

## ABC's Of Autonomics



Gregory Gayer, PhD

Hello everyone. I want to thank you for attending today's discussion on the Autonomic nervous system. My name is Greg Gayer, and I am an associate professor and chair of the basic science department at Touro U, Ca, College of Osteopathic medicine. I have been teaching pharmacology including autonomic function and its role in disease states for over 20 years now. Although I am just a PhD have been working very closely with my colleagues over the past 2 decades to create a more unified approach to medical education that combines core concepts; (spelled CORE) not COAR (al la the great Stacy Pearce Talsma) ---even though Dr. Pearce-Talsma and I did work together to establish several COAR exercises in the first two years that helped solidify both basic and OPP concepts--- of OPP and the foundational sciences.

One example of this that I am most proud of is my work with Dr. Victor Nuno on developing an integrated approach to understanding the role of the autonomic nervous system in normal and abnormal function of the body with a combined view of an osteopath and a pharmacologist. The understanding of the interplay between the autonomic nervous system-- the anatomical, neuronal innervation, and control of organ function and how this relates to OPP principles of biomechanics, circulation and screenings central to many concepts in osteopathic medicine.

I think it is for these reasons that former OPP chairs like John Glover and Mitch Hiserote have adopted me into the profession.

The title combines both what the basics to understanding the role of the ANS in control of body function and is also part of the ABC's of osteopathy (Autonomics, Biomechanics, circulation, and screening) and the picture represents the connection between the concept of mind, body, spirit which is in part resides in the ANS.

# Autonomic Nervous System



The body is a unit; the person is a unit of body, mind, and spirit.



The body is capable of self-regulation, self-healing, and health maintenance.



Structure and function are reciprocally interrelated.



Rational treatment is based upon an understanding of the basic principles of body unity, self-regulation, and the interrelationship of structure and function.

What better exemplifies the concept of the body as a unit than a system that receives input from the environment and the body that prepares the body for survival and helps provide the balance necessary for optimizing survival. In today's lecture I will briefly focus on how the input to the brain from the environment sets the stress/well-being levels and that the adapted output from the "mind" including emotional cues from limbic structures in the "spirit?", are translated to body responses and how sensory input from the body provides feedback to the brain to either increase or decrease a patient's perspective on how they feel.

The role of the ANS is to provide homeostatic regulatory control to optimize health.

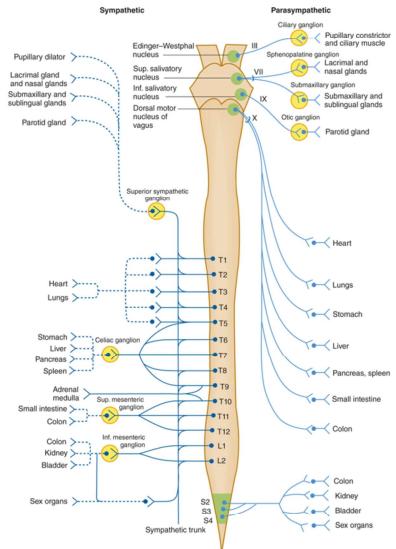
When the discussion of visceral-somatic and somatic-visceral responses are in play they are in part mediated by communication, neuronal and hormonal, from the brain through the body and back. It is these communication pathways that can be affected by the patient's condition and alterations in the communication are the center of many structure function relationships. For example, TART changes in areas that contain neurons that regulate the heart and lungs (T1-T5) may influence activity of these organs.

The focus of this lecture will be to understand the rational treatment, with a focus on

pharmacology, based on understanding the basic principles of the body unity, self-regulation and the interrelationship of structure and function.

Because I am a pharmacologist--I will focus more on the destination treatments that involve control of organ function through receptor-cell- signaling cascades as this is my background (pharmacology perspective) and provides the framework for part of the treatment for many common disease states, including, cardiac related issues (ischemic heart disease, heart failure, hypertension, arrhythmias), respiratory issues (COPD, asthma), GI and GU issues, and eye related (glaucoma, fundus examinations). In addition, the consequences of altering regulatory cascades that are already tightly controlled by many feedback regulatory mechanism at all levels, neuronal, hormonal, and cellular. This will be the main focus of the lecture. I will leave the discussion of using OMT to optimize and balance the autonomics to you as the experts.

# Lecture Outline



Source: Stephen G. Warren: Clinical Neuroanatomy, 2/e  
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Nervous System



Central Regulation of ANS, homeostatic regulation



Functional Role of the ANS



Neurotransmitters involved



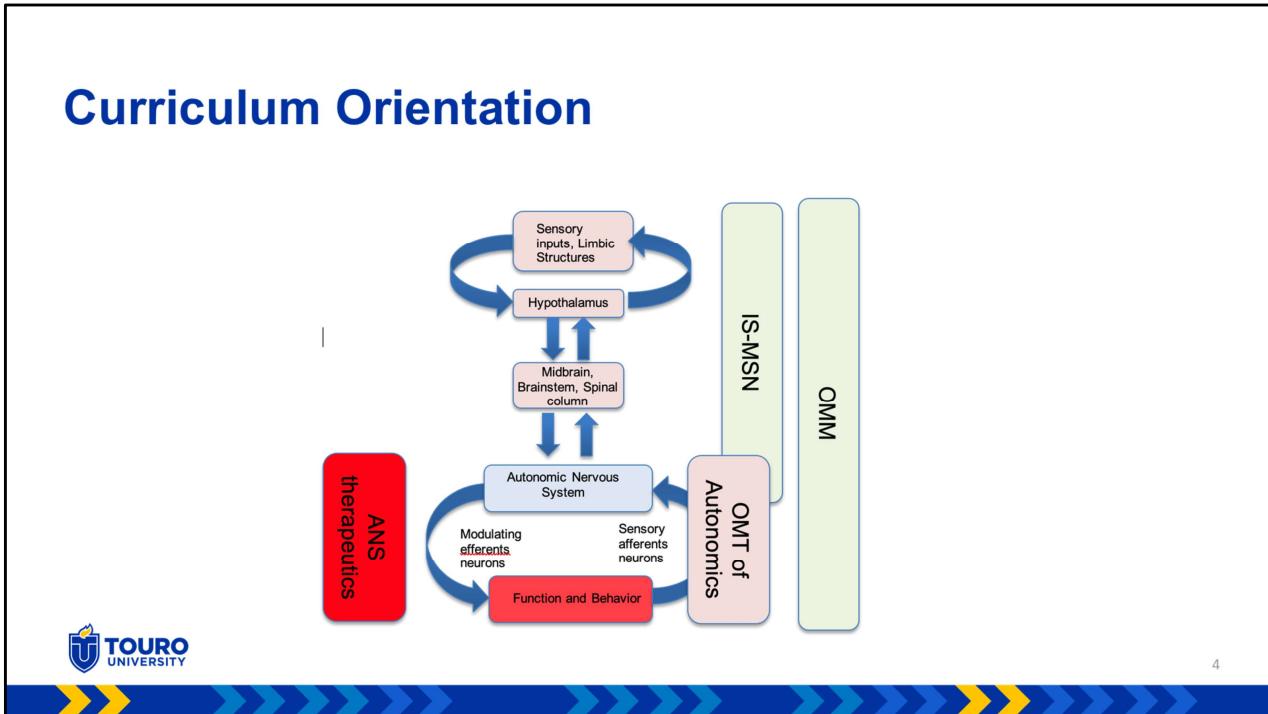
Receptors Utilized (location and signal transduction)

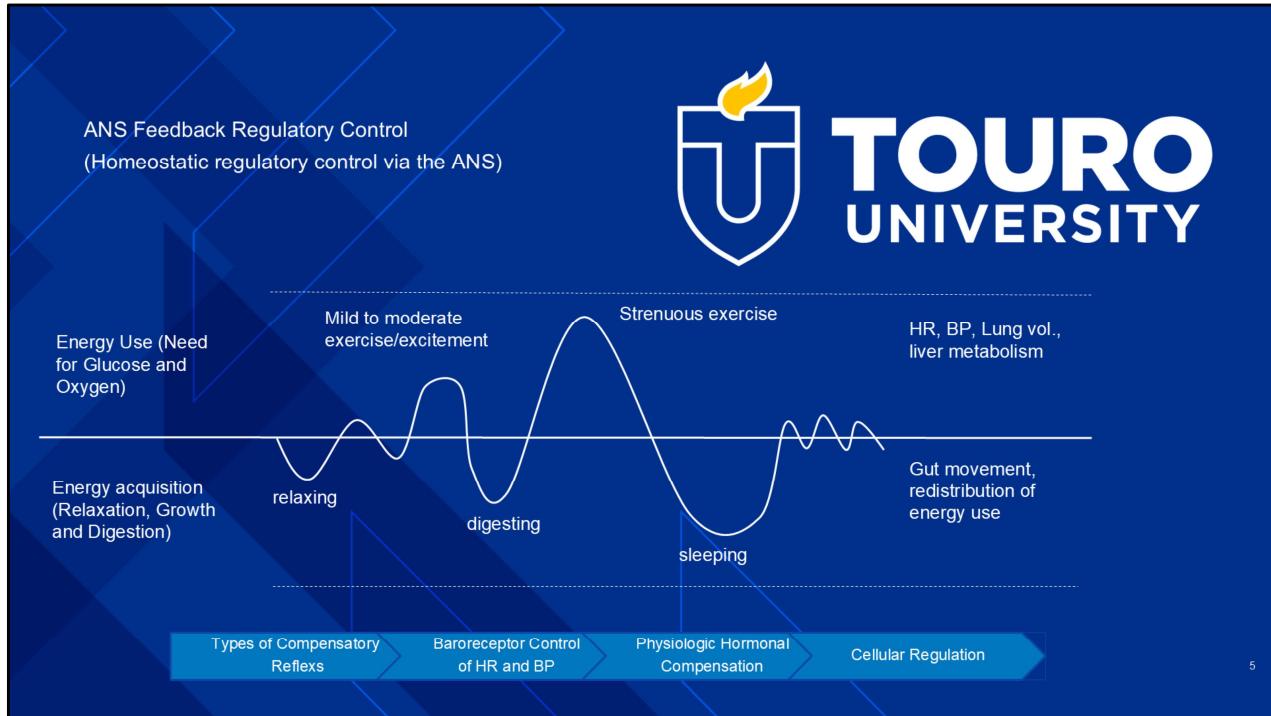


Control of Organ Function

The flow of this lecture and the focus will be directed to defining the ANS, how afferent and efferent communication controls output both centrally and peripherally, what the efferent pathways are, the neurotransmitters involved at the various levels, the receptors that control organ function and how they achieve cellular changes to produce a functional response in the organ and examples of feedback regulation.

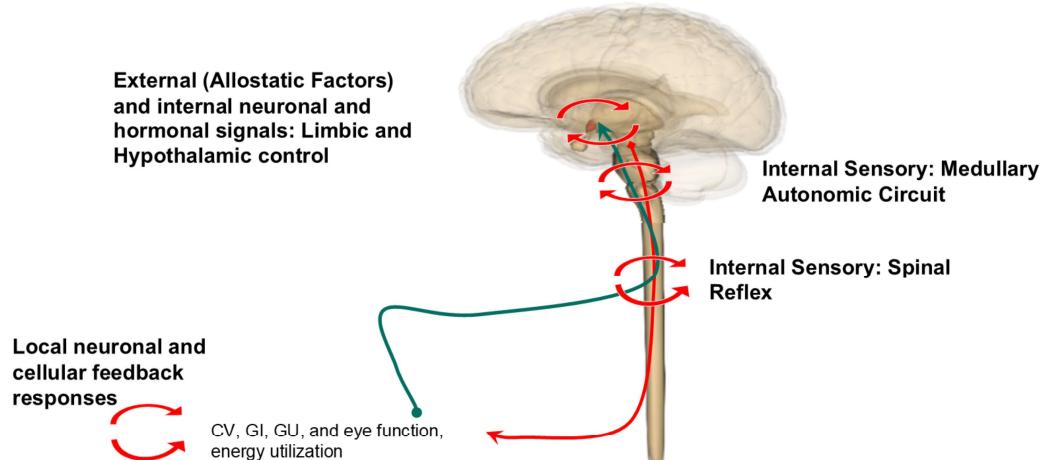
# Curriculum Orientation





Introductory slide: the brain and body communicate to each other to regulate function during times of need and relaxation. This control is discussed in the next section.

## Feedback Regulation Influences ANS Function



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### Feedback Regulation of Autonomic Nervous System Function: A Multilevel Integrative Model

The **autonomic nervous system (ANS)** regulates body function through **hierarchically organized feedback loops** that integrate **external (allostatic)** and **internal (visceral and cellular)** signals. This multilevel system ensures both **moment-to-moment physiological homeostasis** and **long-term adaptability**, aligning organ function with environmental, emotional, and metabolic demands to sustain **survivability**.

At the **highest level**, the **limbic forebrain** and **hypothalamus** integrate **external influences**—such as stress, temperature, circadian rhythms, and emotional state—along with **internal hormonal and visceral inputs** (e.g., from leptin, angiotensin II, or inflammatory cytokines). These **allostatic signals** shape hypothalamic outputs that govern **central sympathetic and parasympathetic tone**, as well as **neuroendocrine axes**. In this role, the hypothalamus acts as an anticipatory modulator, preparing the body for predicted demands (e.g., fight-or-flight or energy conservation) rather than simply reacting.

Beneath this, **medullary reflex circuits**, especially those involving the **nucleus tractus solitarius (NTS)**, **caudal and rostral ventrolateral medulla (CVLM, RVLM)**, and **vagal motor nuclei**, form the core of the **visceral sensory-autonomic reflex arc**. These circuits regulate **cardiovascular, respiratory, and gastrointestinal function** on a beat-to-beat or breath-to-breath basis via **baroreflexes, chemoreflexes**, and

**gastrointestinal motility reflexes.** They operate **independently of cortical awareness** to preserve homeostasis in the face of acute challenges.

At the **spinal level, autonomic reflexes** involving the **intermediolateral cell column (IML)** and local spinal interneurons mediate segmental responses such as **vasoconstriction, bladder emptying, and sexual reflexes.** These circuits are modulated by descending hypothalamic and brainstem input but retain intrinsic autonomy.

