

## Introduction to Autonomic Pharmacology

The nervous system is divided into central nervous system (CNS; the brain and spinal cord) and the peripheral nervous system (nervous tissues outside the CNS). The motor nervous system can be divided into. The somatic division is largely concerned with consciously controlled functions such as movement, posture.), The autonomic nervous system (ANS) is largely autonomous (independent) in that its activities are not under direct conscious control. It is concerned primarily with visceral functions—cardiac output, blood flow to various organs, digestion, etc—that are necessary for life..

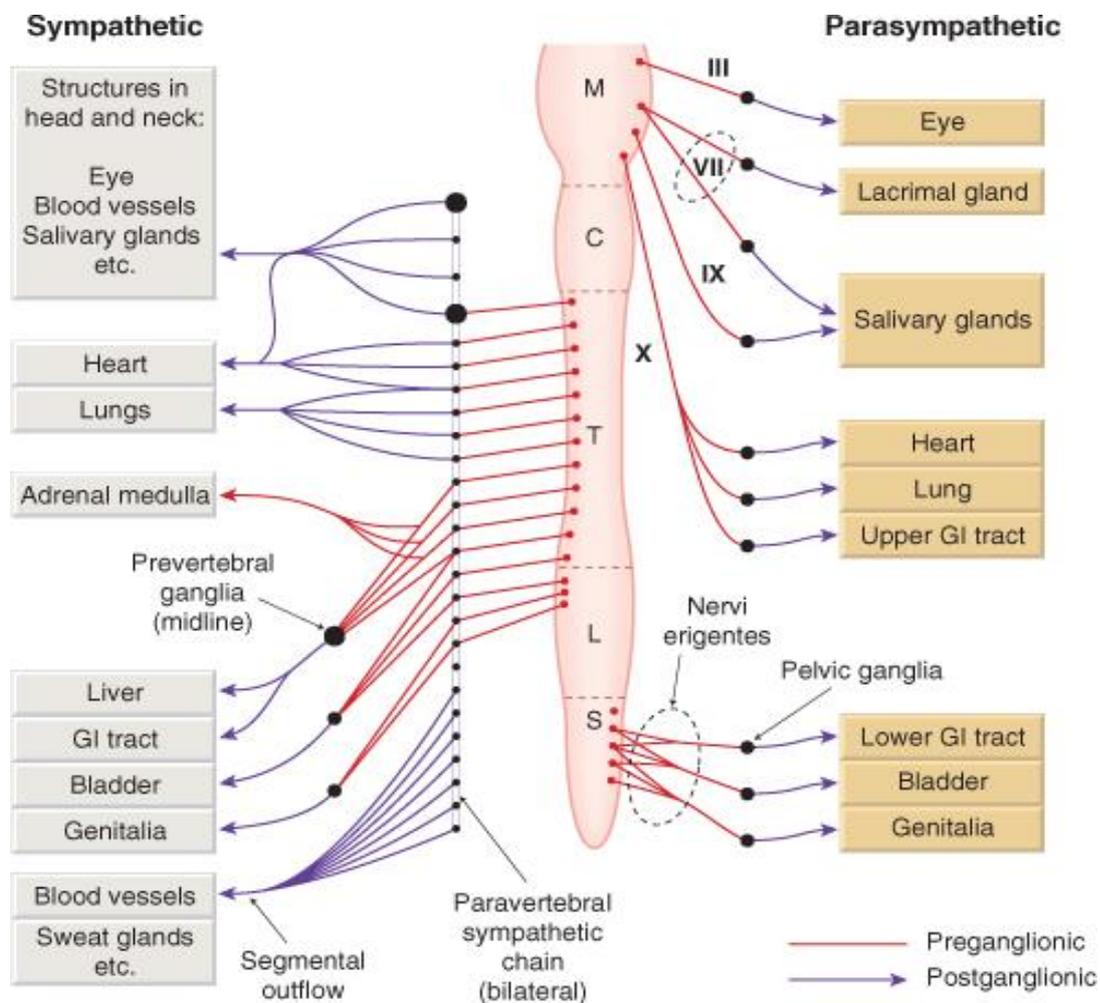
### Anatomy of the Autonomic Nervous System

