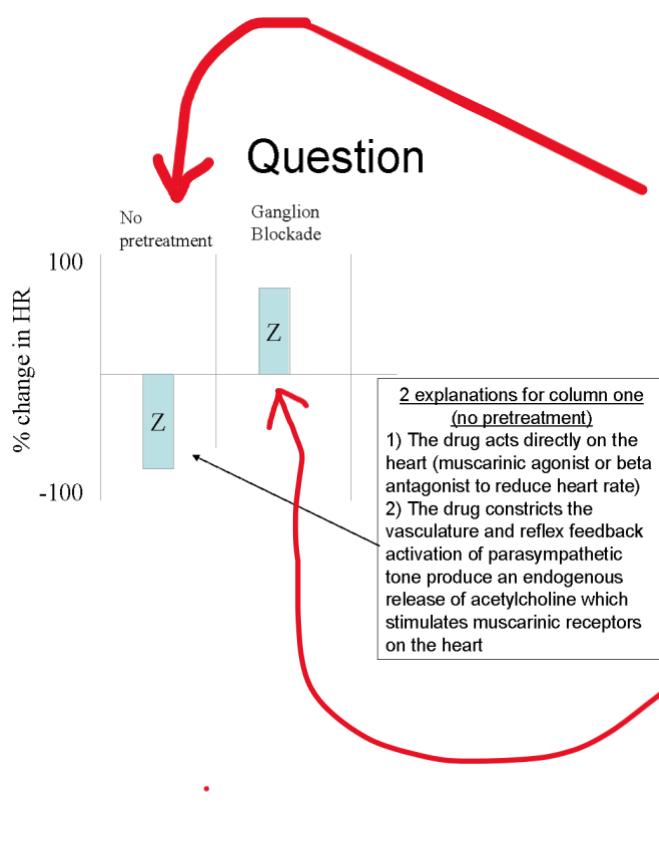
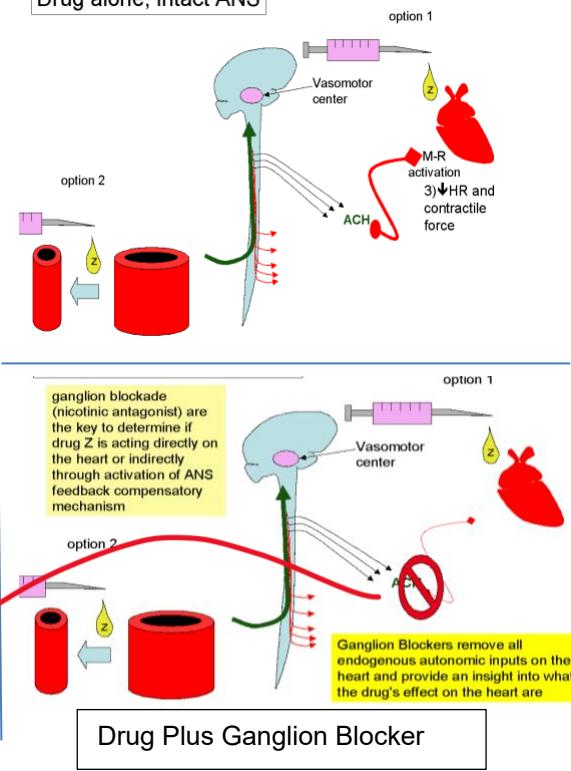
Note: A similar response to drugs would be achieved if a ganglionic blocker (nicotinic-receptor-antagonist) were used in combination with norepinephrine.

Question

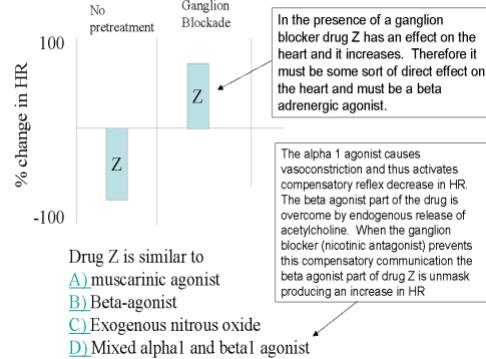


Note that when drug z is given alone it has the opposite effect when a nicotinic antagonist (ganglionic blocker is used)

Can you answer this question? Try to answer before you move on.

