Autonomic nervous system
The Autonomic Nervous System

Autonomic - from the Greek for "self-governing," functioning independently of the will (Langley, 1898)

The **ANS coordinates** cardiovascular, respiratory, digestive, excretory and reproductive systems

- **Visceral afferents** as well as from those parts of the CNS that control the viscera and other autonomic functions.

- **Visceral efferents** (general visceral division of the PNS):
  - Innervates smooth muscle, cardiac muscle, and glands
  - Regulates visceral functions
    - Heart rate, blood pressure, digestion, urination

- rapidity and intensity in changing visceral functions:
  - within 3-5 sec. it can increase 2x the HR
  - within 10-15 sec. the arterial pressure can be doubled

The ANS has three divisions: **sympathetic, parasympathetic**, and **enteric**.

**Sympathetic** and **parasympathetic** normally exert **antagonistic effects** on many of the same target organs.

**Enteric** ANS is a system of afferent neurons, interneurons, and motor neurons that form networks of neurons called **plexuses** that surround GIT; function as a separate and independent nervous system, but it is normally controlled by the CNS through sympathetic and parasympathetic fibers.
CNS
Brain and spinal cord

PNS
Cranial nerves and spinal nerves

Sensory (afferent) division

Somatic sensory
General: Touch, pain, pressure, vibration, temperature, and proprioception in skin, body wall, and limbs
Special: Hearing, equilibrium, vision, smell

Visceral sensory
General: Stretch, pain, temperature, chemical changes, and irritation in viscera; nausea and hunger
Special: Taste

Motor (efferent) division

Somatic motor
General: Motor innervation of all skeletal muscles

Visceral motor
General: Motor innervation of smooth muscle, cardiac muscle, and glands; equivalent to autonomic nervous system (ANS)

Parasympathetic division
Sympathetic division
Comparison of Autonomic and Somatic Motor Systems

- **Somatic motor system**
  - *One motor neuron* extends from the CNS to skeletal muscle:
    - *voluntary*, direct synapse, *excitatory (Ach)*
    - Axons are well *myelinated*, conduct impulses rapidly

- **Autonomic nervous system**
  - Chain of *two motor neurons:*
    - *Involuntary*, disynaptic (Preganglionic /Postganglionic neurons), *excitatory and inhibitory*
    - Smooth muscle and cardiac muscle
  - Conduction is slower due to *thinly or unmyelinated* axons
Motor pathways of the somatic & autonomic nervous system
Basic Structure of a Visceral Reflex

Visceral reflex:
- Visceral sensory and autonomic neurons
- Participate in visceral reflex arcs
  - **PS reflexes** include: gastric and intestinal reflexes, defecation, urination, direct light reflexes, swallowing reflex, coughing reflex, baroreceptor reflex and sexual arousal.
  - **S reflexes**: cardioaccelaratory reflex, vasomotor reflex, pupillary reflex and ejaculation in males.
Divisions of the Autonomic Nervous System

• Sympathetic and parasympathetic divisions
  • Innervate mostly the same structures
  • *Most blood vessels* are innervated only by *sympathetic* nerves. *PS activity* dominates the *heart* and *GI tract*.
  • The two ANS divisions exert cooperative effects on the external genitalia.
  • Cause *opposite* effects

  • **Sympathetic** – wide spread, long-lasting mobilization of the “fight, flight, or fright” response
    - Activated during exercise, excitement, and emergencies
  • **Parasympathetic** effects are highly localized and short lived: “rest and digest”
    - Concerned with conserving energy
Sympathetic nervous system:
- Dilates pupils
- Speeds heart rate
- Speeds breathing
- Inhibits digestion
- Produces sweaty palms

Parasympathetic nervous system:
- Contracts pupils
- Slows heart rate
- Slows breathing
- Stimulates digestion
- Dries palms
Anatomical Differences in Sympathetic and Parasympathetic Divisions

• S&PS originate from different regions of the CNS
  – Sympathetic /thoracolumbar division
  – Parasympathetic /craniosacral division