The autonomic nervous system division into two major portions: the **Sympathetic (Thoraco-lumbar)** division and the **Parasympathetic (cranial-sacral)** originate in nuclei within the central nervous system and give rise to preganglionic efferent fibers that exit from the brain stem or spinal cord and terminate in motor ganglia. Sympathetic preganglionic fibers leave the central nervous system through the thoracic and lumbar spinal nerves. The parasympathetic pre ganglion fibers leave the central nervous system through the cranial nerves (especially the third, seventh, ninth, and tenth) and the third and fourth sacral spinal

### Neurotransmitter Chemistry of the Autonomic Nervous System

An important classification of autonomic nerves is based on the primary transmitter molecules—acetylcholine or norepinephrine—released from terminal fibers. A large number of peripheral autonomic nervous system fibers synthesize and release acetylcholine; they are **cholinergic** fibers, these include all preganglionic efferent autonomic fibers and the somatic (non autonomic) motor fibers to skeletal muscle as well. Thus, almost all efferent fibers leaving the central

nervous system are cholinergic. In addition, most parasympathetic postganglionic and a few sympathetic postganglionic fibers are cholinergic.. Most postganglionic sympathetic fibers release norepinephrine (noradrenalin); they are **noradrenergic** (often called simply "adrenergic") fibers—i.e., they act by releasing norepinephrine., a few sympathetic fibers release acetylcholine.. Adrenal modularly cells, which are embryologically analogous to postganglionic sympathetic neurons, release a mixture of epinephrine and norepinephrine.



## Cholinergic and anticholinergic Drugs

Acetylcholine is a widespread neurotransmitter in the body, mediating a broad range of physiological effects. There are two distinct classes of receptor for acetylcholine defined on the basis of their activation by the alkaloids, nicotine (from tobacco) and muscarine (from a fungus, *Amanita muscaria*).

At cholinergic nerve endings and in erythrocytes there is an enzyme that destroys acetylcholine, *true cholinesterase* or *acetyl cholinesterase*. In various tissues, especially plasma, there are other esterase which are not specific for acetylcholine but which also destroy other esters. These are called nonspecific or *pseudo cholinesterase*.

Stimulation of cholinergic receptors in autonomic ganglia and at the postganglionic endings affects chiefly the following organs:

**Eye:** meiosis and spasm of the ciliary muscle occur so that the eye is accommodated for near vision. Intraocular pressure falls.

**Exocrine glands:** there is increased secretion of the salivary, lachrymal, bronchial and sweat glands. The last are cholinergic, although anatomically part of the sympathetic system; some sweat glands, e.g. axillary, may be adrenergic.

**Heart:** bradycardia occurs with atrioventricular block and eventually cardiac arrest.

**Bronchi:** there is bronchoconstriction and mucosal hyper- secretion that may be clinically serious in asthmatic subjects, in whom cholinergic drugs should be avoided, as far as possible.

**Gut:** motor activity is increased and may cause colicky pain. Exocrine secretion is also increased. Tone in anal sphincters falls which may cause defecation

**Bladder and ureters** contract and the drugs promote micturition.

**Neuromuscular (voluntary) junction:** The neuromuscular junction has a cholinergic nerve ending and so is activated acetylcholine, causing muscle fasciculation.

## Cholinergic drugs(cholinomimetics)

These drugs act on postsynaptic acetylcholine receptors at all the sites in the body where acetylcholine is the effective neurotransmitter.

### CLASSIFICATION

**Direct-acting (receptor agonists)** Choline esters (carbachol, bethanechol)

**Indirect-acting** Cholinesterase inhibitors, or anticholinesterases (physostigmine, neostigmine, pyridostigmine, donepezil), which inhibit the enzyme that destroys acetylcholine, allowing the endogenous transmitter (acetylcholine) to persist and produce intensified effects.

### **Pilocarpine**

acts directly on end-organs innervated by postganglionic nerves (parasympathetic system plus sweat glands). The chief clinical use of pilocarpine is to lower intraocular pressure in chronic simple glaucoma,; it produces miosis, opens drainage channels improves the outflow of aqueous humour..

### **ANTICHOLINESTERASES**

Chemicals which inactivate esterases (anticholinesterases) are used in medicine and in agriculture as pesticides. They act by allowing naturally synthesized acetylcholine to accumulate instead of being destroyed.