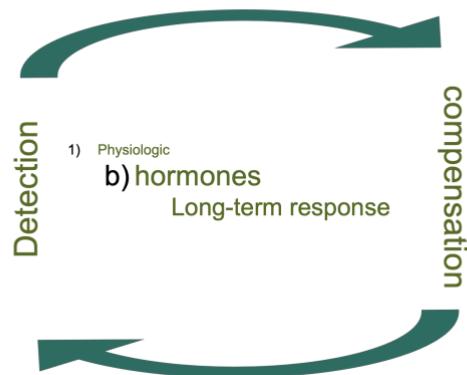
**Drug alone, intact ANS**

In the presence of a ganglion blocker the heart is chemically isolated from parasympathetic and sympathetic efferent communication. Therefore, any changes in the vasculature will not reflect on changes to the heart. If a drug increases heart rate in the presence of a ganglion blocker it must have direct effects on the heart. If the HR goes up when reflexes responses are blocked the drug must be able to bind directly to heart beta-1 receptors. If the HR goes down under these conditions, then the drug must be able to bind to and directly activate M2 receptors on the heart. If the HR doesn't go up or down in the presence of ganglion blocker, then the drug has no direct binding ability on heart receptors. When the drug is given alone and there is a decrease in heart rate it strongly suggests that either the blood pressure is decreased thus producing reflex parasympathetic efferent activity which in turn releases Ach unto the M2 receptor on heart pacemaker cells or the drug can activate M2 receptors directly. This latter effect can be ruled out as when the drug is used with ganglion blocker it increases heart rate (M2 activation would decrease). It is entirely possible that drug induced vasoconstriction via activation of alpha -1 receptors and the compensatory response can overcome the direct effect of the drug on the heart producing the opposite result shown.

Question

B. ANS Hormonal Response

Feedback Regulation Influences ANS Function



The autonomic nervous system (ANS) orchestrates rapid and coordinated hormonal responses essential for maintaining homeostasis, particularly during stress, fluid imbalance, and cardiovascular challenges. Through sympathetic activation, the ANS directly stimulates the adrenal medulla to secrete catecholamines (epinephrine and norepinephrine), which enhance cardiac output, mobilize energy stores, and initiate vasoconstriction.

Simultaneously, sympathetic input to the kidney promotes renin release, activating the **renin-angiotensin-aldosterone system (RAAS)**. This cascade increases angiotensin II levels, leading to potent vasoconstriction and aldosterone-mediated sodium and water retention—critical for blood pressure and volume regulation.

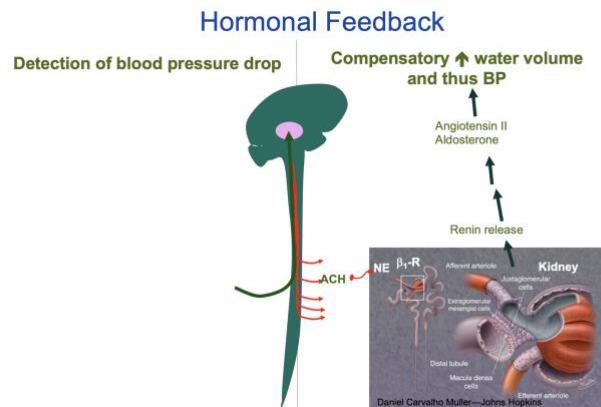
The ANS also modulates the hypothalamic-pituitary-adrenal (HPA) axis by promoting corticotropin-releasing hormone (CRH) secretion, which triggers downstream ACTH and cortisol release. Cortisol supports glucose metabolism, immune modulation, and vascular responsiveness to catecholamines.

Parasympathetic pathways influence hormonal regulation as well, particularly through vagal modulation of pancreatic insulin secretion and gastrointestinal hormone release during rest-and-digest states.

Together, ANS-evoked hormonal responses ensure a tightly integrated neuroendocrine network that supports cardiovascular stability, metabolic flexibility, and fluid-electrolyte balance during both acute and chronic physiologic demands.

ANS Regulation of the RAAS System: The RAAS is a critical hormonal cascade that regulates blood pressure, electrolyte balance, and fluid homeostasis. This system is closely integrated with autonomic nervous system control, particularly through beta-1 adrenergic receptors. It optimizes survival during times of volume contraction (dehydration or excessive bleeding) by maintaining blood flow to vital organs.