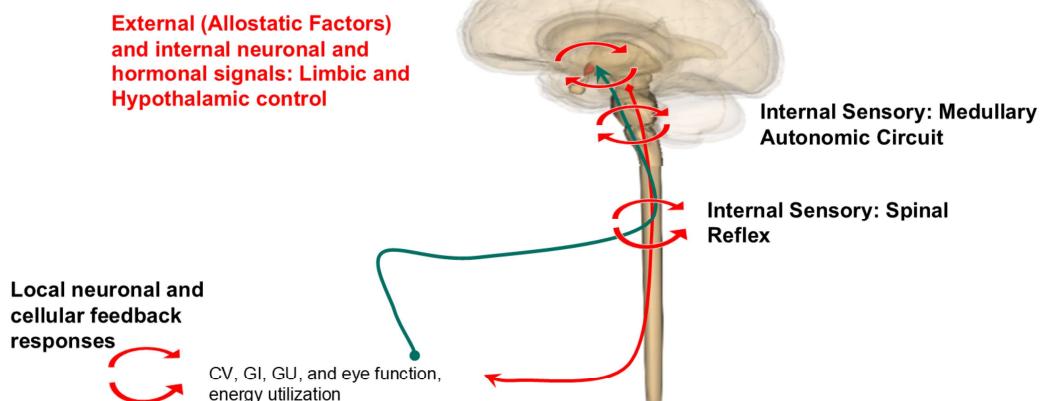
At the **local tissue level, autonomic outputs are further refined by local feedback mechanisms.** These include:

- **Neurotransmitter reuptake and degradation**
- **Paracrine and autocrine signaling** (e.g., nitric oxide, prostaglandins)
- **Immune cell–neuron interactions** (neuroimmune regulation)
- **Receptor desensitization and regulation**, such as:
  - **Downregulation of adrenergic receptors** in chronic sympathetic stimulation (e.g., in heart failure or pheochromocytoma)
  - **Upregulation of muscarinic or adrenergic receptors** in denervation or drug withdrawal states
  - **β-arrestin–mediated receptor internalization** following persistent agonist exposure

These **local cellular adaptations** modulate **sensitivity to autonomic neurotransmitters**, contributing to both **short-term receptor tuning** and **long-term remodeling** of autonomic responsiveness in diseases such as **hypertension, diabetes, and heart failure.**

In sum, the ANS is governed by **nested feedback systems**—from **cortical-limbic allostatic modulation** to **brainstem and spinal reflexes**, down to **cellular receptor plasticity**—that together **optimize organ function** in the face of dynamic internal and external environments. This multi-level regulation enables both **stability and flexibility**, supporting physiological resilience and adaptive energy use.

## Feedback Regulation Influences ANS Function

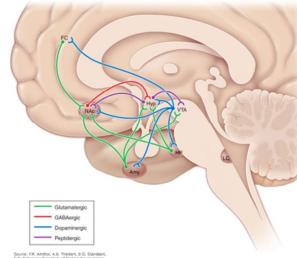
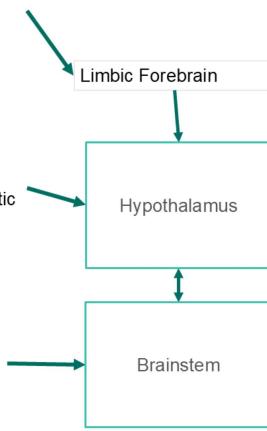


## External (Allostatic Factors) and internal neuronal and hormonal signals: Limbic and Hypothalamic control

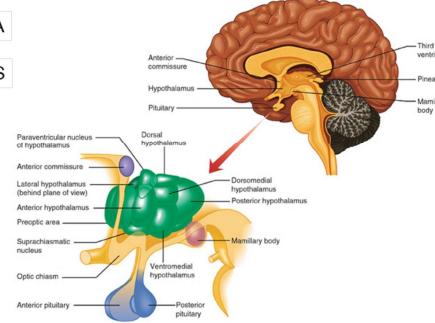
Experiential Factors:  
 Psychogenic and systemic stress signals  
 Sensory inputs (olfaction, vision, auditory)

Integration Center.  
 Regulation of energy, hunger, sleep, temp. Ongoing homeostatic feedback

Homeostatic imbalance  
 Afferent sensory signals:  
 Stretch, Chemo, Temp, Pain



Citation: Chapter 18 Autonomic Nervous System: Sympathetic, Parasympathetic, & Enteric. Ambr FR, Theber AB, Standert DG, Rhee JH. Essentials of Modern Neuroscience. 2020.



### Limbic-Hypothalamic Integration in Autonomic and Stress Regulation

The **limbic forebrain** and **hypothalamus** form the **central integrative axis** through which **emotional, sensory, homeostatic, and hormonal cues** converge to regulate both the **autonomic nervous system (ANS)** and the **hypothalamic–pituitary–adrenal (HPA) axis**, thereby orchestrating adaptive responses to internal and external stressors.

The **limbic system**, particularly the **amygdala, hippocampus, medial prefrontal cortex, and insula**, processes **experiential, emotional, and contextual information**—including psychogenic stress, conditioned fear, social threat, and internal predictions of physiological need. These limbic signals project to the **hypothalamus**, especially the **paraventricular nucleus (PVN)**, which acts as a master controller of neuroendocrine and autonomic outputs.

The **hypothalamus** receives convergent afferent inputs from:

- **Limbic centers** (modulating stress and motivation)
- **Visceral sensory structures** (e.g., nucleus tractus solitarius)
- **Circulating hormones** (e.g., cortisol, leptin, angiotensin II)

Based on this integration, the hypothalamus activates **descending projections to brainstem autonomic nuclei** (modulating sympathetic and parasympathetic tone) and **stimulates the anterior pituitary via corticotropin-releasing hormone (CRH)** to initiate cortisol release. This dual output coordinates the **ANS and HPA axis**,

producing both **rapid physiological adjustments** (e.g., increased heart rate, vasoconstriction, pupil dilation) and **slower endocrine adaptations** (e.g., gluconeogenesis, immune suppression, memory encoding).

Critically, this system enables a **top-down, anticipatory form of regulation**—shifting from reflexive homeostasis to **allostatic control**, where energy and resource allocation are matched to predicted environmental or internal demands. This is essential for survival in complex environments but also vulnerable to dysregulation in chronic stress, leading to **autonomic imbalance, metabolic disease, mood disorders, and impaired cardiovascular recovery**.

In sum, the limbic-hypothalamic axis is a **bidirectional command center**—translating affective and sensory experience into autonomic and endocrine responses, maintaining internal stability while allowing for behavioral and physiological flexibility.

Limbic structures (emotional response centers) coordinate learned experiences and associate them with a positive or negative emotion. Survival depends on an immediate response. The brain is set up to receive sensory signals of taste, smell and sound directly into lower brain centers before they are sent to higher order cortical processing centers. This allows for the priming of the body for action before cortical processing of what to do. Examples of this is hearing a loud sound and the heart starts racing. Or, coming across a smell that initiates a stress fight or flight response. Important structure include the amygdala (fear response), nucleus accumbens (reward center) hippocampus (memory), rhinal cortex, insula, VTA, cingulate cortex, and prefrontal cortex (decision processing) that provide input necessary to balance outputs from the hypothalamus. An interesting note is that chronic stress can increase activity in these limbic structure sensitizing the response experiential factors..

Hypothalamus is a cluster of nuclei that integrates signals it receives from the brain stem, hormonal signals from the body (satiation signals) and brainstem inputs and in turn sends outputs that regulate many major homeostatic functions of the body. It can respond to stress by regulating glucocorticoid release via the hypothalamic-pituitary axis. Regulation of release of vasopressin, oxytocin and antidiuretic hormone occur here as well. It also regulates ANS efferent projections to the body. Various nuclei in the hypothalamus regulate eating and drinking behavior, water and electrolyte balance, body temperature regulation, sexual behavior and circadian rhythms.

Brainstem connects input from the body and higher brain centers (nuclei include pons, medulla oblongata) input responds to both stretch (gut, vasculature [baroreceptors]) and chemo-receptors (CO<sub>2</sub>) and thermoreceptors provide input to the brainstem regarding temperature, blood pressure and carbon dioxide levels to allow for feedback regulatory control. An example is the baroreceptor (vascular stretch receptor) reflex that detects blood pressure drops and produces an increase in sympathetic outflow. These brainstem nuclei (ventrolateral medulla, locus

coeruleus, and raphe nuclei of the pons and medulla) mediate sympathetic influences. An important note here is that input from the body is sent through the dorsal horn of the spinal column at locations that are very close or next to other sensory inputs including pain. This very close proximity of inputs feeding into the same area of the spinal column underlies concepts of referred pain and facilitation.

### Devision Nerve(s) or Segment(s) Structures

Parasympathetic:

Vagus goint to the Esophagus, larynx, trachea

Sympathetic Splanchnic (T7–L1) Stomach, spleen, small viscera, colon, kidney, ureter, bladder

(upper part), uterus (fundus), ovaries, lungs

Somatic (C7–L1) Parietal pleura, diaphragm, parietal peritoneum

Parasympathetic Pelvic (S2–4) Rectum, trigone of the bladder, prostate, urethra, cervix of the

uterus, upper vagina

### AMA Citation

Amthor FR. Amthor F.R. Amthor, Franklin R. Autonomic Nervous System: Sympathetic, Parasympathetic, & Enteric. In: Amthor FR, Theibert AB, Standaert DG, Roberson ED. Amthor F.R., & Theibert A.B., & Standaert D.G., & Roberson E.D.(Eds.),Eds. Franklin R. Amthor, et al.eds. *Essentials of Modern Neuroscience*. McGraw Hill; 2020. Accessed September 26, 2021.

<https://accessmedicine.mhmedical.com/content.aspx?bookid=2938&sectionid=247989153>

*Nat Rev Neurosci.* 2009 June ; 10(6): 397–409. doi:10.1038/nrn2647

### Neural Regulation of Endocrine and Autonomic Stress Responses

**Yvonne M. Ulrich-Lai and James P. Herman**

(Top down; Higher order input

Stress activating inputs

Associational information puts together sensory inputs (olfaction), memory [medial septum, entorhinal cortex, cingulate cortices] with attention and arousal (locus coeruleus, raphe nuclei). Central nucleus of the Amygdala [CeA] (stress integration) priming for fight or flight or fear response. Medial [MeA] and basolateral [BLA] mediate psychogenic stress not homesostatic stressors

Stress Inhibitory inputs

1) Hippocampal input suppress HPA axis. Hippocampus can influence autonomic tone—

decreases heart rate, blood pressure and respiratory rate (input from medial prefrontal cortex)

2) Medial prefrontal cortex [mPFC]: Inhibits HPA-axis responses to psychogenic stressors

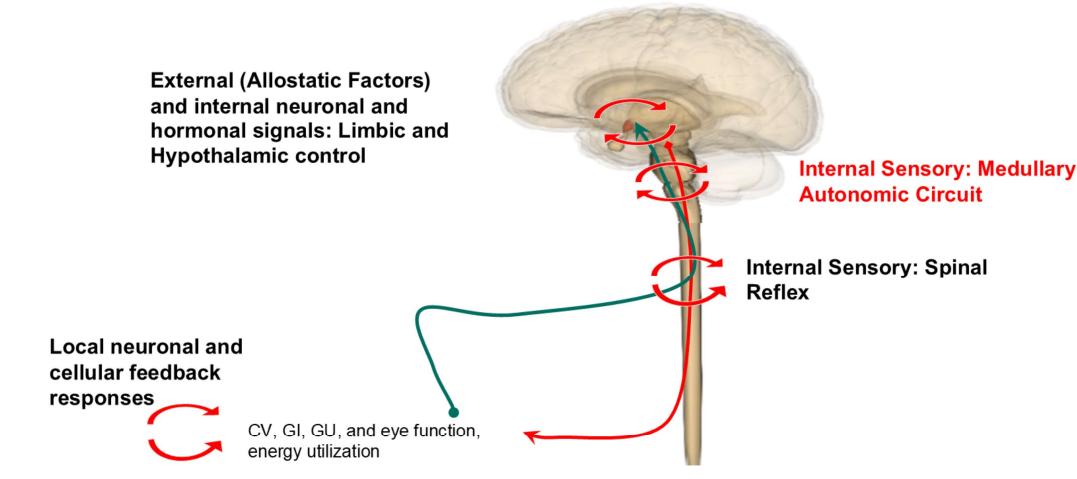
Note: Ventral medial PFC (including infralimbic PFC) can initiate autonomic and HPA responses to psychogenic stimuli

Middle management: integration of excitatory and inhibitory responses

Most limbic-PVN connections relay through GABA-rich cell groups in the bed nucleus of the stria terminalis (BST) and hypothalamus<sup>3</sup>. These

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## Feedback Regulation Influences ANS Function



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### Medullary Autonomic Circuits: The Core Reflexive Regulators of Autonomic Function

The **medulla oblongata** houses the **principal brainstem circuits responsible for moment-to-moment autonomic control**, particularly of cardiovascular, respiratory, and visceral function. This region forms the **intermediate tier** of the autonomic hierarchy, receiving input from both **peripheral sensory afferents** and **higher centers** such as the hypothalamus and limbic system, and coordinating rapid reflexive adjustments in autonomic tone.

#### Afferent Integration: The Nucleus Tractus Solitarius (NTS)

The **NTS** is the primary sensory nucleus for **visceral afferents** carried via cranial nerves IX and X. It receives input from:

- **Baroreceptors** (e.g., aortic arch, carotid sinus)
- **Chemoreceptors** (e.g., carotid and aortic bodies)
- **Pulmonary and gastrointestinal stretch receptors**
- **Pain, temperature, and metabolic signals from viscera**

This information reflects the **internal physiological state** and serves as the foundation for **short-loop reflexes** to maintain homeostasis.

#### Sympathetic Modulation: CVLM and RVLM

The **NTS** sends **inhibitory projections** to the **caudal ventrolateral medulla (CVLM)**, which in turn **inhibits** the **rostral ventrolateral medulla (RVLM)**—the main **sympathoexcitatory center**. The **RVLM** provides **tonic excitatory drive** to

**preganglionic sympathetic neurons** in the spinal cord (especially in the IML column).

- **When baroreceptors are stretched** (e.g., in hypertension), NTS activation increases → CVLM inhibition of RVLM → **decreased sympathetic tone**
- **When baroreceptors are unloaded** (e.g., in hypotension or volume loss), NTS activity is reduced → disinhibition of RVLM → **increased sympathetic outflow**

### Heart Parasympathetic Modulation: Dorsal Motor Nucleus of the Vagus (DMV) and Nucleus Ambiguus

The **NTS also activates vagal efferent nuclei**, including the DMV and nucleus ambiguus, which provide **parasympathetic output to the heart, lungs, and GI tract**.

- In states of elevated blood pressure or visceral distension, **increased vagal efferent activity** promotes **bradycardia, enhanced digestion, and reduced cardiac output**.

### Brain Bidirectional Integration with Hypothalamus and Limbic Forebrain

While medullary circuits can operate **reflexively and independently**, they are also modulated by **descending projections** from the hypothalamus and limbic structures. These higher centers integrate **motivational, emotional, circadian, and metabolic signals**, allowing **context-appropriate adjustment** of the reflex circuits (e.g., increased sympathetic tone during emotional stress or exercise).

