

# Autonomic Nervous

## System

### (Drugs & Facts)

The motor (efferent) portion of the ANS is a pathway for information transmission from CNS to efferent muscles (smooth muscle, vascular endothelium, cardiac muscle, exocrine glands).

They're also many sensory afferent fibers. .

1. Parasympathetic preganglionic motor fibers originate from cranial nerve nuclei ( III, VII, IX, X) and sacral segment from spinal cord (S2-S4)
2. Sympathetic preganglionic fibers originate from thoracic T1-T2, and lumbar segment of the cord L1-L5.

## Location of ganglia

1. Sympathetic: two Para vertebral chains along the cord.
2. Parasympathetic: ganglia are located in the organs innervated.

The length of preganglionic and postganglionic fibers.

1. Preganglionic sympathetic are short.
2. Preganglionic parasympathetics are long.

## Uninnervated receptors

Autonomic transmitters receive no innervations. These include muscarinic receptors on the endothelium of blood vessels and adrenergic receptors on apocrine sweat glands.

## Neurotransmitter Facts

1. Major Transmitter
  - Acetylcholine: major transmitter in all autonomic ganglia, and at parasympathetic post ganglionic cell synapses.
  - Norepinephrine (NE): primary transmitter at sympathetic postganglionic neuron.
  - Dopamine (DA): Vasodilator transmitter in some splanchnic vessels, especially renal vessel.
2. Synthesis of transmitter
  - Acetylcholine is synthesized by the enzyme choline acetyltransferase from acetylCoA and choline.

- **NE: Tyrosine is hydroxylated to Dopa, decarboxylated to Dopamine and hydroxylated to NE.**

## **Metabolism of neurotransmitters**

- Acetylcholine: is normally terminated by metabolism by cholinesterase to choline and acetate.**
- Catecholamines: Diffusion and reuptake reduce the concentration of NE and Dopamine in the synaptic cleft and stops their action. Metabolism is not responsible for the termination of catecholamines transmitters.**

## **Receptor characteristics**

- 1. Acetylcholine receptors: respond to Acetylcholine**
  - Muscarinic receptors: respond to muscarine and acetylcholine analog. Located on effector cells of the heart, vascular endothelium, smooth muscle and exocrine glands.**
  - Nicotinic receptors: respond to nicotine and acetylcholine analog. Located in ganglia and in skeletal muscle endplates.**
- 2. Adrenoceptors (adrenergic receptors)**
  - Alpha-receptors: located on vascular smooth muscle, presynaptic nerve terminals, fat cells and the brain.  
Two major subtypes: Alpha-1 and Alpha-2.**
  - Beta-receptors: smooth muscle, cardiac muscle, fat cells, and in the brain.  
Two major subtypes: Beta-1 and Beta-2.**
- 3. Dopamine receptors: Located in renal, splanchnic vessels and in the brain.  
Two subtypes: D1 and D2.**

## **Effects of the activation of the autonomic nerves.**

**Dually innervated organs: iris of the eye, and senatorial node of the heart.**

**Removal of both sympathetic and parasympathetic tone, the muscle will respond depends on which system is predominant. Both pupil and SA node are dominated by parasympathetic system. Blockade of both systems resembles an increase in sympathetic activity (mydriasis and tachycardia)**

### **Acetylcholine Receptor stimulants/ cholinomimetics**

**Direct acting agonists**

- Choline esters: Acetylcholine, Methacholine, and Carbachol.**
- Alkaloids: Muscarinic, Pilocarpine, Nicotine.**

## **Action**

- Coupling of muscarinic receptors to phospholipase C, to adenylate cyclase and to potassium channels.**

- b. **Coupling of nicotinic receptors to Acetylcholine channels on ganglion cells and neuromuscular endplates.**

## Clinical Use

1. **Bethanecol: post-op neurogenic ileus and urinary retention. Stimulates bowel and bladder smooth muscle.**
2. **Pilocarpine: glaucoma**
3. **Neostigmine, Pyridostigmine: Myasthenia Gravis. Increase efficiency of cholinergic transmission.**
4. **Physostigmine: glaucoma**

## Toxicity

- A. **Muscarinic effects: CNS stimulation, miosis, bronchoconstriction, and increase gastro- intestinal and genitourinary smooth muscle activity.**
- B. **Nicotinic effects: CNS stimulation, neuromuscular endplate depolarization leading to fasciculation and paralysis.**

## Indirect acting agonists

- **Carbamates: Neostigmine**
- **Organophosphates: Echotiophate**
- **Edrophonium**

## Action

- A. **Carbamates and organophosphates bind to the enzyme cholinesterase and are quickly hydrolyzed or metabolized.**
- B. **They inhibit cholinesterase and result in an increase in the concentration and action of Acetylcholine in the synapses.**

## Clinical Use

- A. **Carbamates: Neostigmine: post- op neurogenic ileus and urinary retention. Some of them are used as insecticides.**
- B. **Organophosphates:**
  - **Echotiophate: treatment of glaucoma.**
  - **Malathion: scabicide**
  - **Metrifonate: anthelminitic.**

☼ **Scabies (pubic lice): The transmission of mites during sexual intercourse. Nocturnal itching of the wrists, hands, genital area, breasts, and Buttock.**

☼ **Ileus: Inhibition of bowel motility.**

## Toxicity

- **Loss of consciousness**

- Increase sweating, salivation, lacrimation
- Shallow breathing, tightness in chest (bronchoconstriction), increase bronchial secretions, dyspnea.
- Increase GI motility, abdominal cramps, N & V, diarrhea, involuntary defecation.
- Eyes: miosis, blurred vision
- Urinary tract: frequent urination, incontinence
- Muscular; fatigue
- CNS: circulatory and respiratory depression. Severe demyelination of peripheral nerves resulting in weakness and sensory loss.
- ☀ Treatment:
  - Atropine: muscarinic antagonist
  - Pralidoxime (2-PAM): regenerate Acetyl cholinesterase at NMJ. Stop fasciculation.