Renin, an enzyme produced and stored in the juxtaglomerular (JG) cells of the kidney, is central to the RAAS. These specialized smooth muscle cells are located in the walls of the afferent arterioles near the glomerulus. The release of renin is triggered by several factors, including decreased renal perfusion pressure, reduced sodium chloride delivery to the distal tubules, and direct stimulation by sympathetic neurons via beta-1 adrenergic receptors. When beta-1 receptors are activated, they stimulate renin release, setting the RAAS into motion.



Once released, renin catalyzes the conversion of angiotensinogen, a liver-produced protein, into angiotensin I. Angiotensin I is then converted into the more active angiotensin II by the angiotensin-converting enzyme (ACE), primarily in the lungs.

Actions of Angiotensin II: Angiotensin II is a potent vasoconstrictor, significantly increasing blood pressure by narrowing blood vessels. Additionally, it stimulates the adrenal cortex to release aldosterone, which promotes sodium and water retention by the kidneys, further increasing blood volume and pressure. Angiotensin II also stimulates the release of antidiuretic hormone (ADH), enhancing water reabsorption in the kidneys and contributing to overall fluid retention.

Integration with Autonomic Control: Through this mechanism, the autonomic nervous system, particularly the sympathetic branch via beta-1 receptor activation, plays a crucial role in the hormonal regulation of cardiovascular function. This integration ensures that the body can respond to changes in blood pressure and volume through both immediate neuronal adjustments and longer-term hormonal effects, maintaining overall cardiovascular homeostasis.

The renin-angiotensin cascade has a strong influence on blood pressure. The sympathetic ANS can activate renin release in the kidneys via _____-receptor activation. Renin is an important enzyme that produces angiotensin II. Angiotensin II causes aldosterone release and direct vasoconstriction.

Juxtaglomerular cells also have stretch receptors and can detect a decrease in vascular tone. When the blood pressure drops cells in the juxtaglomerular apparatus can also release renin.

Direct acting vasodilators can produce compensatory increases in _____ release from the kidneys which can lead to an increase in water volume.

Clinical Correlate: Early-Stage Heart Failure

Patient Background: A 62-year-old male with a history of hypertension and type 2 diabetes, presents to his primary care physician with complaints of increasing fatigue, shortness of breath on exertion, and mild swelling in his ankles over the past few months. He has also noticed that he needs to use two pillows to sleep comfortably at night, as lying flat makes him feel short of breath. On examination, his blood pressure is 150/90 mmHg, and there is evidence of mild bilateral ankle edema. His heart rate is 88 beats per minute, and auscultation reveals an S3 gallop. An echocardiogram shows a mildly reduced left ventricular ejection fraction (LVEF) of 40%.

Pathophysiology: This patient is experiencing the sequelae of heart failure, reduced pumping action so volume can't be ejected, the subsequent back up of fluid into lungs, preventing him from breathing especially when he lies down, and then fluid back up into the body (ankle edema). The result of this poor pumping action is to evoke all the compensatory sympathetic activity discussed in this packet in an attempt to increase cardiac output in a failing nonfunctional heart. However, these compensatory mechanisms can be detrimental over time, leading to worsening heart failure.

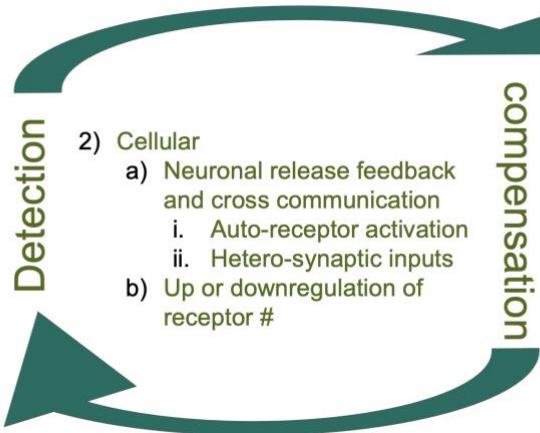
Guideline Treatments Targeting Reflex Compensatory Mechanisms In heart failure, the body activates compensatory mechanisms, such as increased sympathetic nervous system activity and the renin-angiotensin-aldosterone system (RAAS), to maintain cardiac output. Guideline-directed medical therapy (GDMT) aims to counteract these effects.

1. Beta-Blockers: Beta-blockers, are fundamental in treating heart failure with reduced ejection fraction (HFrEF). They work by inhibiting the effects of the sympathetic nervous system, which is often overactivated in heart failure. By blocking beta-adrenergic receptors, beta-blockers decrease heart rate and contractility, reduce myocardial oxygen demand, and protect the heart from harmful effects of chronic sympathetic stimulation. This helps to improve symptoms, reduce hospitalizations, and increase survival in heart failure patients.