• S&PS anatomical differences
  -Length of postganglionic fibers
    – S: long postganglionic fibers
    – PS: short postganglionic fibers
  -Branching of axons
    – S: highly branched, influences many organs
    – PS: few branches, localized effect
Anatomical Differences in Sympathetic and Parasympathetic Divisions

(a) Sympathetic pathway

(b) Parasympathetic pathway
Neurotransmitters of Autonomic Nervous System

- Neurotransmitter released by preganglionic axons
  - Acetylcholine for both S&PS branches (cholinergic)
- Neurotransmitter released by postganglionic axons
  - Sympathetic – most release norepinephrine (adrenergic), also neuropeptide Y and ATP.
  - Parasympathetic – release acetylcholine, also neuropeptides (VIP)
Autonomic postganglionic neurons can change their transmitters phenotype!

Some ANS neurons can change their transmitter phenotypes under appropriate environmental conditions, demonstrated both in vitro and in vivo – phenotypic switching/plasticity:

– During development (e.g. innervation of sweat glands by S postganglionic neurons that are cholinergic)
– Postganglionic cells grown in vitro in the presence of heart conditioned medium changed from an adrenergic to a cholinergic phenotype.
Secretion of Acetylcholine and Norepinephrine by Postganglionic Nerve Endings

• Many of the PS nerve fibers and almost all the S fibers connect with the effector cells or terminate in connective tissue located adjacent to the target cells.

• Postganglionic fibers present bulbous enlargements = varicosities, where transmitter vesicles of Ach or NE are synthesized and stored.

• Also in the varicosities are large numbers of mitochondria that supply ATP, required to energize Ach or NE synthesis.

• AP ➔ depolarization ➔ calcium ions inflow into nerve ➔ transmitter substance is secreted.

• Synthesis of Ach

\[
\text{Acetyl-CoA} + \text{Choline} \xrightarrow{\text{choline acetyltransferase}} \text{Acetylcholine}
\]

Ach ➔ acetate ion and choline, catalyzed by acetylcholinesterase (bound with collagen and glycosaminoglycans in the local connective tissue) ➔ fast end of Ach action.
Synthesis of norepinephrine
-begins in the axoplasm of the terminal adrenergic nerve endings, completed inside the secretory vesicles.

Transport of dopamine into the vesicles

\[
\text{Tyrosine} \xrightarrow{\text{hydroxylation}} \text{Dopa} \\
\text{Dopa} \xrightarrow{\text{decarboxylation}} \text{Dopamine}
\]

In the adrenal medulla, this reaction goes still one step further to transform about 80% of the NE into E:

\[
\text{Dopamine} \xrightarrow{\text{hydroxylation}} \text{Norepinephrine} \\
\text{Norepinephrine} \xrightarrow{\text{methylation}} \text{Epinephrine}
\]

NE is removed from the secretory site by:

1. reuptake into the adrenergic nerve endings by an active transport process (50 - 80%);
2. diffusion away from the nerve endings into the surrounding body fluids and then into the blood - accounting for removal of most of the remaining NE;
3. destruction of small amounts by tissue enzymes (\textit{monoamine oxidase} in the nerve endings, and \textit{catechol-O-methyl transferase}, in all tissues).
Sympathetic Division of the ANS

Sympathetic division (thoracolumbar)

Greater thoracic splanchnic nerve
Lesser thoracic splanchnic nerve
Celiac ganglion
Splanchnic nerves
Superior mesenteric ganglion
Inferior mesenteric ganglion
Inferior hypogastric ganglia

Sympathetic trunk (chain) ganglia
Middle cervical ganglion
Inferior cervical ganglion
Superior cervical ganglion

White rami communicantes

T1, L2

Cardiac and pulmonary plexuses

Eye
Lacrimal gland
Nasal mucosa
Blood vessels; skin (arrector pili muscles and sweat glands)
Salivary glands
Heart
Liver and gallbladder
Stomach
Spleen
Adrenal gland
Kidney
Small intestine
Large intestine
Rectum
Genitalia (uterus, vagina, and penis) and urinary bladder