#### **Physostigmine**

#### **Neostigmine**

#### **Pyridostigmine (mestinone)**

**.Donepezil and rivastigmine**

### **Anticholinesterase poisoning**

The anticholinesterases used in therapeutics are Reversibly inactivate cholinesterase only for a few hours. Poisoning with *reversible* anticholinesterases is appropriately treated by atropine and the necessary general support; it lasts only hours. In poisoning with *irreversible* agents the *organophosphate* insecticide irreversibly inactivate cholinesterase which used in agricultural, industrial, also used in war called nerve 'gas'

## **Anti C H O L I N E R G I C D R U G S**

Acetylcholine antagonists (blockers) that block the nicotine-like effects (neuromuscular blockers and autonomic ganglion blockers). Acetylcholine antagonists that block the muscarine-like effects, e.g. atropine, are called anticholinergics. The more precise term antimuscarinic is preferred here

### **Antinicotinic drug**

#### **Ganglion-blocking drugs**

##### **Hexamethonium**

##### **Trimethaphan,**

#### **Neuromuscular blocking. Drugs**

There are two principal mechanisms by which drugs used clinically interfere with neuromuscular transmission:

**By competition** with acetylcholine (atracurium, pancuronium, rocuronium, vecuronium).

**By depolarization** of the motor endplate (suxamethonium).

## **USES OF NEUROMUSCULAR BLOCKING DRUGS**

- 1- They are used to provide muscular relaxation during surgery and occasionally to assist mechanical ventilation in intensive therapy units.
- 2- They are used during electroconvulsive therapy to prevent injury to the patient due to excessive muscular contraction.

### Antimuscarinic drugs

which act principally at postganglionic cholinergic (parasympathetic) nerve endings, Muscarinic receptors can be subdivided according to their principal sites, namely in the brain and gastric parietal cells (M1), heart (M2) and glandular and smooth muscle cells (M3). Atropine is the prototype drug of this group.

**Exocrine glands.** All secretions except milk are diminished. Dry mouth and dry eye are common. Gastric acid secretion is reduced, Bronchial secretions are reduced

**Smooth muscle** is relaxed. In the gastrointestinal tract there is reduction of tone and peristalsis. Atropine relaxes bronchial muscle, an effect that is useful in some asthmatics. Micturition is slowed and urinary retention may be induced.

**Ocular effects.** Mydriasis occurs with a rise in intraocular pressure in eyes. An attack of glaucoma may be induced. The ciliary muscle is paralysed and so the eye is accommodated for distant vision.

**Cardiovascular system.** Atropine reduces vagal tone thus increasing the heart rate, and enhancing conduction in the bundle of His. Atropine has no significant effect on peripheral blood vessels in therapeutic doses

**Pharmacokinetics.**

Atropine is readily absorbed from the gastrointestinal tract and may also be injected by the usual routes.. Atropine is in part destroyed in the liver and in part excreted unchanged by the kidney. for chronic use it has largely been replaced by other antimuscarinic drugs..Poisoning with atropine (and other antimuscarinic drugs) presents with obvious dry mouth (with dysphagia), mydriasis, blurred vision, hot, flushed, dry skin, and, in addition, hyperthermia, restlessness, anxiety, excitement, hallucinations, delirium, mania. and coma

**Other antimuscarinic drugs**

**Hyoscine (scopolamine)**

**Hyoscine butylbromide( Buscopan)**

**Homatropine**

**Ipratropium (Atrovent)**

**Flavoxate**

**Oxybutynin**

**Therapeutic Applications****1-CENTRAL NERVOUS SYSTEM DISORDERS**

**a- Parkinson's disease:,**

**b- Motion sickness:.**

**2- OPHTHALMOLOGIC DISORDERS**

**3. RESPIRATORY DISORDERS**

**4- CARDIOVASCULAR**

**5- GASTROINTESTINAL DISORDERS:**

**6- URINARY DISORDERS**

**7-. OTHER APPLICATIONS**

**SIDE EFFECT**

At higher concentrations, atropine causes block of all parasympathetic functions. However, atropine is a remarkably safe drug in adults produce dry mouth, mydriasis, tachycardia, hot and flushed skin, agitation, and delirium for as long as a week. Body temperature is frequently elevated.

**Contraindications.**

Antimuscarinic drugs are contraindicated in patients with glaucoma,. In elderly men, antimuscarinic drugs should always be used with caution and should be avoided in those with a history of prostatic hyperplasia.