2. RAAS Inhibitors (ACE Inhibitors, ARBs, and ARNI): These drugs inhibit the angiotensin-converting enzyme (ACE), which is a key component of the RAAS. By reducing the production of angiotensin II, ACE inhibitors decrease vasoconstriction and sodium retention, lower blood pressure, and reduce the workload on the heart. They also decrease aldosterone secretion, leading to less sodium and water retention, which helps reduce preload and cardiac remodeling.

C. Neuronal autoregulation

Feedback Regulation Influences ANS Function

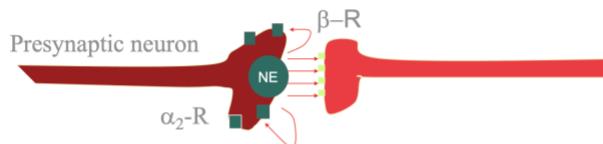


Feedback autoreceptors are specialized receptors located on the presynaptic terminals of autonomic neurons, both sympathetic and parasympathetic. These receptors play a critical role in regulating neurotransmitter release through a negative feedback mechanism.

How They Act: When an autonomic neuron releases its neurotransmitter—such as norepinephrine from a sympathetic neuron or acetylcholine from a parasympathetic neuron—some of the released neurotransmitter can bind to autoreceptors on the same presynaptic neuron. This binding typically inhibits further release of the neurotransmitter by reducing the influx of calcium ions into the presynaptic terminal, which is necessary for vesicle fusion and neurotransmitter exocytosis.

Physiologic Feedback Regulation Influences ANS Function

- **Autoreceptors:** receptors located on pre-synaptic neuron and activated by the same transmitter released by itself.



- **Examples**

NT Release Inhibitors (“Self-regulating break”):

- Activation of presynaptic α_2 adrenergic receptors (\downarrow cAMP) by released norepinephrine inhibits further release of norepinephrine
- Activation of M2 receptors (\downarrow cAMP), by acetylcholine on vagal presynaptic neuron inhibit release of acetylcholine

Increase in NT Release

- presynaptic β receptors activation (\uparrow cAMP) enhance norepinephrine release

Functional Consequences: The presence of autoreceptors allows the neuron to self-regulate its activity, preventing excessive neurotransmitter release. This regulation is crucial for maintaining balance within the autonomic nervous system. For example, if too much norepinephrine is released during a sympathetic response, it could lead to excessive vasoconstriction and hypertension. Autoreceptors help to prevent such

outcomes by dampening further norepinephrine release once a certain level has been reached.

This feedback mechanism ensures that neurotransmitter levels are kept within a range that is effective for physiological function but not so high as to cause overstimulation or damage to tissues. It is a key component in the fine-tuning of autonomic responses, ensuring that the nervous system can adapt to changing conditions while maintaining homeostasis.

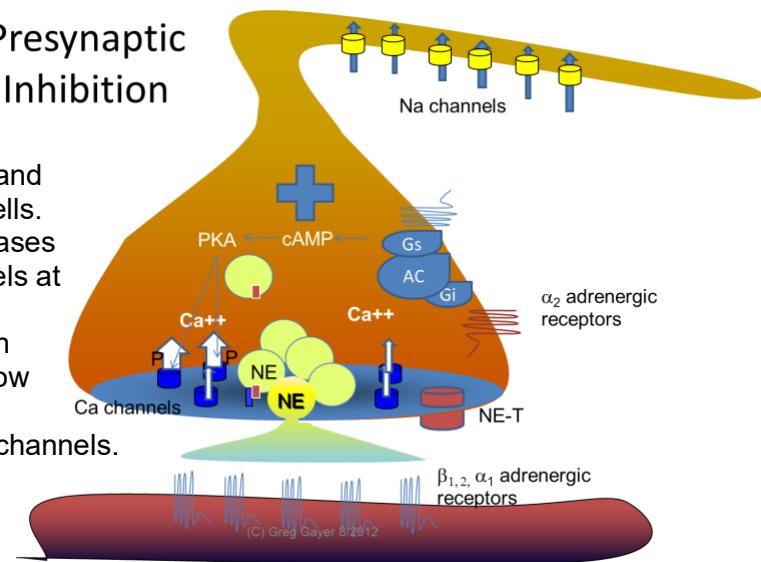
The mechanism involves neurotransmission, where neurotransmitter release depends on increased intracellular calcium via voltage-gated calcium channels in neurons. These channels are phosphorylated and activated by PKA, similar to those in cardiac cells. Therefore, preventing intracellular cAMP increases reduces the activation of these calcium channels at the synaptic endplate. Additionally, the beta-gamma subunits of the activated Gi protein can open potassium channels, increasing the outflow of positive charge, which further raises the activation threshold for voltage-gated calcium channels.