Midbrain
Pons
Medulla
Signal transmission in ANS

A. Sympathetic

- Preganglion secretes Acetylcholine (Cholinergic)
  - Postganglion – receptor = Nicotinic

- Postganglion secretes Norepinephrine (Adrenergic), NPY, ATP
  - Target (smooth muscle, cardiac muscle, glands)
    Receptor = Adrenergic (α 1,2; β 1,2,3)
    ! **Sweat glands, some blood vessels, piloerector muscle**
      - Preganglion secretes Acetylcholine
      - Postganglion – Nicotinic receptor
      - Postganglion secretes Acetylcholine (Cholinergic/nitroxidergic)
      - Target:
        - sweat gland – muscarinic receptor
        - postganglionic fibers that innervate smooth m. in the small arteries in skeletal muscles and the brain release NO, that promotes vasodilation.

- Stimulation of S division has two distinctive results:
  - release of NE at specific locations
  - secretion of E and NE (4:1) into the general circulation.
  - alpha receptors: activated by NE > E, isoproterenol; blocked by: phenoxybenzamine
  - beta receptors: activated by E; blocked by propranolol
Signal transmission in ANS

B. Parasympathetic

• Preganglion secretes Acetylcholine (Cholinergic)
• Postganglion – receptor = Nicotinic
• Postganglion secretes Acetylcholine, VIP
• Target receptor = muscarinic (smooth muscle, heart, glands)

Outflow via the Vagus Nerve (X)

• Fibers innervate visceral organs of the thorax and most of the abdomen (75%...)
• Stimulates - digestion, reduction in heart rate and blood pressure
• Preganglionic cell bodies
  – Located in dorsal motor nucleus in the medulla
• Ganglionic neurons
  – Confined within the walls of organs being innervated

Sacral Outflow

• Emerges from S₂⁻S₄
• Innervates organs of the pelvis and lower abdomen
• Preganglionic cell bodies
  – Located in visceral motor region of spinal gray matter
Parasympathetic fibers:
- leave CNS through cranial n. III (pupillary sphincter and ciliary muscle of the eye), VII (lacrimal, nasal, and submandibular glands), IX (parotid gland), X (heart, lungs, esophagus, stomach, entire small intestine, proximal half of the colon, liver, gallbladder, pancreas, kidneys, and upper portions of the ureters);
- additional PS fibers leave the lowermost part of the spinal cord S2-S3 spinal nerves (pelvic nerves) and occasionally S1, S4 nerves (descending colon, rectum, urinary bladder, and lower portions of the ureters).
- about 75% of all PS nerve fibers are in the vagus nerves (cr. N. X), passing to the entire thoracic and abdominal regions of the body.
Sympathetic division

Most target tissues innervated by the sympathetic division have adrenergic receptors. When norepinephrine (NE) binds to adrenergic receptors, some target tissues are stimulated, and others are inhibited. For example, smooth muscle cells in blood vessels are stimulated to constrict, and stomach glands are inhibited.

Sympathetic division

Some sympathetic target tissues, such as sweat glands, have muscarinic receptors, which respond to acetylcholine (ACh). Stimulation of sweat glands results in increased sweat production.

Parasympathetic division

All parasympathetic target tissues have muscarinic receptors. The general response to ACh is excitatory, but some target tissues, such as the heart, are inhibited.
# Signaling Pathways for Nicotinic, Muscarinic, Adrenergic, and Dopaminergic Receptors