### Clinical Relevance

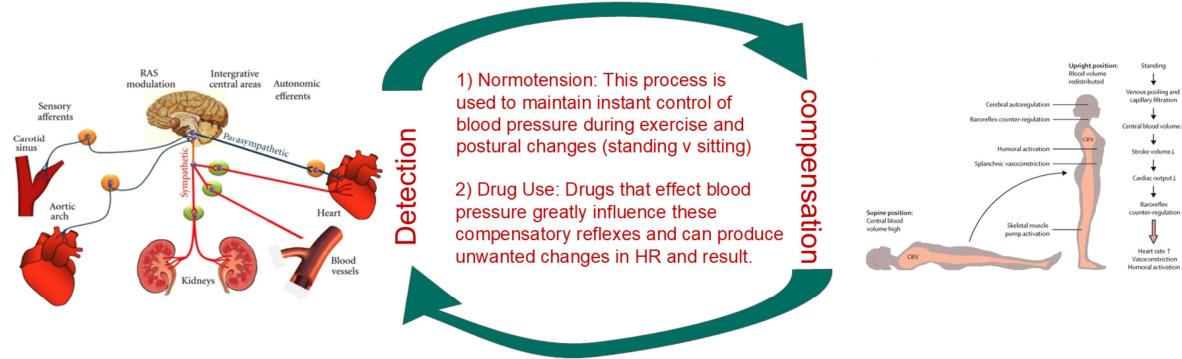
Disruption of medullary autonomic circuits can lead to life-threatening autonomic instability:

- **Impaired baroreflex** (e.g., in neurodegenerative synucleinopathies) → orthostatic hypotension
- **Brainstem stroke or trauma** → central hypoventilation, cardiovascular dysregulation
- **Dysautonomia** in diabetes or spinal cord injury often reflects failure of medullary or spinal autonomic integration

### Summary

The **medullary autonomic circuit** is the **reflexive control center** of the ANS, integrating **visceral sensory input** and coordinating **sympathetic and parasympathetic output** through interactions between the **NTS, CVLM, RVLM, DMV, and nucleus ambiguus**. It provides the necessary physiological stability upon which higher-order hypothalamic and cortical influences can operate—balancing **reflexive homeostasis** with **adaptive allostasis**.

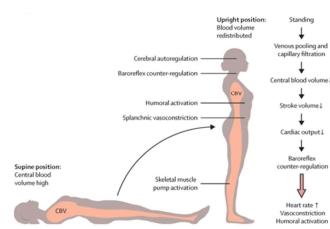
## Blood Pressure Regulation and the ANS Baroreceptor-Mediated Feedback Control



### THM:

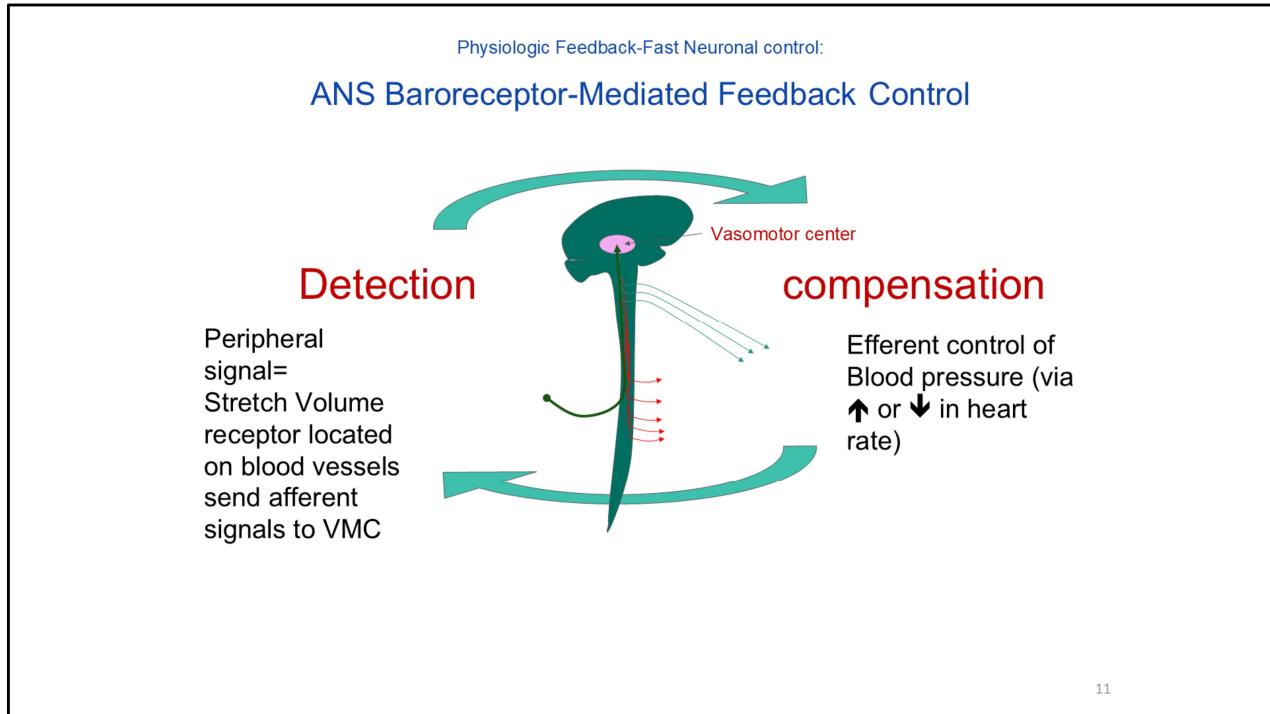
- Continual adjustments of vascular tone, heart rate and hormonal release are necessary to maintain the optimal blood pressure at rest and during activity. In addition, adjustments to blood pressure locally occur to optimize blood flow to vital organs like the brain.
- Drugs that interfere with the communication to the body at any location in the output pathway can prevent these adjustments and produce the unwanted side effects.

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### Related Objectives:

Know the functional importance of autonomic feedback regulation at both the physiologic and cellular levels.



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#### Related Objectives:

Know the functional importance of autonomic feedback regulation at both the physiologic and cellular levels.

# Baroreceptors

## Baroreceptor Reflex

### Sensors & Location:

High-pressure **arterial baroreceptors** in the carotid sinuses and aortic arch detect stretch in vessel walls. Low-pressure **cardiopulmonary receptors** in the heart and lungs sense volume and venous return

### Afferent Signaling:

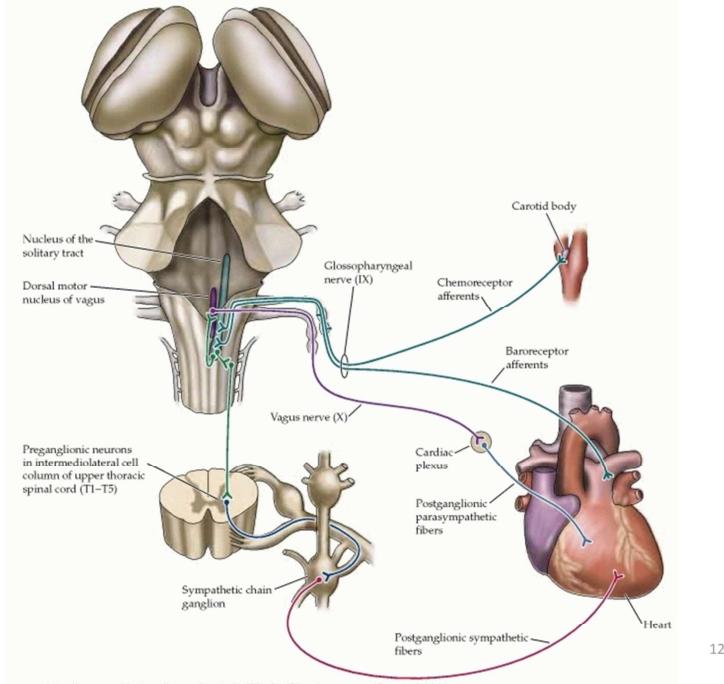
Stretch increases baroreceptor firing via **myelinated A-fibers** for beat-to-beat changes and **C-fibers** for basal tone control. These afferents project to the **nucleus tractus solitarius (NTS)** in the medulla

### Central Integration:

The NTS modulates sympathetic and parasympathetic tone via central autonomic networks. Increased blood pressure → increased afferent firing → ↑ **parasympathetic (vagal)** and ↓ **sympathetic output**, reducing heart rate, contractility, and vascular resistance. Conversely, low pressure triggers the opposite → ↑ **sympathetic**, ↓ **parasympathetic**, raising blood pressure.

### Physiological Flexibility:

This Feedback loop maintains **short-term blood pressure homeostasis**, such as during posture changes or blood loss



## Related Objectives:

Know the functional importance of autonomic feedback regulation at both the physiologic and cellular levels.

Physiologic feedback peripheral function is very important in both the instantaneous as well as stable long-term control. Neurotransmission provides 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 baro-receptor feedback mechanism. Changes in blood pressure are detected by stretch 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.

## Examples of Homeostatic Regulation

Sensory Input (to CNS)	Sensory Origin	Environmental Cue or Condition	Autonomic Compensatory Output
↓ Arterial pressure (baroreceptors)	Carotid sinus, aortic arch	Hemorrhage, orthostatic stress	↑ Sympathetic tone → ↑ HR, ↑ vasoconstriction, ↑ contractility
↑ Arterial pressure	Carotid sinus, aortic arch	Hypertension	↑ Parasympathetic tone → ↓ HR; ↓ Sympathetic tone → vasodilation
↓ Blood O <sub>2</sub> / ↑ CO <sub>2</sub> / ↓ pH (chemoreceptors)	Carotid and aortic bodies	Hypoxia, acidosis, hypercapnia	↑ Sympathetic tone → vasoconstriction; ↑ respiratory drive via brainstem centers
Bladder wall stretch	Mechanoreceptors in bladder wall	Full bladder	Parasympathetic outflow → detrusor contraction; inhibition of sympathetic outflow
Rectal distension	Rectal wall stretch receptors	Fecal buildup	Parasympathetic activation → colon contraction, internal sphincter relaxation
Gastric distension	Stretch receptors in gastric wall	Food intake	Vagal afferents → increased GI motility and secretion (PANS-mediated)
Low blood glucose	Hypothalamic glucose-sensing neurons	Fasting or insulin overdose	↑ Sympathetic outflow → epinephrine release, glycogenolysis, ↑ blood glucose
Cold exposure (skin thermoreceptors)	Cutaneous thermoreceptors	Cold ambient temperature	↑ Sympathetic output → cutaneous vasoconstriction, shivering (via somatic pathways)
Fear or acute emotional stress	Cortical-limbic integration	Threatening situation	↑ Sympathetic tone → ↑ HR, ↑ BP, pupil dilation, ↓ GI motility
Pain (visceral or somatic nociception)	Nociceptors via spinal/cranial afferents	Injury, ischemia	Sympathetic activation → ↑ BP, ↑ HR (e.g., guarding response)



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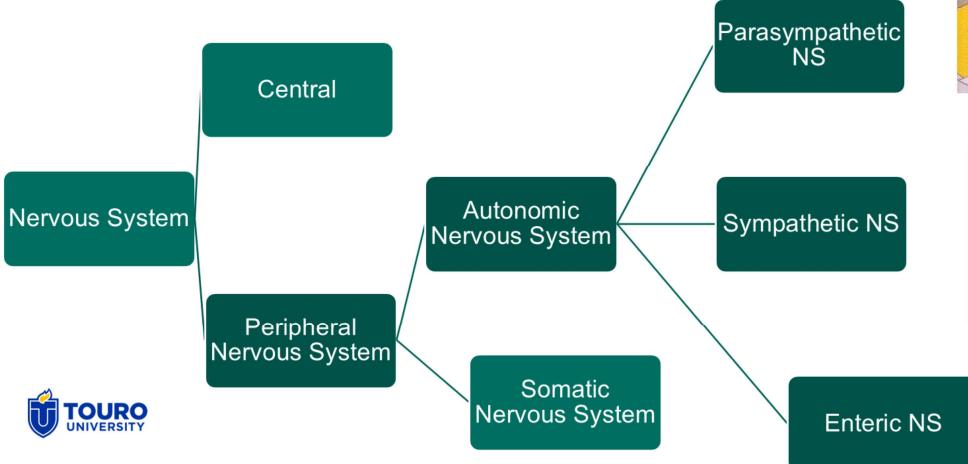
# **ANS Review of Function**

## Neurotransmitters And Receptors

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## Nervous System Organization



The nervous system is comprised of the brain and spinal cord or central nervous system. All neurons that exit the spinal cord are part of the peripheral nervous system. The central nervous system provides higher order processing of internal and external information and the organization of subsequent responses.

The somatic nervous system is the conscious, voluntary, control of function with a focus on skeletal muscle activity.

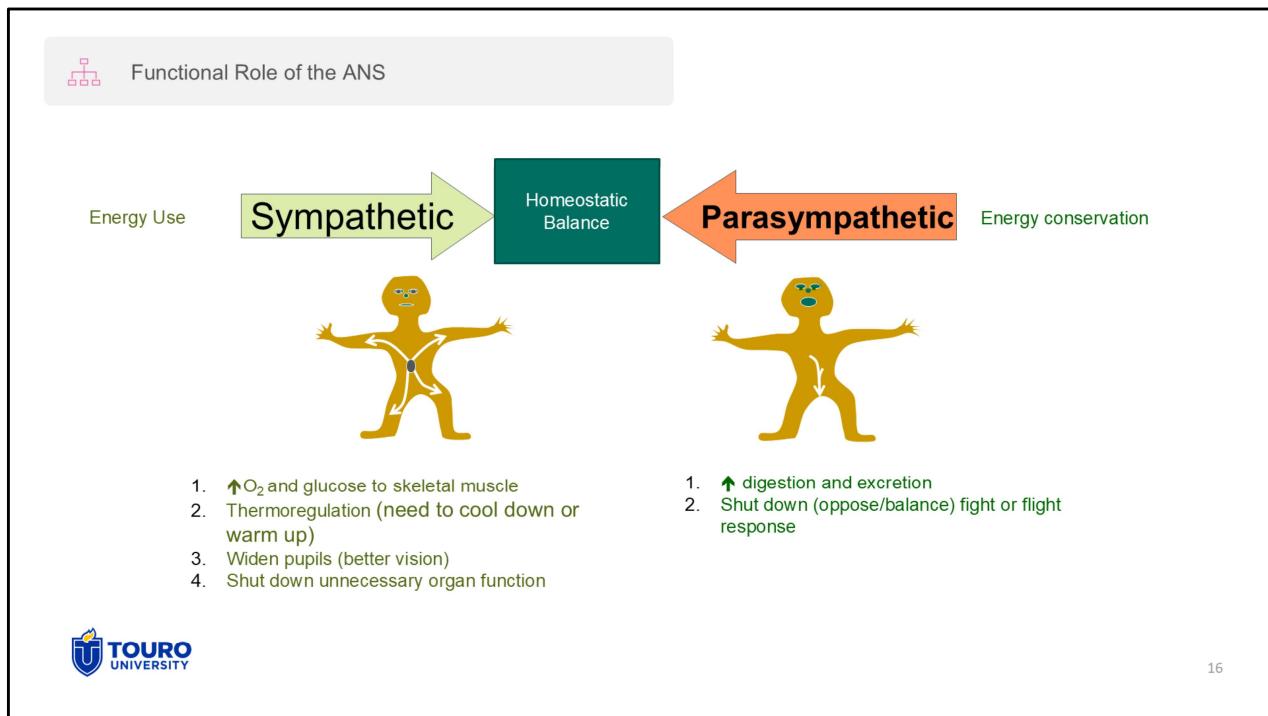
The autonomic nervous system or involuntary nervous system is responsible for a dynamic balance between priming the body for fight or flight and creating a homeostatic maintenance of function to optimize survival.