Receptors located on pre-synaptic neurons that are activated by the same neurotransmitter released by the pre-synaptic neuron are called _____, whose function is to provide a self-regulating feedback loop to reduce the volume of continual neurotransmitter release.

These auto-receptors can act as a break or provide a self-checking mechanism preventing excessive release of neurotransmitter. Auto-receptors that inhibit neurotransmitter release are associated with a decrease in the intracellular concentration of the second messenger _____ which is required for activation of PKA -- the kinase that phosphorylates and helps open voltage gated calcium channels. The docking and fusion of intracellular synaptic vesicles with the plasma membrane and neurotransmitter release requires this rise in intracellular calcium.

Norepinephrine released from sympathetic neurons can diffuse back on itself and activate alpha-2 adrenergic receptors. When alpha-2-receptors are activated _____ norepinephrine is released.

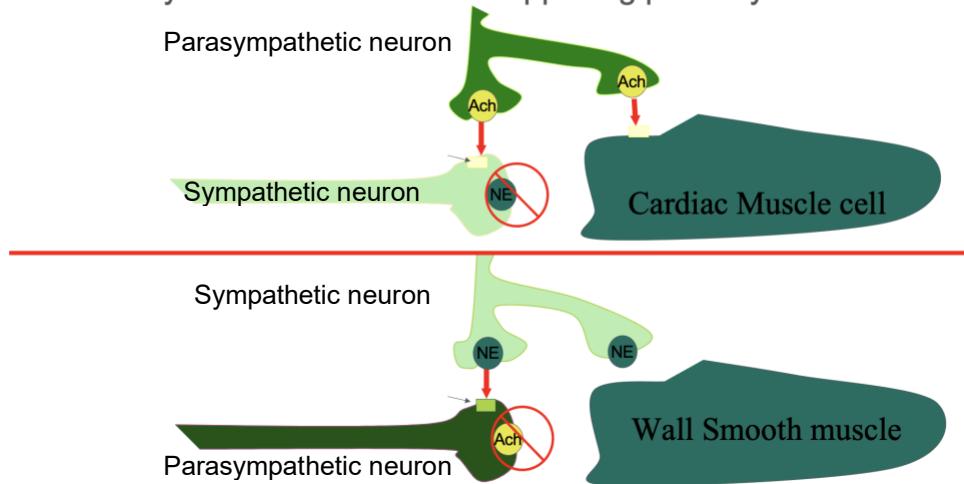
Clinical Correlate: Alpha-2 agonists are used to inhibit norepinephrine release and are used to treat hypertension or neuronal states such as opioid withdrawal that is associated with excess noradrenergic activity.



D. Neuronal heterosynaptic regulation

Physiologic Feedback Regulation Influences ANS Function

- Heteroreceptor presynaptic regulation
 - Usually allows for inhibition of opposing pathway



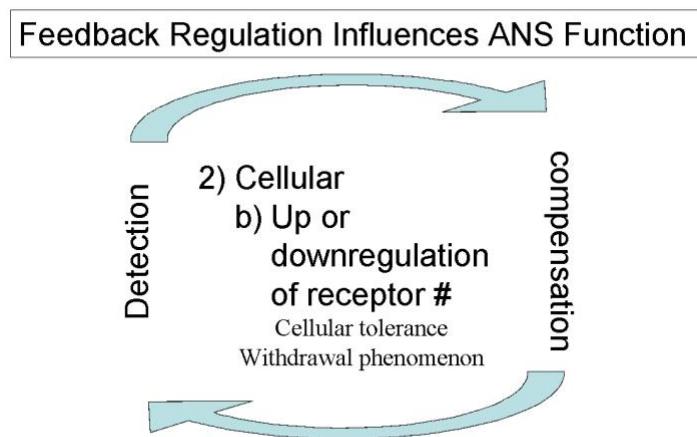
Heterologous neuronal connections between parasympathetic and sympathetic neurons refer to the synaptic interactions where parasympathetic neurons can influence sympathetic neurons and vice versa. These connections allow one branch of the autonomic nervous system to modulate the activity of the other, providing a mechanism for cross-talk and coordination between the parasympathetic and sympathetic divisions.