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Agonists*</th>
<th>Antagonists</th>
<th>G Protein</th>
<th>Linked Enzyme</th>
<th>Second Messenger</th>
</tr>
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<tbody>
<tr>
<td>N&lt;sub&gt;1&lt;/sub&gt; nicotinic ACh</td>
<td>ACh (nicotine, decamethonium)</td>
<td>d-Tubocurarine, α-bungarotoxin</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>N&lt;sub&gt;2&lt;/sub&gt; nicotinic ACh</td>
<td>ACh (nicotine, TMA)</td>
<td>Hexamethonium</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>M&lt;sub&gt;1&lt;/sub&gt;, M&lt;sub&gt;3&lt;/sub&gt;, M&lt;sub&gt;5&lt;/sub&gt; muscarinic ACh</td>
<td>ACh (muscarine)</td>
<td>Atropine, pirenzepine (M&lt;sub&gt;1&lt;/sub&gt;)</td>
<td>G&lt;sub&gt;α&lt;/sub&gt;&lt;sub&gt;q&lt;/sub&gt;</td>
<td>PLC</td>
<td>IP&lt;sub&gt;3&lt;/sub&gt; and DAG</td>
</tr>
<tr>
<td>M&lt;sub&gt;2&lt;/sub&gt;, M&lt;sub&gt;4&lt;/sub&gt; muscarinic ACh</td>
<td>ACh (muscarine)</td>
<td>Atropine, methoctramine (M&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>G&lt;sub&gt;α&lt;/sub&gt;&lt;sub&gt;i&lt;/sub&gt; and G&lt;sub&gt;α&lt;/sub&gt;&lt;sub&gt;o&lt;/sub&gt;</td>
<td>Adenylyl cyclase</td>
<td>↓ [cAMP]&lt;sub&gt;i&lt;/sub&gt;</td>
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<tr>
<td>α&lt;sub&gt;1&lt;/sub&gt;-Adrenergic</td>
<td>NE ≥ Epi (phenylephrine)</td>
<td>Phentolamine</td>
<td>G&lt;sub&gt;α&lt;/sub&gt;&lt;sub&gt;q&lt;/sub&gt;</td>
<td>PLC</td>
<td>IP&lt;sub&gt;3&lt;/sub&gt; and DAG</td>
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<tr>
<td>α&lt;sub&gt;2&lt;/sub&gt;-Adrenergic</td>
<td>NE ≥ Epi (clonidine)</td>
<td>Yohimbine</td>
<td>G&lt;sub&gt;α&lt;/sub&gt;&lt;sub&gt;i&lt;/sub&gt;</td>
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<td>↓ [cAMP]&lt;sub&gt;i&lt;/sub&gt;</td>
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<td>β&lt;sub&gt;1&lt;/sub&gt;-Adrenergic</td>
<td>Epi &gt; NE (dobutamine, isoproterenol)</td>
<td>Metoprolol</td>
<td>G&lt;sub&gt;α&lt;/sub&gt;&lt;sub&gt;s&lt;/sub&gt;</td>
<td>Adenylyl cyclase</td>
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<tr>
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<td>Epi &gt; NE (terbutaline, isoproterenol)</td>
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<td>SR-59230A</td>
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S/PS Tone....

Normally, the sympathetic and parasympathetic systems are continually active, and the basal rates of activity are known, respectively, as sympathetic tone and parasympathetic tone. The value of tone is that it allows a single nervous system both to increase and to decrease the activity of a stimulated organ.

Ex. vasoconstriction/dilation of the vessels
   background "tone" of the PS in the gastrointestinal tract

Effect of Loss of Sympathetic or Parasympathetic Tone After Denervation.

Immediately after a S/PS nerve is cut, the innervated organ loses its tone.

In the case of the blood vessels, cutting the S nerves results within 5 -30 sec in almost maximal vasodilation. Over minutes, hours, days, or weeks, intrinsic tone in the smooth muscle of the vessels increases-that is, increased tone caused by increased smooth muscle contractile force that is not the result of sympathetic stimulation but of chemical adaptations in the smooth muscle fibers themselves. This intrinsic tone eventually restores almost normal vasoconstriction.

However, in the PS system, the compensation sometimes requires many months. Loss of PS tone to the heart after cardiac vagotomy increases the heart rate to 160 beats /min in a dog, and this will still be partially elevated 6 months later.