It is easy and perhaps too simplistic to think of the sympathetic side as the fight or flight part of the ANS. This is true in part. The sympathetic role is to prime the body for fight or flight and shunt oxygen and glucose to your muscles and brain on demand. In fact, the mountain bike rider provides a prime example of this. I guarantee you that there is an immediate response to their heart rate, pupillary diameter, and respiratory rate— all important features to increase supply of oxygen and glucose to his muscles and brain or increase the ability to see and respond to danger. I would also venture to guess there is a fair amount of sphincter

constriction. Taken together the processes that stimulate oxygen uptake and distribution, increased glucose production and movement combined with diverting energy from unnecessary functions like digestion are part of the role of the ANS. This dynamic balance is necessary for survival.

Likewise, when the need for movement is reduced 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.



Related objectives:

Know the effects of both norepinephrine and acetylcholine in peripheral homeostatic regulation.

Know in general the role of ANS in the regulatory control of organ function. Have a strong understanding of the normal parasympathetic and sympathetic effects on organ function.

The S-ANS promotes arousal, skeletal and brain energy consumption, as well as, energy conservation to non-immediate-survival-related organs (GI, GU). The central role of the S-ANS is to increase supply and delivery of oxygen and glucose to skeletal muscle and the brain. The variety of mechanism that the body uses to achieve this goal will be the focus of this lecture.

In contrast, the P-ANS regulates bodily functions necessary during a relaxed state; digestion, urination, and defecation and slows down energy use not required for growth (heart rate, etc).

Note: always refer back to the concepts in this slide when trying to figure

out detailed functional aspects of drug action. For example, what will happen when drugs used to stimulate the sympathetic NS are used? Effects on the eye—dilation of pupil, on the heart—increased cardiac output to speed oxygen delivery, on the liver—increase glucose production and release into blood or anything else like bronchodilation that would optimize oxygen and glucose delivery to muscle and brain tissue, etc. Similarly, when the parasympathetic system is activated you would expect, defecation, urination, slowing heart rate, decreasing lung expansion, and the general conservation of energy, etc.

 Functional Role of the ANS

**Sympathetic**

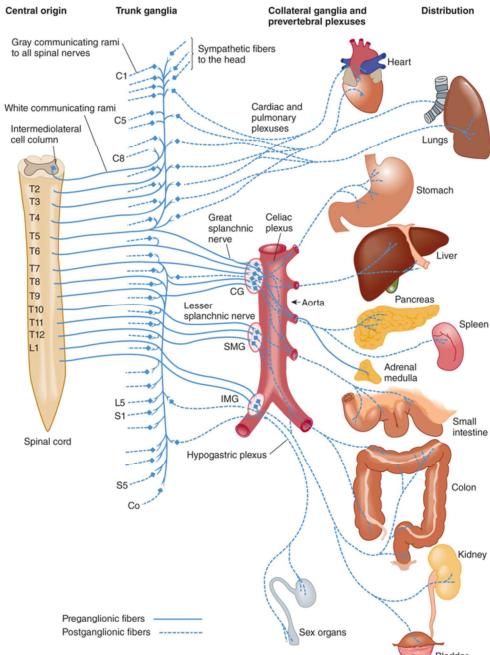
$\uparrow$ O<sub>2</sub> and glucose to skeletal muscle

- relax bronchi
- shunt blood from organs to muscle
- Vasoconstrict organ blood flow
- Vasodilate skeletal muscle flow
- ↑ glucose production (liver)
- ↑ Heart rate and contractile force
- ↑ water volume through hormones

$\downarrow$ Shut down unnecessary organ function

- Relax bladder walls
- Constrict bladder sphincters
- Relax gut walls
- Constrict gut sphincters





The diagram illustrates the sympathetic nervous system's pathway from the spinal cord to various organs. It shows the central origin (Spinal cord) with levels T2-L1 and C8-T1. Gray and white communicating rami connect to trunk ganglia (C1-C8). From these, sympathetic fibers travel to the head, cardiac and pulmonary plexuses, and collateral ganglia and prevertebral plexuses. The distribution is shown to the heart, lungs, stomach, liver, pancreas, spleen, small intestine, colon, kidney, sex organs, and bladder. Key structures labeled include the Aorta, CG (Celiac ganglion), SMG (Splanchnic ganglion), and Hypogastric plexus.

Source: Stephen G. Waxman: Clinical Neuroanatomy, 29e  
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Related objectives:

Know the effects of both norepinephrine and acetylcholine in peripheral homeostatic regulation.

Know in general the role of ANS in the regulatory control of organ function. Have a strong understanding of the normal parasympathetic and sympathetic effects on organ function.

Students should focus on the role of the sympathetic nervous system in providing oxygen and glucose to muscle in brain. The regulation of organ function is the basis for autonomic pharmacology.

Reference only:

Brain: Central autonomic centers distributed throughout the brain (limbic cortical areas, amygdala, hypothalamus, and numerous brainstem nuclei).

Cortical and amygdala: initiate autonomic responses in response to pain and emotion

Brainstem provide control of visceral information in and out.

Hypothalamus is central to autonomic regulation.

Cranial roots:

1) Vagus (X) =lung, heart, stomach, pancreas, small intestine.

2) IX and VII tear and salivary glands

3) III eye

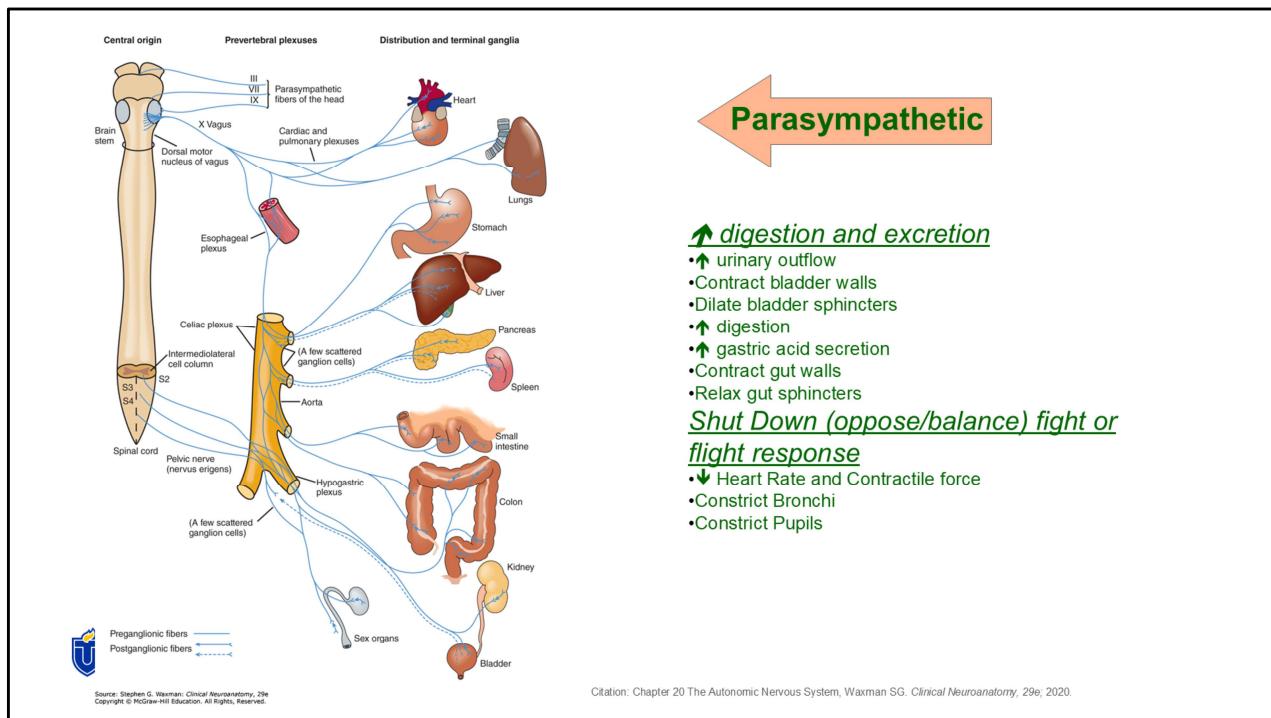
Sacral roots:

1) Large intestine

2) Rectum

3) Bladder

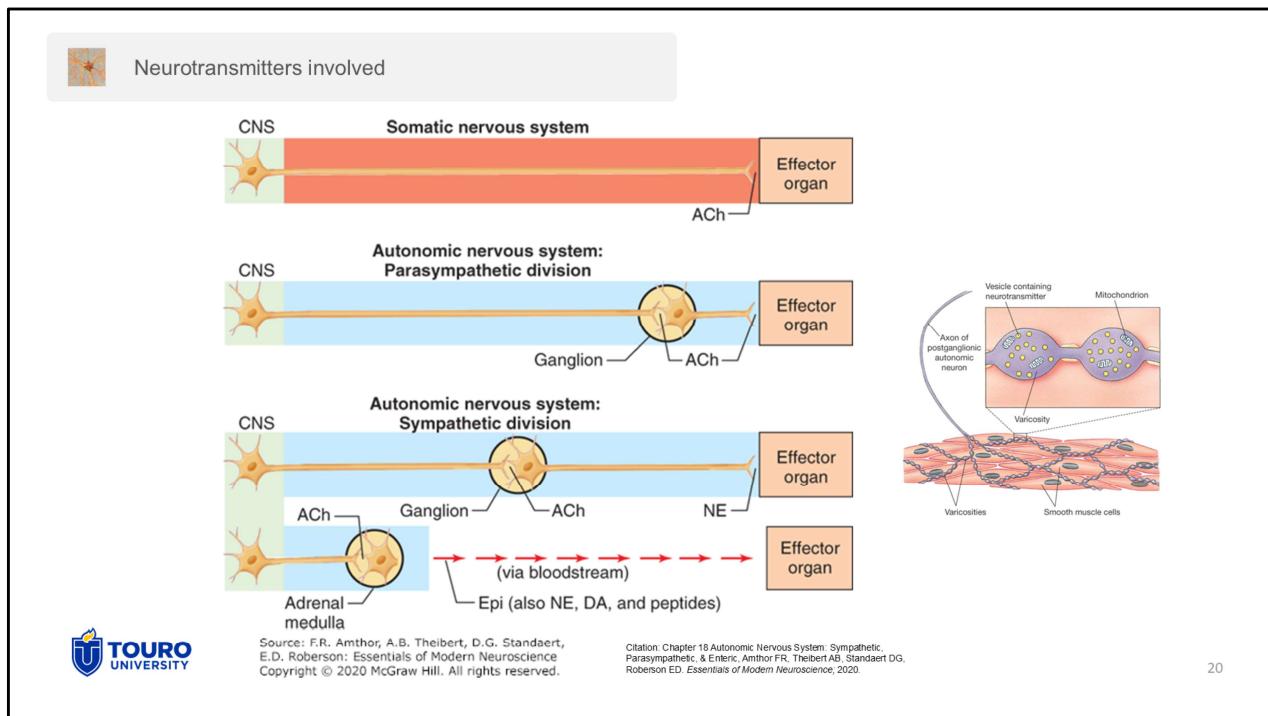
4) Reproductive organs.



## ABC'S AND OMT

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.



Related objectives:

Know the effects of both norepinephrine and acetylcholine in peripheral homeostatic regulation.

Know in general the role of ANS in the regulatory control of organ function. Have a strong understanding of the normal parasympathetic and sympathetic effects on organ function.

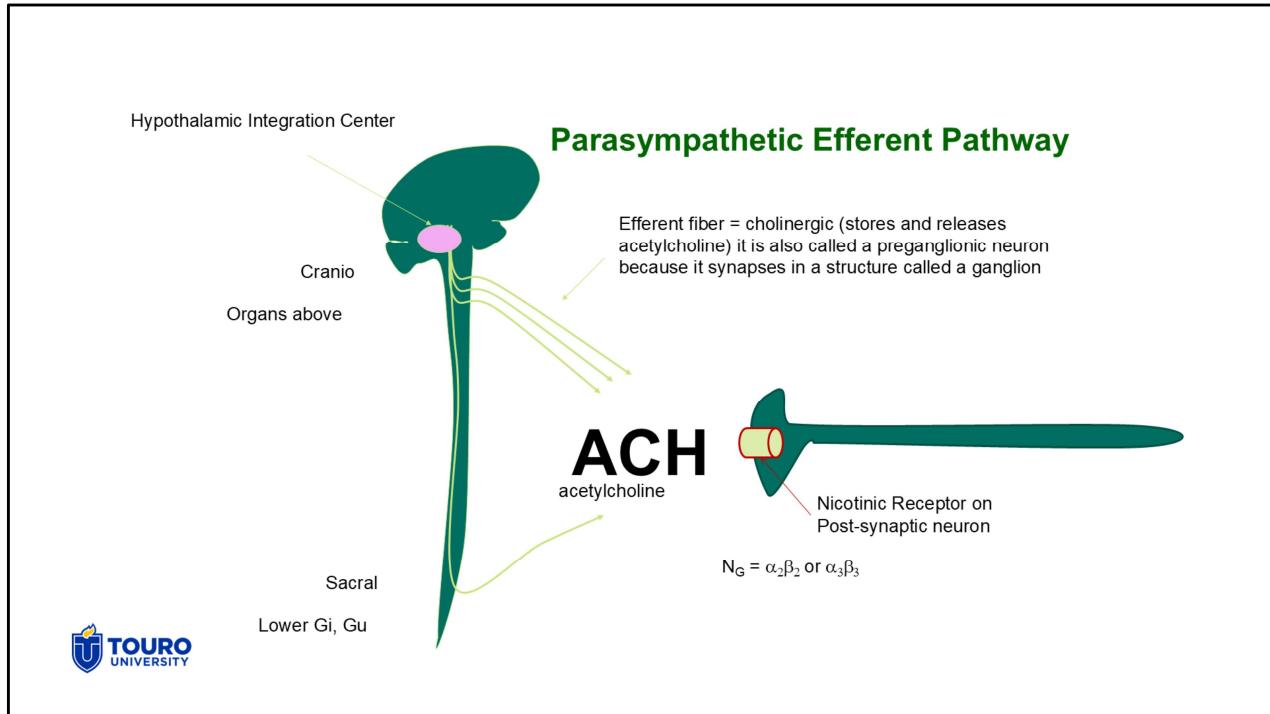
Somatic Nervous System: Pathways from the motor cortex provide voluntary skeletal muscle control.