Functional Consequences: Such connections can lead to more nuanced regulation of physiological functions, ensuring that the actions of the sympathetic and parasympathetic systems are not completely independent but instead can be coordinated. For example, after the stress response, sympathetic activation might be modulated by parasympathetic input to prevent excessive sympathetic output, thereby protecting against conditions like hypertension. Conversely, parasympathetic activity can be dampened by sympathetic input during situations requiring increased alertness or physical exertion, ensuring that energy is not diverted to non-essential processes.

These heterologous connections enable a more integrated and balanced autonomic response, helping the body to maintain homeostasis by appropriately adjusting the balance between "fight-or-flight" and "rest-and-digest" activities based on the physiological needs of the moment.

Acetylcholine released by parasympathetic neurons can directly reduce the release of _____ from sympathetic nerve fibers.

E. Receptor up and downregulation



G protein-coupled receptors (GPCRs) are essential for transmitting signals from the outside of a cell to the inside, influencing various physiological responses. The regulation of GPCRs is crucial for maintaining the balance of these signaling pathways. Two key regulatory mechanisms are upregulation and downregulation, which refer to the increase or decrease in receptor number and activity, respectively.

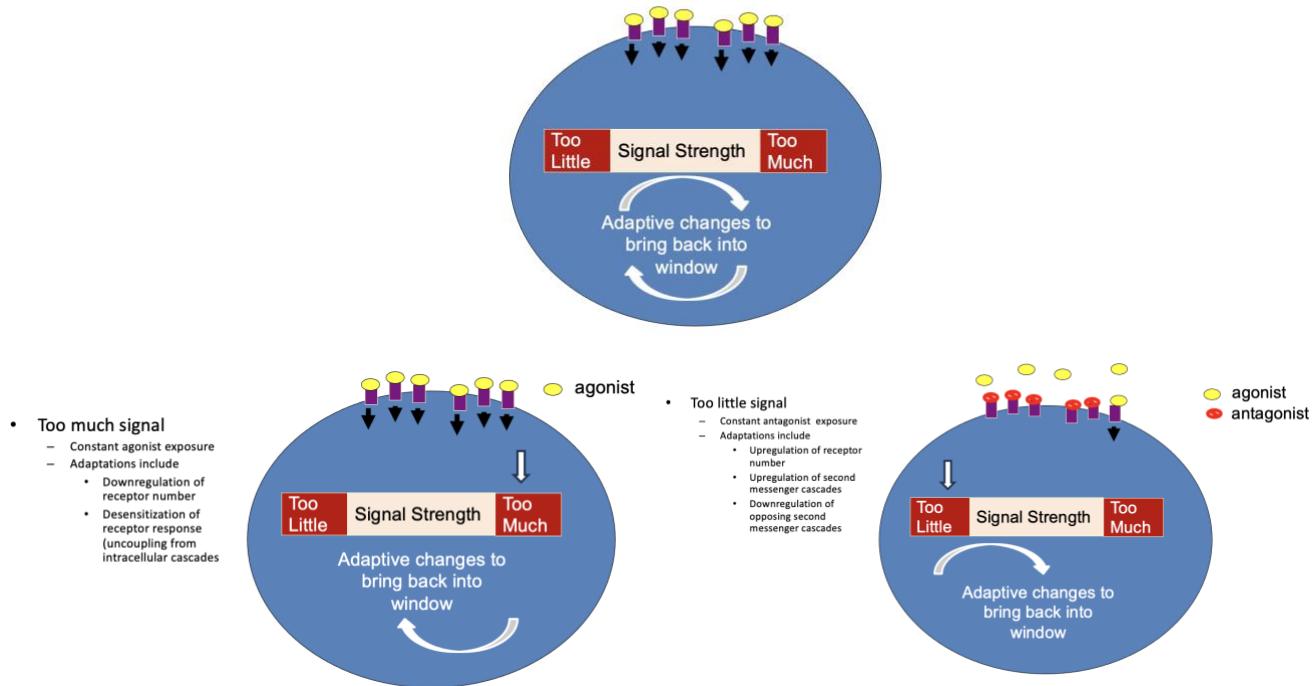
1. Upregulation: This occurs when there is a decrease in the availability of the ligand, neurotransmitter or hormone (the molecule that binds to the receptor), or when there is a chronic blockade of the receptor with drugs. The cell compensates by increasing the number of receptors on its surface or by making the existing receptors more sensitive. This process can extend to upregulation of intracellular cascades. This mechanism can make cells more responsive to low levels of the ligand.