## Cholinoceptor Blockers

- ☀ Muscarinic antagonists
  - Prototype: Atropine. From the plant *Atropa Belladonna*. Well distributed into the CNS and other organs. Eliminated by metabolism in the Liver and by renal excretion.
  - These drugs are used for their anitsecretory or antispastic actions in the gut, the GU tract, and the bronchi.
  - Receptor subgroup: M1 and M2 Pirenzepine selective for M1 subgroup and used for the treatment of peptic ulcer.

## Action

- ☀ Muscarinic blocking agents
  - Sedation.
  - The reduction of motion sickness.
  - The reduction of some signs in Parkinsonism.
  - Cardiovascular: decrease heart rate.

## Clinical Use

- Eye: Atropine, Homatropine, Tropicamide dilate pupil, paralyze accommodation
- Gut: Atropine, Methscopolamine, Propantheline Acid-peptic disease: decrease acid secretion. Not as effective as H2-Blockers: Cimetidine.
- Bladder: Atropine, Methscopolamine, Propantheline, reduce urgency
- CNS: Scopolamine, Standard therapy for motion sickness.
- Airways: Parental Atropine: decrease airway secretion during surgery. Ipratopium: Inhalation, Decrease bronchoconstriction in asthma.

## Toxicity

- ☀ Young children: Atropine fever.
- ☀ Elderly: eye- glaucoma

- ☀ **Bladder: urinary retention**
- ☀ **CNS: sedation, amnesia, delirium, hallucinations**
- ☀ **Cardiovascular: Atropine flush**

## Nicotinic Antagonists

1. **Ganglion Blocking Drugs: Hexamethonium**  
A severe blockade of sympathetic and parasympathetic.  
Treatment of severe accelerated hypertension.
2. **Neuromuscular Blocking Drugs: Complete skeletal muscle relaxation in surgery.**
  - a. **Non depolarizing group**
    - **Tubocurarine: flaccid paralysis**
  - b. **Depolarizing group:**
    - **Succinylcholine: produces fasciculation's during induction of paralysis. Patients often complain of muscle pain after surgery.**

## Adrenoceptor stimulants/ Agonists

### Spectrum of action

- **Epinephrine affects all receptor types: Alpha- 1, Alpha-2, Beta-, and Beta-2.**
- **Phenylephrine: Alpha**
- **Isoproterenol: Beta**

### Action

Directly or indirectly activate their receptors to increase the release of endogenous catecholamines.

### Effects

1. **Alpha-1 agonists: increase smooth muscle tone, increase blood pressure, reflex bradycardia.**
2. **Alpha-2 agonists: Clonidine. Cause vasoconstriction when given IV or topically (nasal spray), they accumulate in the CNS and cause hypotension.**
3. **Beta-1 agonists: increase cardiac rate and force of contraction.**
4. **Beta-2 agonists: dilate skeletal muscle, blood vessels, and bronchi. Decrease uterine and bladder tone.**
5. **Dopamine: vasodilatation of splanchnic and renal vessels.**

### Clinical Use

- A. **Cardiovascular applications**
  - **Heart failure**
  - **Homeostatic or decongestant, maintenance of blood pressure under emergency conditions: Alpha-1 agonists**
- B. **Other applications**
  - **Smooth muscle relaxation (asthma, premature labor)**
  - **CNS stimulation: Phenmetrazine (narcolepsy, obesity, hyperkinetic attention deficit disorder).**
  - **Phenylephrine: nasal decongestant**

## Toxicity

### a. Catecholamines

- In the periphery: excessive vasoconstriction, cardiac necrosis, pulmonary edema or hemorrhage, ectopic cardiac rhythms.

### b. Other sympathomimetics

- Small doses: nervousness, anorexia, and insomnia
- Higher doses: anxiety, aggressiveness, and paranoid behavior

## Adrenoceptor Blockers

Phentolamine: reversible (competitive) alpha-2 blocker

Phenoxybenzamine: irreversible alpha-1 blocker

Prazosin: reversible (competitive) alpha-1 blocker

## Clinical Use

- Presurgical management of Pheochromocytoma and as antidotes in accidental over dosage of alpha agonists
- Prazosin: hypertension

## Toxicity

- N& V (oral administration)
- The first dose causes an exaggerated hypotension. Therefore the first dose must be small and taken just before going to bed.

## Beta- Blocking Drugs

Propranolol, Metoprolol, Timolol reduce cardiac output, Treatment of hypertension

### ☀ Propranolol, Nadolol

- Reduce cardiac rate and force of contraction.
- Treatment of angina pectoris.

### ☀ Propranolol

- Reduce cardiac rate and force of contraction.
- Treatment of hypertrophy cardiomyopathy, migraine, thyroid storm, familial tremor.

■ Acebutolol, Pindolol: treatment of asthma

### ☀ Clinical Use

- Reduction of skeletal muscle tremor
- Reduction of aqueous humor: glaucoma
- Blockade of sympathetic discharge

### ☀ Toxicity

- Cardiovascular: bradycardia, congestive heart failure
- CNS: sedation, fatigue, sleeps alterations.