Autonomic Nervous System: Pathways from lower brain regions regulate involuntary (not controlled by conscious thought) body homeostasis (HR, BP, Smooth muscle tone, secretion, energy regulation, etc.).

Students should at this point be familiar with the distinction between somatic and autonomic nervous system.

Some take home features:

- 1) All efferent neurons that exit the spinal cord into the body synthesize store and release acetylcholine (cholinergic neurons). This includes both somatic and autonomic preg-ganglionic nerve fibers.
- 2) Most autonomic neurons form a synapse at specific ganglia in the body except for neurons that regulate the adrenal medulla (these connections are direct).
- 3) Post-ganglionic synaptic varicosities allow one autonomic neuron to regulate a region of smooth muscle.
  - 4) The parasympathetic post-ganglionic neuron is always cholinergic.
- 5) The sympathetic post-ganglionic neuron can either be cholinergic (sweat glands), noradrenergic (most organs), or dopaminergic (kidneys).



Related objectives:

Know the effects of both norepinephrine and acetylcholine in peripheral homeostatic regulation.

Be able to describe neurons with respect to transmitter released, location, and most prevalent pre and post-synaptic receptors.

Take home features:

- 1) Acetylcholine is released at ganglionic junctions
- 2) Acetylcholine activates nicotinic cholinergic receptors on post-ganglionic neurons

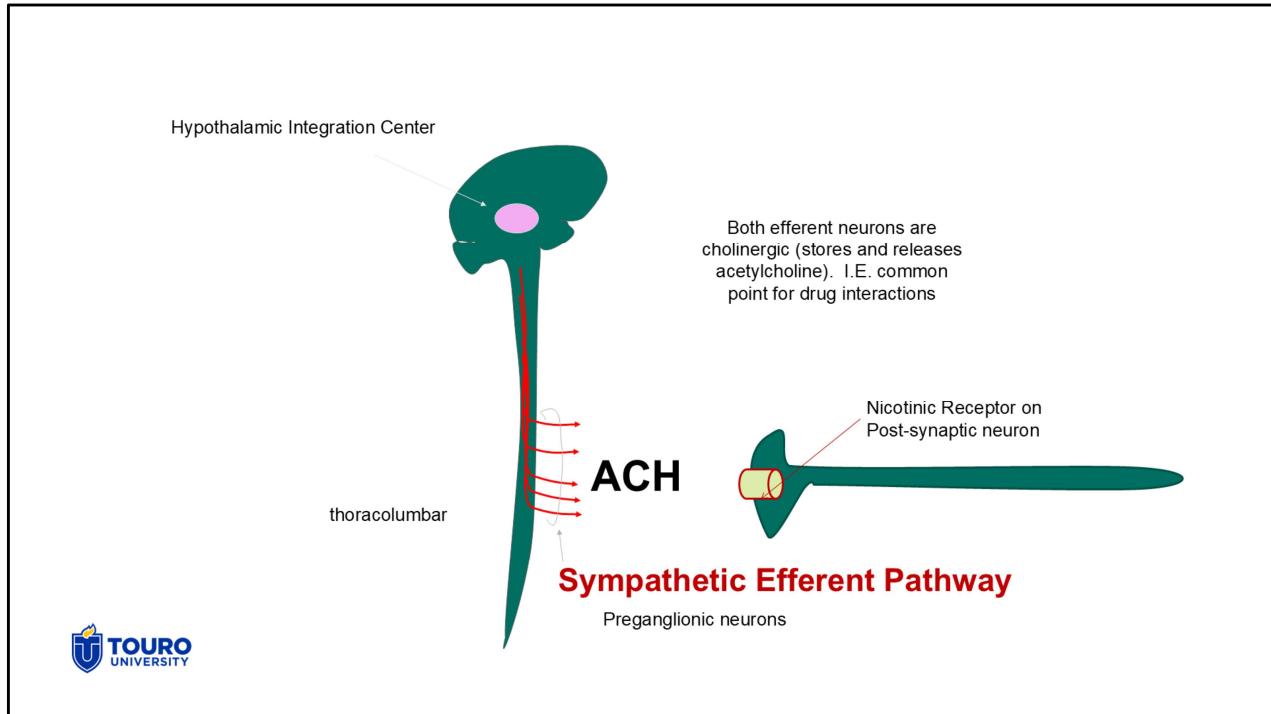
Cranial roots:

- 1) Vagus (X) = lung, heart, stomach, pancreas, small intestine.
- 2) IX and VII tear and salivary glands
- 3) III eye

Sacral roots:

- 1) Large intestine
- 2) Rectum
- 3) Bladder

4) Reproductive organs.



Related objectives:

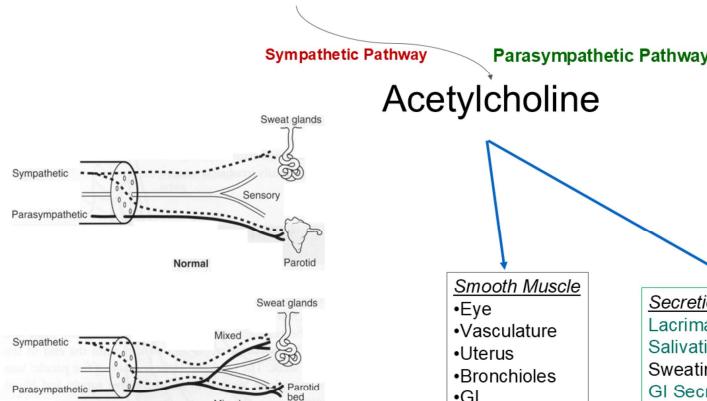
Know the effects of both norepinephrine and acetylcholine in peripheral homeostatic regulation.

Be able to describe neurons with respect to transmitter released, location, and most prevalent pre and post-synaptic receptors.

Take home features:

- 1) Acetylcholine is released at both sympathetic and parasympathetic ganglionic junctions
- 2) Acetylcholine activates nicotinic cholinergic receptors on sympathetic post-ganglionic neurons
- 3) The distinction between sympathetic and parasympathetic is functional. Both systems have similar neuronal types and receptors up until the post-ganglionic neurons.

## Clinical Pearl: Autonomic Neurotransmitters



### Smooth Muscle

- Eye
- Vasculature
- Uterus
- Bronchioles
- GI
- GU

### Secretion

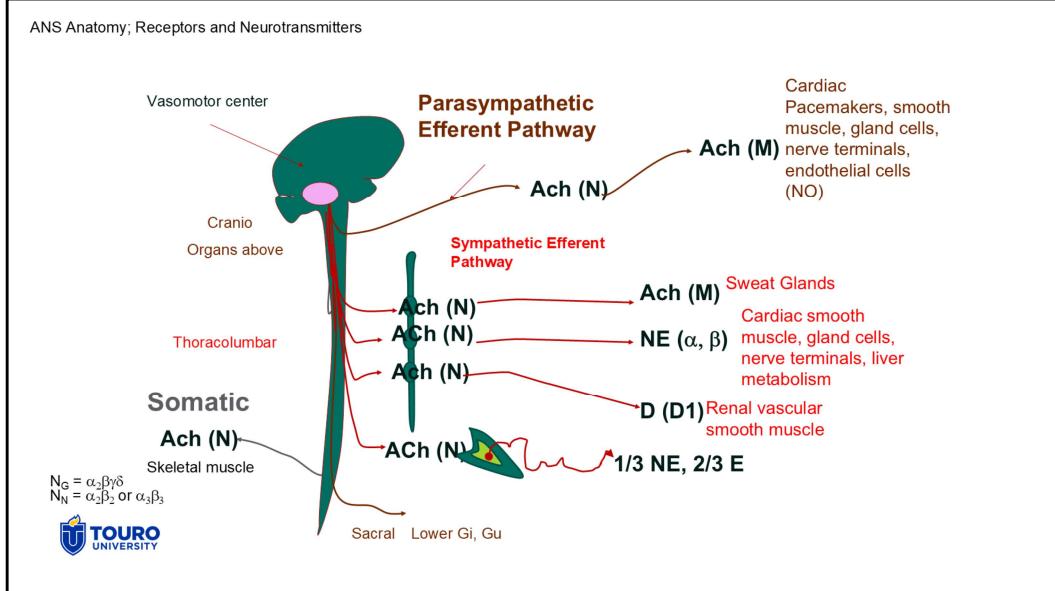
- Lacrimation
- Salivation
- Sweating
- GI Secretions
- Lung mucus

- Take home message (THM):**
- 1) All neurons that exit the spinal cord are cholinergic neurons (synthesize and release the neurotransmitter acetylcholine)
  - 2) Norepinephrine is the principal NT for most sympathetic function except for thermoregulatory sweating. In this case the post ganglionic sympathetic neuron is a cholinergic neuron to support heat regulation during energy expenditure.
  - 3) Secretory cells of all types are stimulated by Ach-M3 cholinergic receptor cascades.
  - 4) Above case is an example to illustrate the concept of Frey's syndrome after a superficial parotidectomy (salivary gland removal). Cutting neurons to sweat and salivary gland occurs during the surgery. When neurons grow back, they can become cross-wired resulting in parasympathetic cholinergic neurons activating muscarinic receptors on sweat glands normally controlled by sympathetic cholinergic neurons that control sweating. This cross wiring of cholinergic neurons results in the patient sweating when presented with food.

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Related objectives:

Know the effects of both norepinephrine and acetylcholine in peripheral homeostatic regulation.



Related objectives:

Know the effects of both norepinephrine and acetylcholine in peripheral homeostatic regulation.

Be able to describe neurons with respect to transmitter released, location, and most prevalent pre and post-synaptic receptors.

Take home features:

- 1) Sympathetic and parasympathetic nervous systems differ in their post-ganglionic neurons.
- 2) Note the types of post-ganglionic neurons for both systems.

**Clinical relevance:** Drugs that block ACH receptor function (especially nicotinic blockers, also called ganglion-blockers because of location) effect both sympathetic and parasympathetic pathways. In addition, drugs that increase ACH at the synapse affect both pathways.

The final organ effect is a sum of both inputs. The outcome is dependent on which system has a higher input representation. Rule of thumb:

Sympathetic V Parasympathetic:

Parasympathetic influence dominates in most organs except for the vasculature

Sympathetic influences dominate the vasculature

For example, ganglionic-blockers produce hypotension (a decrease in blood pressure) because the sympathetic side tends place a vasoconstrictive tone on peripheral vascular resistance and the parasympathetic side has little influence on vascular tone.

Note: The somatic nervous system controls voluntary muscle movement.

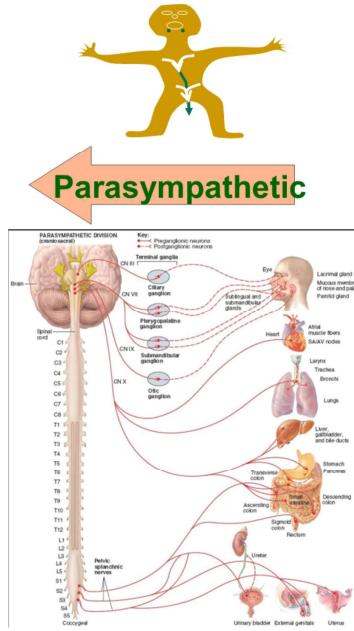
The motor-neurons that control muscle movement are also cholinergic (release acetylcholine) and activate contraction by stimulating a nicotinic receptor on muscle cells. This nicotinic receptor functions as an ion channel similar to ganglionic nicotinic receptors but differs in subunit composition.

**Clinical relevance:** A patient with myasthenia gravis (autoimmune disease that attacks nicotinic receptors) can be given a drug that increases acetylcholine at the synapse by preventing its breakdown. The patients on these drugs perform better with daily task but will have all of the side effects of increased parasympathetic tone on organs and secretory glands as well as increased sympathetic tone on the vasculature.

## PANS: NT and Receptors

Effect Produced	Physiologic effect	NT, R	ISM
<b>↑ digestion and excretion</b>			
↑ urinary outflow	Contract bladder walls Dilate bladder sphincters	Ach, M3 ACh, M3/NO	IP3 cGMP, K+ outflow
↑ digestion	↑ gastric acid and salivary secretion Contract gut walls Relax gut sphincters	Ach, M3 Ach, M3 ACh, M3/NO	IP3 IP3 cGMP, K+ outflow
<b>Shut down unnecessary organ function</b>			
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.



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## SANS: NT and Receptors



**Sympathetic**

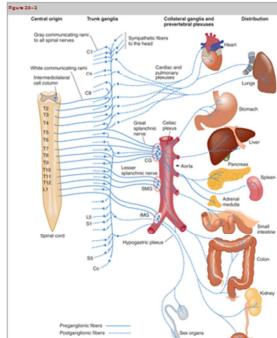


Figure 18-3

Source: McConnell, M., Clinical Neuroscience, 2nd edition  
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Effect Produced	Physiologic effect	NT, R	ISM
<b>↑O<sub>2</sub> and glucose to skeletal muscle and brain:</b>			
relax bronchi	↑ Surface area = more O <sub>2</sub> exchange	NE, β2	cAMP
Shunt blood from organs to muscle	Vasoconstrict organ blood flow	NE, α1	IP <sub>3</sub>
	Vasodilate skeletal muscle flow	NE, β2	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
<b>Shut down unnecessary organ function</b>			
Relax bladder walls	Reduces urgency	NE, β3>2	cAMP
Constrict bladder sphincters	Reduces urgency	NE, α1	IP <sub>3</sub>
Relax gut walls	Reduces gut muscle activity	NE, β2>3	cAMP
Constrict gut sphincters	Reduces defecation	NE, α1	IP <sub>3</sub>

The sympathetic nervous system primarily uses norepinephrine to activate alpha and beta receptors, triggering cAMP or IP<sub>3</sub> signaling based on tissue needs. An exception is thermoregulatory sweating, where acetylcholine stimulates muscarinic receptors to promote heat loss during activity.