2. Downregulation: In contrast, downregulation happens when there is chronic stimulation of the GPCR by its ligand. This can lead to a decrease in receptor number (by internalization and degradation) or a decrease in receptor sensitivity (desensitization). Desensitization involves phosphorylation of the receptor, which prevents it from coupling effectively with its G-protein, leading to reduced signaling despite the continued presence of the ligand.

3. Desensitization and Downregulation: These are part of the body's feedback mechanisms to prevent overstimulation and maintain homeostasis. Desensitization happens rapidly (within minutes to hours) and involves the temporary inactivation of receptors, while downregulation is a longer-term response (hours to days) involving a reduction in receptor numbers on the cell surface.

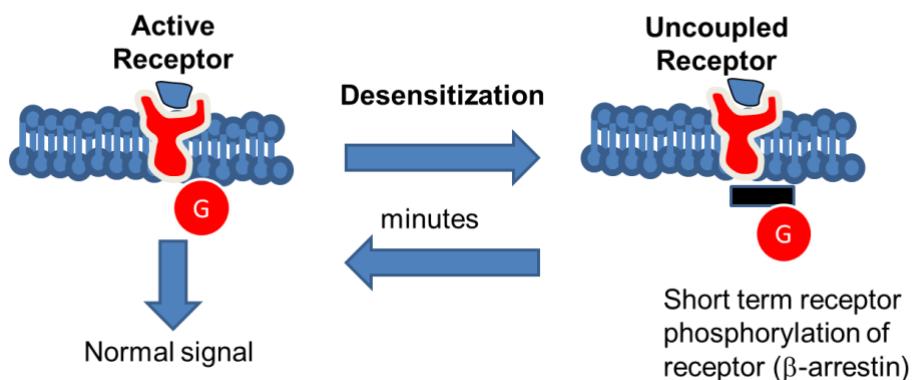
This process occurs through intracellular feedback mechanisms. Cells have an innate sense as to how much intracellular signal they should produce. Upon over or under activation of transmembrane receptors the cellular response is to adapt in a fashion to move back into the desired response range. For example, over activation will lead to a

decrease in receptor response and under activation will produce the opposite effect.



Examples of receptor processing are shown below. Step one receptor is activated. Within minutes of activation intracellular cascades are initiated that feedback and uncouple the activated receptors from its intracellular partners.

Receptor Regulation (step one)

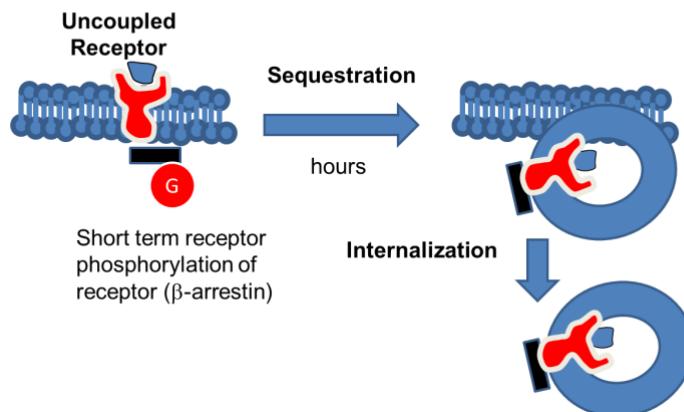


This “uncoupling” of the receptors from the intracellular component is called desensitization. It occurs within minutes and can be reversed in minute. In the case of g-proteins it involves phosphorylation of the receptor at the g-protein binding site and attachment of the blocking protein **beta-arrestin**.

[Chapter Review 14](#)

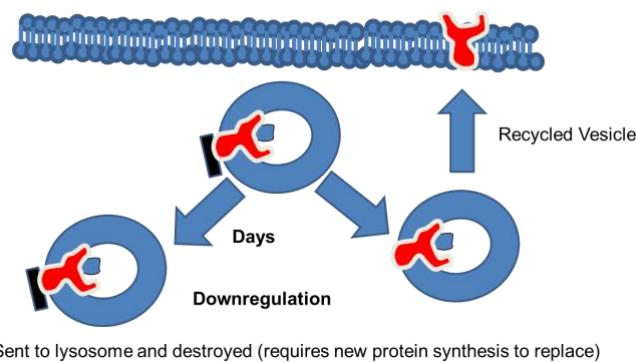
The next phase involves moving the receptors from the cell surface via clathrin coated vesicles. This can last for hours and is reversible. The intracellular vacuoles can move in and then re-insert into the plasma membrane.