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Related objectives:

Know the effects of both norepinephrine and acetylcholine in peripheral homeostatic regulation.

Know in general the role of ANS in the regulatory control of organ function. Have a strong understanding of the normal parasympathetic and sympathetic effects on organ function.



## Control of Organ Function

Smooth Muscle (GI, GU, Vasculature, Eye).

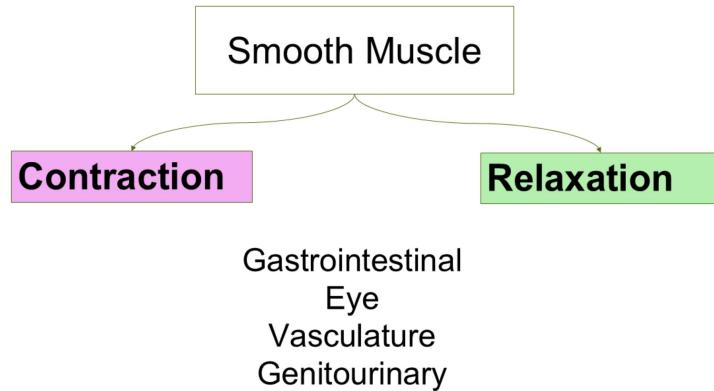
Heart

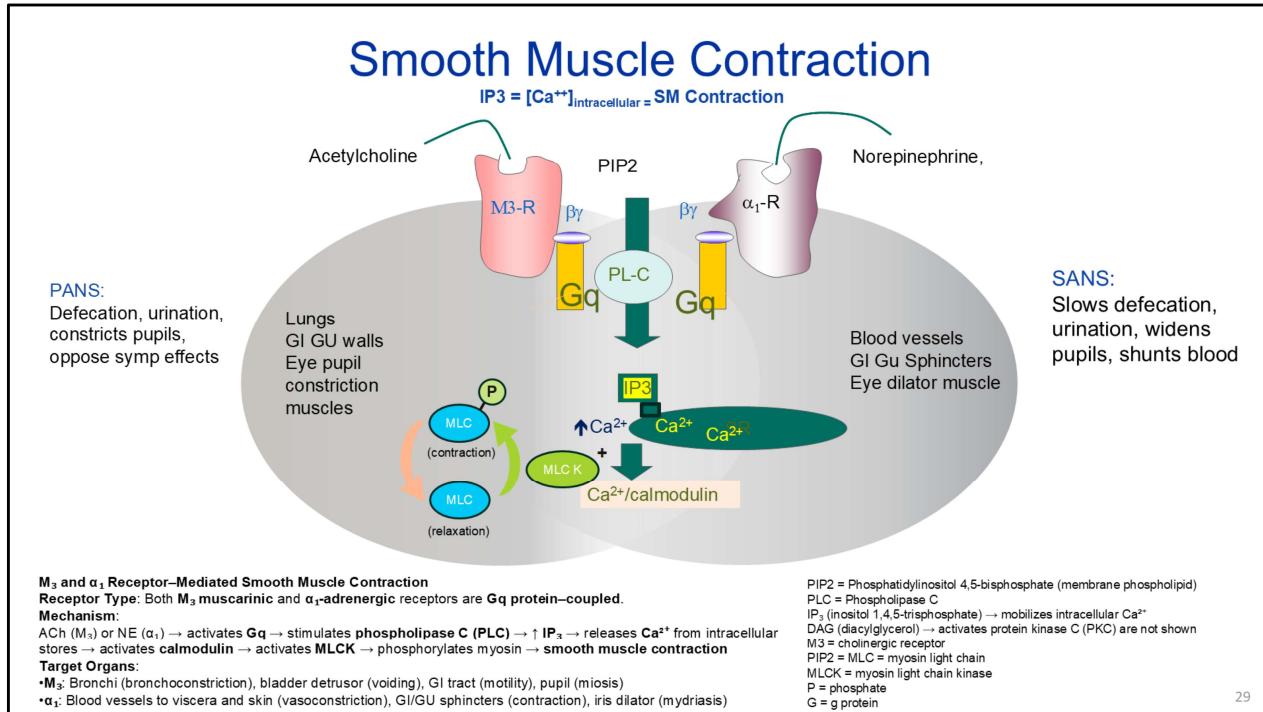
Liver

Neuronal Alpha-2



Control of Organ Function





Related Objectives:

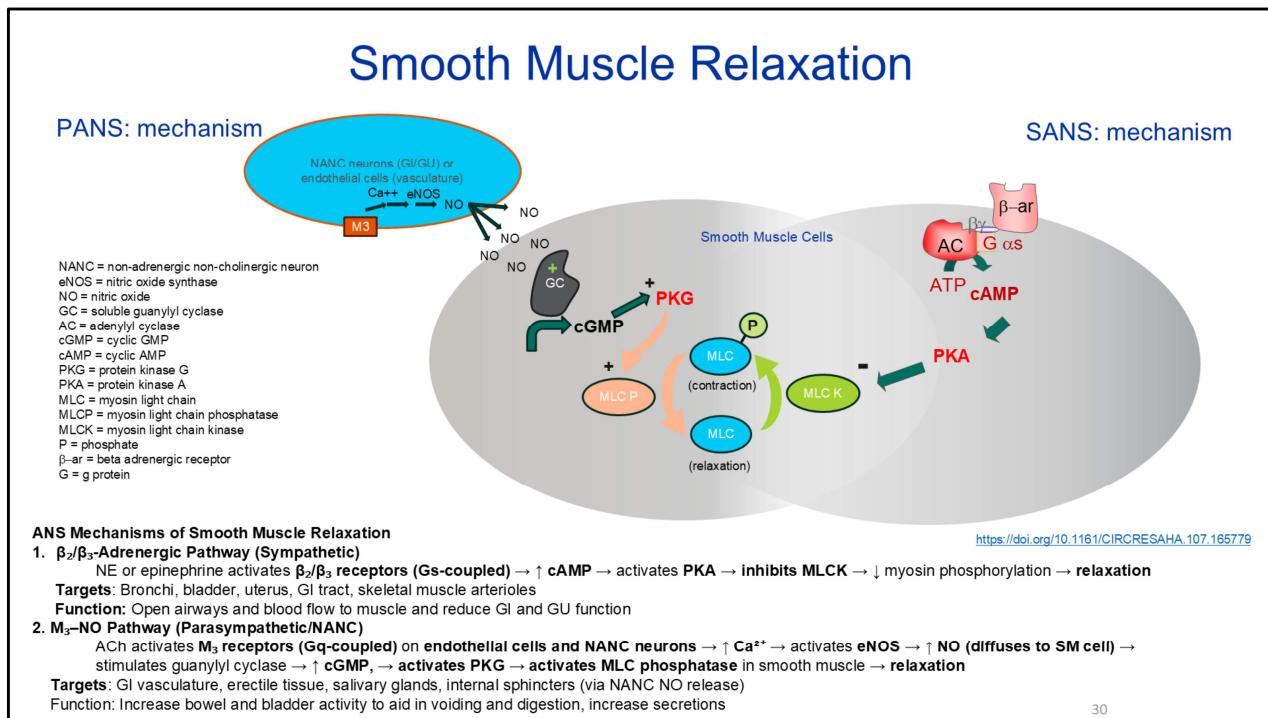
Know the receptors involved, their location, organ effects and intracellular cascades.

Receptor location as summarized in table 6-2, 6-3, 6-4, and figure 6-1

Receptor intracellular cascades as summarized in tables 7-1 (only peripheral subtypes, M<sub>1,2,3</sub>, N<sub>M,N</sub>), 8-1, 9-1 (only general types, a<sub>1,2</sub>, b<sub>1,2</sub>, D1, 2), and 9-3.

Receptors coupled to the G-protein Gq result in the increase of intracellular calcium.

The rise in intracellular calcium activates smooth muscle contraction by forming a tri-valent-complex with calmodulin that is required to activate myosin light chain kinase (MLCK). When MLCK is activated it phosphorylates myosin light chain allowing contraction of smooth muscle. The rise in intracellular calcium starts with agonist bound receptor activated the Gq. Gq, in turn, activates phospholipase C which cleaves a membrane lipid (phosphoinositide bis phosphate, PIP<sub>2</sub>) into the sugar (inositol tris-phosphate, IP<sub>3</sub>) and diacylglycerol (not shown). IP<sub>3</sub> binds to receptors on the specialized endoplasmic reticulum responsible for storing calcium (sarcoplasmic reticulum, SR). IP<sub>3</sub> binding results in opening of calcium channels and the release of calcium into the intracellular compartment.



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### Related Objectives:

Know the receptors involved, their location, organ effects and intracellular cascades.

Receptor location as summarized in table 6-2, 6-3, 6-4, and figure 6-1

Receptor intracellular cascades as summarized in tables 7-1 (only peripheral subtypes,  $M_{1,2,3}, N_{M,N}$ ), 8-1, 9-1 (only general types,  $a_{1,2}$ ,  $b_{1,2}$ , D1, 2), and 9-3.

### Smooth muscle relaxation:

There are two mechanisms to produce smooth-muscle-relaxation.

- 1) Direct: S-ANS-induced bladder and gut wall relaxation decreases unnecessary GI and GU functions. Vasodilation of vessels located in the skeletal muscle increases blood flow to this tissue and bronchiole-smooth muscle-relaxation increases oxygen exchange. S-ANS-mediated relaxation occurs when released NE activates **beta-adrenergic-receptor-mediated phosphorylation of myosin-light-chain-kinase (MLCK)**. In smooth muscle phosphorylation of myosin light chain (MLC) by MLCK is required for contraction (key difference from

cardiac and skeletal muscle). MLC-kinase has multiple phosphorylation sights in which some activate and some inhibit MLCK function.

Phosphorylation of MLCK by PKA occurs on an inhibitory site that leads to inactivation of MLCK. Remember: without MLCK activation the smooth muscle cells are unable to contract.

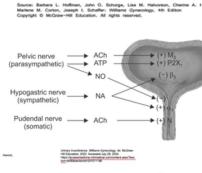
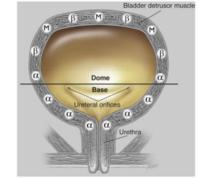
- 2) Indirect (P-ANS): Smooth muscle relaxation is produced via activation of nitrous oxide (**NO**). NO is released when muscarinic receptors are activated on adjacent nerves or endothelial cells. NO activates guanylyl cyclase and produces increases in intracellular cGMP. The cGMP cascades leads to opening of potassium channels and the activation of a phosphatase that dephosphorylates ML-chain. Both events lead to relaxation.

M-R on nerve or endothelial cells produces and release nitric oxide (NO). NO diffuses into smooth muscle cell.

(NO → ↑GC → ↑cGMP → ↑Phosphatase → inactivates ML-chain via removal of MLC-phosphate from myosin → muscle relaxation)

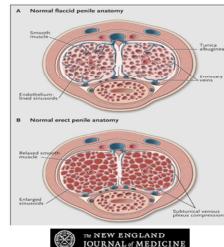
## Beta-2 and Beta-3 Agonist

Drug Name	Receptor Target	Location of Action	Clinical Use	Route of Administration	Side Effects
Albuterol	$\beta_2$	Bronchial smooth muscle	Acute bronchospasm in asthma and COPD, hyperkalemia	Inhaled	Tremor, tachycardia, hypokalemia
Levalbuterol			Acute bronchospasm (fewer side effects vs. racemic albuterol)		Similar to albuterol, possibly reduced tremor
Salmeterol			Maintenance therapy in asthma/COPD (LABA)		Tachycardia, tremor, paradoxical bronchospasm
Formoterol			Maintenance therapy in asthma/COPD (LABA)		Tachycardia, tremor, paradoxical bronchospasm
Indacaterol			Once-daily maintenance in COPD (ultra-LABA)		Cough, nasopharyngitis
Olodaterol			Once-daily maintenance in COPD (ultra-LABA)		Cough, nasopharyngitis
Terbutaline		Uterine and bronchial smooth muscle	Preterm labor (tocolysis), asthma	Subcutaneous, oral	Tachycardia, hyperglycemia, hypokalemia
Mirabegron	$\beta_3$	Bladder detrusor muscle	Overactive bladder, urinary urgency	Oral	Hypertension, nasopharyngitis, urinary retention
Vibegron		Bladder detrusor muscle	Overactive bladder	Oral	Headache, diarrhea, nasopharyngitis



## Phosphodiesterase Inhibitors

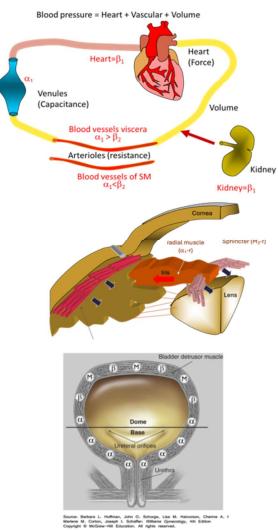
PDE Inhibitor	PDE Isoform Targeted	Location of Action	Clinical Use	Route of Administration	Side Effects
Sildenafil	PDE5	Corpus cavernosum, pulmonary vasculature	Erectile dysfunction, pulmonary arterial hypertension	Oral	Headache, flushing, dyspepsia, visual disturbances
Tadalafil	PDE5	Corpus cavernosum, pulmonary vasculature	Erectile dysfunction, BPH, pulmonary arterial hypertension	Oral	Back pain, dyspepsia, flushing, myalgia
Vardenafil	PDE5	Corpus cavernosum	Erectile dysfunction	Oral	Headache, flushing, rhinitis
Avanafil	PDE5	Corpus cavernosum	Erectile dysfunction	Oral	Flushing, headache, nasal congestion
Mirinone	PDE3	Heart and vascular smooth muscle	Acute heart failure (short-term IV use)	IV	Arrhythmias, hypotension, thrombocytopenia
Amrinone	PDE3	Heart and vascular smooth muscle	Acute heart failure (less used now)	IV	Arrhythmias, hypotension, liver toxicity
Roflumilast	PDE4	Lung tissue, immune cells	Severe COPD	Oral	Weight loss, GI upset, psychiatric effects
Theophylline	Non-selective (mainly PDE4)	Airways, inflammatory cells	Asthma, COPD (rarely used)	Oral	Nausea, tremor, insomnia, arrhythmias
Cilostazol	PDE3	Platelets, vascular smooth muscle	Intermittent claudication	Oral	Headache, palpitations, bleeding risk
Pentoxifylline	Non-selective	RBCs, vascular endothelium	Chronic peripheral vascular disease	Oral	GI upset, dizziness, hypotension
Apremilast	PDE4	Immune cells (T cells, monocytes), skin, joints	Psoriatic arthritis, plaque psoriasis, Behcet's disease (oral ulcers)	Oral	GI upset (nausea, diarrhea), headache, weight loss, depression
Roflumilast	PDE4	Lung tissue, immune cells	Severe COPD with chronic bronchitis, reduces inflammatory burden	Oral	Weight loss, GI upset, psychiatric effects (e.g., depression, insomnia)



PDE Type	Primary Substrate	Tissue Location
PDE3	cAMP >> cGMP	Heart, platelets, vascular smooth muscle
PDE4	cAMP	Immune cells, airway epithelium, brain
PDE5	cGMP	Corpus cavernosum, pulmonary vasculature, platelets

## Alpha-1 receptor agonist

Drug Name	Receptor Target	Location of Action	Clinical Use	Route of Administration	Side Effects
Phenylephrine	$\alpha_1$	Vascular smooth muscle (arterioles, nasal mucosa)	Nasal decongestant, hypotension, mydriasis (without cycloplegia)	Oral, IV, topical (nasal, ophthalmic)	Hypertension, reflex bradycardia, rebound congestion, possible urinary retention
Midodrine	$\alpha_1$	Vascular smooth muscle (arterioles, venous system)	Orthostatic hypotension	Oral	Supine hypertension, piloerection, potential urinary and retention
Methoxamine	$\alpha_1$	Vascular smooth muscle	Hypotension during anesthesia (rare use)	IV	Bradycardia (reflex), hypertension, potential urinary retention
Norepinephrine	$\alpha_1, \alpha_2, \beta_1$	Vascular smooth muscle, heart	Acute hypotension, septic shock	IV	Arrhythmias, ischemia, extravasation necrosis
Epinephrine	$\alpha_1, \alpha_2, \beta_1, \beta_2$	Heart, vasculature, lungs	Anaphylaxis, cardiac arrest, severe asthma	IV, IM, SC, inhaled	Tachycardia, hypertension, arrhythmias, anxiety
Dopamine (high dose)	$\alpha_1, \beta_1$ (at high doses)	Heart, vasculature	Shock (with low cardiac output)	IV	Tachycardia, ischemia, nausea
Oxymetazoline	$\alpha_1$ (partial $\alpha_2$ activity)	Nasal mucosa, conjunctival vessels	Nasal congestion, eye redness	Topical (nasal, ophthalmic)	Rebound congestion (rhinitis medicamentosa), possible urinary retention
Ephedrine	$\alpha_1, \beta_1, \beta_2$	Heart, vasculature, bronchi	Nasal decongestant, hypotension, bronchospasm	Oral, IM, IV	Hypertension, tachyphylaxis, CNS stimulation



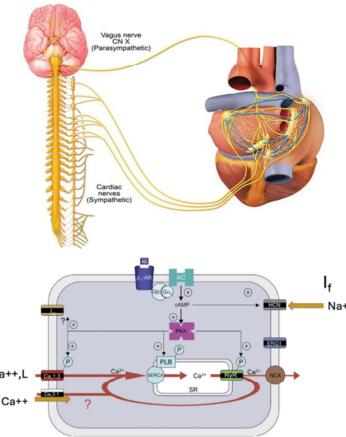
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## Alpha 1 Antagonists

Drug Name	Selectivity	Clinical Use	Side Effects
Prazosin	Alpha-1 selective	Hypertension, PTSD-associated nightmares	First-dose orthostatic hypotension, dizziness
Terazosin	Alpha-1 selective	Hypertension, BPH	Dizziness, fatigue, nasal congestion
Doxazosin	Alpha-1 selective	Hypertension, BPH	Hypotension, reflex tachycardia
Tamsulosin	Alpha-1A selective	Benign prostatic hyperplasia (BPH)	Ejaculatory dysfunction, hypotension
Alfuzosin	Alpha-1A selective	Benign prostatic hyperplasia (BPH)	Dizziness, headache
Silodosin	Alpha-1A selective	Benign prostatic hyperplasia (BPH)	Retrograde ejaculation, dizziness
Phenoxybenzamine	Non-selective (alpha-1 and alpha-2)	Pheochromocytoma (preoperative)	Orthostatic hypotension, reflex tachycardia
Phentolamine	Non-selective (alpha-1 and alpha-2)	Pheochromocytoma (diagnostic or intraoperative use)	Reflex tachycardia, GI upset

## Beta-1 Agonist

Drug Name	Receptor Target	Location of Action	Clinical Use	ROA	Side Effects
Dobutamine	$\beta_1 > \beta_2$ (some $\alpha_1$ activity)	Heart (myocardium, SA and AV nodes)	Cardiogenic shock, acute heart failure, stress echocardiography	IV	Tachycardia, arrhythmias, hypertension
Dopamine (moderate dose)	$\beta_1$ (at moderate doses), $\alpha_1/\beta_2$ at higher doses	Heart ( $\beta_1$ ), vasculature ( $\alpha_1$ at higher doses)	Shock with bradycardia or low cardiac output	IV	Tachycardia, arrhythmias, ischemia (dose-dependent)
Isoproterenol	$\beta_1 = \beta_2$ (non-selective $\beta$ agonist)	Heart, bronchial smooth muscle, vasculature	Bradycardia, heart block, rarely for asthma	IV	Palpitations, hypotension, tachycardia
Epinephrine	$\alpha_1, \alpha_2, \beta_1, \beta_2$ (non-selective adrenergic agonist)	Heart, vasculature, lungs	Cardiac arrest, anaphylaxis, severe asthma	IV, IM, SC, inhaled	Hypertension, arrhythmias, anxiety, tremor



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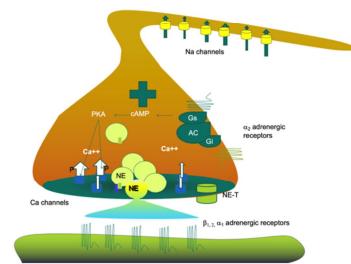
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## Beta Receptor Antagonist

Drug Name	Category	Intrinsic Sympathomimetic Activity (ISA)	Beta-1 Selective	Clinical Use	Side Effects
Acebutolol	Beta blocker with ISA	Yes	Partial	Hypertension in patients with bradycardia	Fatigue, bradycardia, mild CNS effects
Pindolol	Beta blocker with ISA	Yes	No	Mild hypertension, rarely used	Bradycardia, fatigue, less CNS depression
Carteolol	Beta blocker with ISA	Yes	Partial	Ophthalmic use for glaucoma	Local ocular irritation
Atenolol	Beta-1 selective	No	Yes	Hypertension, angina, post-MI	Bradycardia, fatigue, cold extremities
Metoprolol	Beta-1 selective	No	Yes	Heart failure, post-MI, hypertension	Bradycardia, hypotension, dizziness
Esmolol	Beta 1 selective	No	Yes	Acute supraventricular arrhythmias	Hypotension, bradycardia, short duration
Bisoprolol	Beta-1 selective	No	Yes	Heart failure, hypertension	Bradycardia, fatigue
Betaxolol	Beta-1 selective	No	Yes	Glaucoma	Blurred vision, eye discomfort
Propranolol	Non-selective	No	No	Hypertension, migraine prophylaxis, essential tremor	Depression, fatigue, bronchospasm
Nadolol	Non-selective	No	No	Long-term hypertension management	Fatigue, bradycardia
Timolol	Non-selective	No	No	Glaucoma	Eye irritation, bradycardia
Sotalol	Non-selective	No	No	Ventricular arrhythmias	QT prolongation, torsades de pointes
Carvedilol	Non-selective (also alpha-1)	No	No	Heart failure, hypertension	Orthostatic hypotension, dizziness
Labetalol	Non-selective (also alpha-1)	No	No	Hypertensive emergencies, pregnancy	Orthostatic hypotension, dizziness, hepatotoxicity

## Alpha 2 Agonist

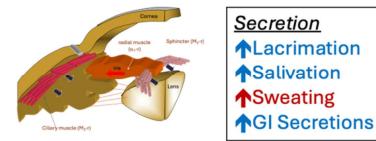
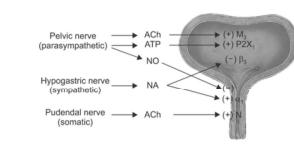
Alpha-2 Agonist	Location of Action	Clinical Use	Route of Administration	Side Effects
Clonidine	CNS (brainstem), peripheral sympathetic nerves	Hypertension, ADHD, withdrawal syndromes (opioid, alcohol, nicotine)	Oral, transdermal	Sedation, dry mouth, bradycardia, rebound hypertension if stopped abruptly
Dexmedetomidine	Locus coeruleus, spinal cord	Sedation in ICU and procedural settings	IV	Hypotension, bradycardia, dry mouth, sedation
Tizanidine	Spinal cord (presynaptic α2 receptors)	Muscle spasticity, multiple sclerosis	Oral	Drowsiness, dry mouth, hypotension, hepatotoxicity (rare)
Guanfacine	Prefrontal cortex, brainstem	ADHD (non-stimulant), hypertension	Oral	Sedation, dry mouth, hypotension
Methyldopa	CNS (converted to active form α-methylnorepinephrine)	Hypertension during pregnancy	Oral	Sedation, hemolytic anemia (rare), orthostatic hypotension
Brimonidine	Ciliary body (eye)	Open-angle glaucoma	Topical (ophthalmic)	Ocular irritation, dry eyes, allergic conjunctivitis
Apraclonidine	Ciliary body (eye)	Short-term IOP reduction after laser procedures	Topical (ophthalmic)	Eye discomfort, allergic reactions, dry mouth



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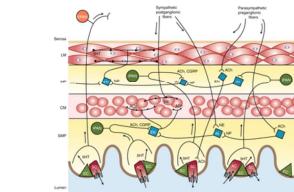
## Muscarinic Agonists

Drug Name	Receptor Target	Location of Action	Clinical Use	Route of Administration	Side Effects
Bethanechol	Muscarinic (M3 >> M2)	Bladder detrusor muscle, GI smooth muscle	Urinary retention, neurogenic bladder	Oral	Diarrhea, sweating, salivation, urinary urgency, hypotension
Pilocarpine	Muscarinic (non-selective)	Lacrimal, salivary glands, ciliary muscle	Glaucoma, xerostomia (e.g., in Sjögren's)	Topical (ocular), oral	Lacrimation, sweating, salivation, bradycardia, bronchospasm
Cevimeline	Muscarinic (M3 selective)	Salivary and lacrimal glands	Dry mouth in Sjögren's syndrome	Oral	Sweating, nausea, rhinitis, increased urinary frequency
Carbachol	Muscarinic (non-selective), some nicotinic	Eye (ciliary muscle, iris sphincter)	Glaucoma (topical)	Topical (ocular)	Miosis, decreased night vision, brow ache
Methacholine	Muscarinic (non-selective)	Airway smooth muscle	Bronchial hyperreactivity test (diagnostic)	Inhaled	Bronchospasm, hypotension, bradycardia



**Secretion**

- ↑Lacrimation
- ↑Salivation
- ↑Sweating
- ↑GI Secretions



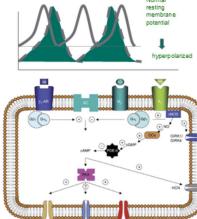
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## Acetylcholine Esterase Inhibitors

Drug Name	Mechanism / Type	Location of Action	Clinical Use	Route of Administration	Side Effects
Neostigmine	Reversible AChE inhibitor (quaternary amine)	NMJ, peripheral synapses (does not cross BBB)	Myasthenia gravis, reversal of neuromuscular blockade, urinary retention	IV, IM, oral	Bradycardia, diarrhea, abdominal cramping, salivation
Pyridostigmine	Reversible AChE inhibitor (quaternary amine)	NMJ, peripheral synapses (does not cross BBB)	Myasthenia gravis, prophylaxis against nerve agent exposure	Oral, IV	Similar to neostigmine; muscle cramps, GI upset
Physostigmine	Reversible AChE inhibitor (tertiary amine, crosses BBB)	Central and peripheral synapses (crosses BBB)	Anticholinergic toxicity (e.g., atropine overdose)	IV, IM	Seizures (CNS penetration), bradycardia, GI upset
Edrophonium	Short-acting AChE inhibitor	NMJ (short-acting, peripheral)	Diagnosis of myasthenia gravis (Tensilon test)	IV	Bradycardia, syncope, rarely used now
Donepezil	Reversible CNS-selective AChE inhibitor	CNS (basal forebrain, cortex)	Alzheimer's disease	Oral	Nausea, diarrhea, insomnia, bradycardia
Rivastigmine	Reversible CNS AChE and butyrylcholinesterase inhibitor	CNS and periphery	Alzheimer's disease, Parkinson's dementia	Oral, transdermal	GI upset, dizziness, weight loss
Galantamine	Reversible AChE inhibitor, also modulates nicotinic receptors	CNS	Alzheimer's disease	Oral	GI upset, bradycardia, dizziness

## Muscarinic and Nicotinic Antagonists

Drug Name	Class	Location of Action	Clinical Use	ROA	Side Effects
Atropine		Heart, eye, salivary glands, GI tract	Bradycardia, mydriasis, cholinergic toxicity	IV, IM, ophthalmic, oral, IV	Dry mouth, tachycardia, urinary retention, blurred vision
Scopolamine	Muscarinic antagonist	CNS (vestibular nuclei), salivary glands	Motion sickness prevention	Transdermal, oral, IV	Sedation, dry mouth, blurred vision, confusion (elderly)
Glycopyrrrolate	Muscarinic antagonist 4 amine	Peripheral muscarinic sites (does not cross BBB)	Pre-op secretion reduction, bradycardia prevention	IV, IM	Dry mouth, urinary retention, minimal CNS effects
Oxybutynin	Muscarinic antagonist (M3)	Bladder detrusor muscle, CNS	Overactive bladder, urinary incontinence	Oral, transdermal	Dry mouth, constipation, blurry vision, CNS effects
Tolterodine		Bladder detrusor muscle	Overactive bladder	Oral	Dry mouth, constipation, headache
Ipratropium	Muscarinic antagonist 4 amine	Bronchial smooth muscle	COPD, asthma (acute bronchodilation)	Inhaled	Dry mouth, cough, throat irritation
Tiotropium		Bronchial smooth muscle (long-acting)	COPD, asthma (long-acting maintenance)	Inhaled	Dry mouth, urinary retention, minimal systemic effects
Benztropine	Muscarinic antagonist (CNS-penetrant)	CNS (striatum), peripheral muscarinic receptors	Parkinsonism, drug-induced extrapyramidal symptoms	Oral	Dry mouth, blurred vision, confusion, urinary retention
Trihexyphenidyl		CNS (basal ganglia)	Parkinson disease	Oral	Cognitive impairment, dry mouth, dizziness
Mecamylamine	Ganglionic blocker (nicotinic)	Autonomic ganglia (nicotinic receptors)	Hypertensive crisis (off-label), tobacco cessation (investigational)	Oral	Orthostatic hypotension, constipation, dry mouth
Hexamethonium		Autonomic ganglia (historical, no longer used)	Hypertension (obsolete)	IV (historic)	Severe hypotension, constipation, blurred vision
Tubocurarine	Non-depolarizing neuromuscular blocker	Neuromuscular junction	Muscle relaxation during surgery	IV	Histamine release, hypotension, prolonged blockade
Rocuronium		Neuromuscular junction	Rapid-onset muscle paralysis for intubation	IV	Hypotension, minimal histamine release, fast onset
Succinylcholine	Depolarizing neuromuscular blocker	Neuromuscular junction	Rapid paralysis, short procedures	IV	Hyperkalemia, malignant hyperthermia, bradycardia