Receptor Regulation (step two)



The third phase is influenced by the type of drug binding to the receptor, the concentration of the drug, and the time of exposure. With long term use of the drug the sequestered receptor vacuoles can either return to the cell surface or be moved into the lysosomal compartment where the receptors are destroyed. This process is called receptor downregulation and can last for days. New receptors must be transcribed and translated into protein before initial levels returned to baseline.

Receptor Regulation (step 3)



[Chapter Review 14](#)

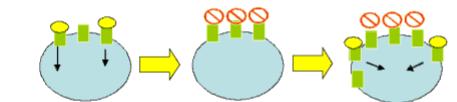
Drug induced compensatory changes at the cellular level mediate pharmacodynamics tolerance (loss of effect) and drug dependence (withdrawal features).

Cellular Regulatory Controls

- Postsynaptic Receptor Regulation

– Up-regulation leads to super-sensitivity

- Produced via absence of NT signal



– Downregulation leads to tolerance

(Loss of response over time)

- chronic agonist pressure on receptors



Connection to Tolerance, Dependence, and Withdrawal:

- **Tolerance:** With chronic exposure to a drug that activates GPCRs, downregulation and desensitization lead to reduced receptor activity. As a result, the same dose of the drug becomes less effective over time, a phenomenon known as tolerance. This means higher doses are required to achieve the same effect.
- **Dependence:** Dependence develops when the body adapts to the presence of the drug, making its absence noticeable. The changes in receptor regulation, such as downregulation, mean that normal physiological processes now rely on the drug's presence to maintain homeostasis.
- **Withdrawal:** When a drug that activates GPCRs is suddenly removed, the downregulated receptors and desensitized pathways lead to a lack of normal signaling activity. This causes withdrawal symptoms, as the body struggles to function without the overstimulation it has adapted to.

Understanding these mechanisms is crucial in the context of pharmacology and drug therapy, as they influence the effectiveness of drugs and the management of conditions such as heart failure, pain, anxiety, and addiction.

Clinical Correlate: Propranolol (antagonist that blocks beta 1 and 2 receptors) used to treat hypertension, ischemic heart disease, essential tremor and other diseases. Chronic use produces beta-receptor upregulation.

From UpToDate--*Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia in patients with*

underlying cardiovascular disease. Mechanism: Dose-dependent; related to the pharmacologic action. Beta blockade causes upregulation of beta-receptors, enhanced receptor sensitivity, and decreased sympathetic nervous system response. Abrupt withdrawal leads to a transient sympathetic hyper-response.

Clinical Correlate: Clonidine (agonist that activates alpha 2 adrenergic receptors) used to treat hypertension of states of excess noradrenergic activity. Chronic use produces alpha-2 receptor downregulation and because its mechanism is to inhibit norepinephrine release upregulation of post synaptic alpha and beta receptors can occur.

From UpToDate--Warning/Precaution with use: • *Discontinuation of therapy: Gradual withdrawal is needed (discontinue oral immediate release or epidural dose gradually over 6 to 10 days to avoid rebound hypertension) if drug needs to be stopped. Patients should be instructed about abrupt discontinuation (causes rapid increase in BP and symptoms of sympathetic overactivity). In patients on both a beta-blocker and clonidine where withdrawal of clonidine is necessary, withdraw the beta-blocker first and several days before clonidine withdrawal, then slowly decrease clonidine.*

If a drug over-stimulates a cell, i.e. receptor agonist, receptors are removed from the cell surface or inactivated. This receptor downregulation and desensitization produces drug _____ or the loss of drug response over time.

The opposite is true for drugs that are receptor antagonist. Receptor antagonist can lead to the compensatory upregulation of receptors. Antagonist-induced receptor _____ is responsible for drug tolerance as well.

Note: if you remove a drug rapidly in cells that have changed their receptor number you may observe a rebound effect until the receptors re-equilibrate. This is why some drug when administered for long-periods have their drug dose tapered gradually and is the cellular basis for the withdrawal phenomenon.

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