**Secretion**

- ↑Lacration
- ↑Salivation
- ↑Sweating
- ↑GI Secretions

Neuromuscular junction (skeletal muscle)  
Autonomic ganglia (post-synaptic neurons), adrenal medulla  
Lipid-gated ion channel  
Na<sup>+</sup>/K<sup>+</sup> influx → depolarization  
Skeletal muscle contraction  
Autonomic transmission, catecholamine release from adrenal medulla



## Case study

Review of ANS function

**Immediate signs and symptoms of ??? exposure**

- People may not know they were exposed to ??? because it has no odor.
- People exposed to a low or moderate dose of ??? by inhalation, ingestion (swallowing), or skin absorption may experience some or all of the following symptoms within seconds to hours of exposure:
  - Abnormally low or high blood pressure
  - Blurred vision
  - Chest tightness
  - Confusion
  - Cough
  - Diarrhea
  - Drooling and excessive sweating
  - Drowsiness
  - Eye pain
  - Headache
  - Increased urination
  - Nausea, vomiting, and/or abdominal pain
  - Rapid breathing
  - Runny nose
  - Slow or fast heart rate
  - Small, pinpoint pupils
  - Watery eyes
  - Weakness
- Even a tiny drop of nerve agent on the skin can cause sweating and muscle twitching where the agent touched the skin.
- Exposure to a large dose of ??? by any route may result in these additional health effects:
  - Convulsions
  - Loss of consciousness
  - Paralysis
  - Respiratory failure possibly leading to death
- Showing these signs and symptoms does not necessarily mean that a person has been exposed to ???.



<https://emergency.cdc.gov/agent/vx/basics/facts.asp>

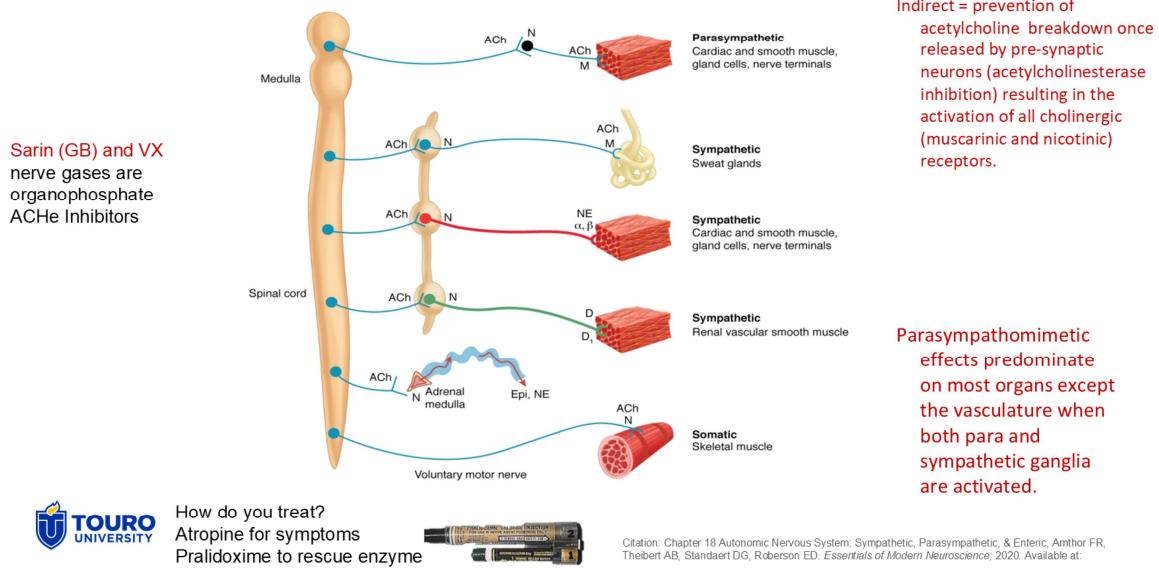
What is the likely diagnosis?

What pathways are involved in this patient's pathology?

What are the antidotes and their mechanism of action?

What adverse events are associated with this treatment?

## Cholinesterase Inhibitors Poisoning



Know pharmacodynamic differences between direct-acting and indirect-acting cholinomimetic agents

List major signs and symptoms of AChE inhibitor poisoning

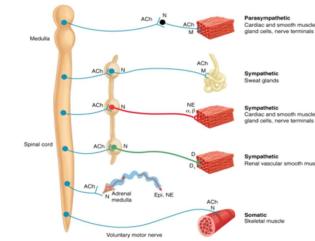
Direct = muscarinic agonist. Muscarinic receptors are located on smooth muscle, endothelium, and cardiac muscle.

Indirect = prevention of acetylcholine breakdown once released by pre-synaptic neurons (acetylcholinesterase inhibition). Increased synaptic acetylcholine will produce a post-synaptic receptor activation (nicotinic and muscarinic) at all junctions that release ACh (neuromuscular junction, parasympathetic, and sympathetic ganglion, as well as, neuronal-organ synapses).

When activated equally (nicotinic receptors on both parasympathetic and sympathetic post-synaptic ganglionic neurons) the parasympathetic effects predominate on most organs except for the vasculature. There is no direct innervation of the vasculature by the parasympathetic system. Sympathetic response to the vasculature is to produce vasoconstriction. Parasympathetic effects on the other organs include ↑bowel movement, bronchoconstriction, urination, miosis, bradycardia, lacrimation, sweating and salivation.

**Table 1.** Details on Five Pesticide Classes

Pesticide Class	Example Compound	Use	Some Symptoms of Acute Pesticide Poisoning <sup>35</sup>	Function
Carbamates	carbofuran	Control of aphids, beetles and weevils in alfalfa and corn	Malaise, weakness, dizziness, sweating, headache, salivation, nausea, and vomiting.	Reversible inhibition of acetyl-cholinesterase affecting neuromuscular functions. <sup>34</sup>
Organochlorine compounds	chlordane	Formerly used for residential termite control. No longer approved for use in the United States.	Excitability, dizziness, headache, restlessness, tremors, and convulsions.	Interferes with the functioning of the nerve cell membranes. <sup>35</sup>
Organophosphates	chlorpyrifos	Formerly used for residential termite control. Currently used on a variety of food and feed crops to control spiders and mites.	Headache, dizziness, weakness, anxiety, excessive sweating, vomiting, diarrhea, and abdominal cramps,	Inhibits acetyl-cholinesterase which affects neuromuscular functions and is more difficult to reverse than carbamates <sup>36</sup>
Pyrethrins/ Pyrethroids	Pyrethrum	Used to control insects and is present in veterinary flea powders for cats and dogs.	Allergic reactions, dermatitis, wheezing, seizures, coma, breathing difficulties, diarrhea, and abdominal pain	Interferes with the functioning of the nerve cell membrane. Pyrethroid is the manmade version of pyrethrin. Pyrethrin is made from the flowers of chrysanthemums. <sup>37</sup>



**Toxicity**  
 Diarrhea  
 Urination  
 Miosis  
 Bronchospasm  
 Bradycardia  
 Excitation of skeletal muscle and CNS  
 Lacrimation  
 Sweating  
 Salivation

DUMBBELSS



[https://www.cdc.gov/pictureofamerica/pdfs/picture\\_of\\_america\\_poisoning.pdf](https://www.cdc.gov/pictureofamerica/pdfs/picture_of_america_poisoning.pdf)



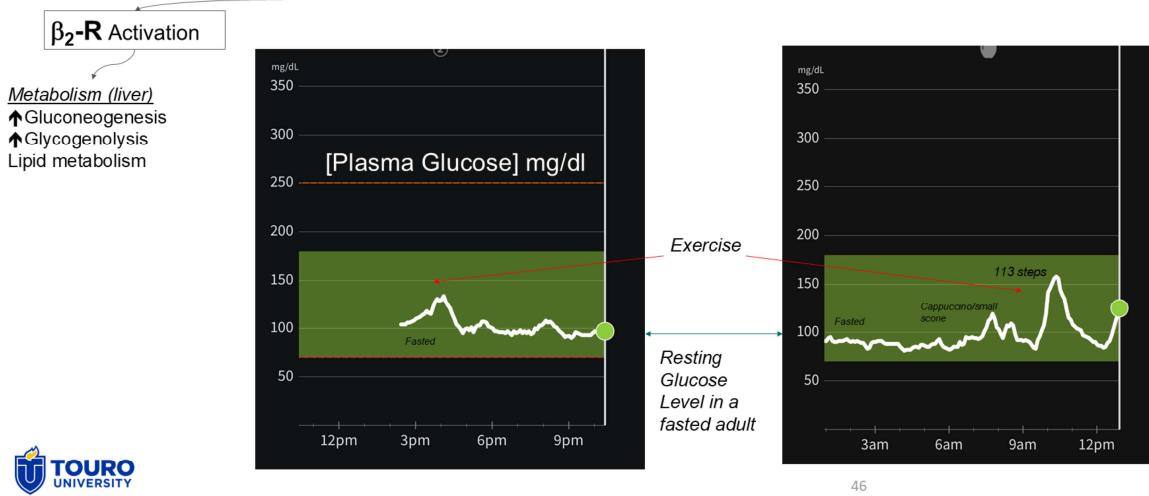
## CASE STUDY

### PATIENT GGG

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## Autonomic Control of Liver Glucose Production

### Norepinephrine



Related Objectives:

- Know the effects of both norepinephrine and acetylcholine in peripheral homeostatic regulation.
- Know in general the role of ANS in the regulatory control of organ function. Have a strong understanding of the normal parasympathetic and sympathetic effects on organ function.

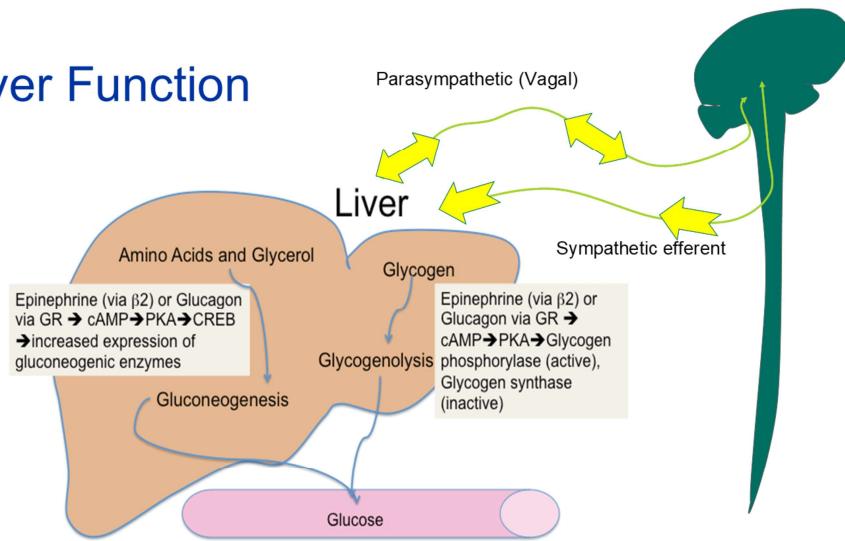
## Liver Innervation and the Neural Control of Hepatic Function

By Takashi Shimazu

Control of glucose metabolism in the liver is a complex coordination between blood glucose detection, circulating hormones, and central control of ANS function. Blood glucose levels are primarily controlled during fasting by glucagon and cortisol to induce gluconeogenic enzymes and repress glycolytic enzymes to increase blood glucose levels. During feeding, insulin is released to induce glycolytic enzymes and repress gluconeogenic enzymes. The autonomic nervous system

can be segregated into sympathetic efferents traveling down the splanchnic nerve to increase gluconeogenesis and glycolysis. The parasympathetic has both a afferent (sensory) and efferent component that senses changes in osmolarity and can decrease hepatic glucose output. When needed the sympathetic neurons can increase blood glucose via activation of glycogen breakdown. During this process, norepinephrine or circulating epinephrine activates beta 2 receptors resulting in cAMP-induced activation of PKA which in turn phosphorylates and activates glycogen phosphorylase (increases glycogen breakdown) and inhibits glycogen synthase (decreases glycogen synthesis). Continued need for blood glucose will also result in increased gluconeogenesis by increasing the gene expression of gluconeogenic synthetic enzymes. Both glycogenolysis and gluconeogenesis are stimulated by sympathetic ANS activation of beta-2 receptors and provide a necessary increase in blood glucose when needed and protect against hypoglycemia when reserves are depleted or when produced by anti-diabetic medication use. Energy Metabolism in the Liver, Rui, Compr Physiol. 2014 January ; 4(1): 177–197, Liver Innervation and the Neural Control of Hepatic Function, Takashi Shimazu

## ANS/Liver Function



The SANS increases hepatic glucose production during stress or increased activity. Norepinephrine, acting primarily via  $\beta_2$ -adrenergic receptors, activates the Gs protein-cAMP-PKA pathway, which stimulates glycogenolysis (glycogen breakdown) and gluconeogenesis (new glucose synthesis). This ensures a rapid increase in circulating glucose to fuel muscle and brain activity.

In contrast, the PANS, through acetylcholine acting on muscarinic receptors, has a more modulatory or permissive role in liver function, primarily during rest and feeding states. While not directly promoting glucose release, parasympathetic input supports pancreatic insulin secretion and liver glycogen synthesis, helping to restore or store glucose postprandially. Thus, parasympathetic withdrawal and sympathetic dominance during stress tip the balance toward hepatic glucose output.

Exp Mol Med. 2022 Apr;54(4):370–376.

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**Thank You . Have Fun!**

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**Office Hours TBA depending on optimal time for class.**

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**Good Luck**