

COURSE CODE/TITLE:PCO353/AUTONOMIC NERVOUS SYSTEMPHARMACOLOGY.

TOPIC: PARASYMPATHETIC DRUGS; SKELETAL MUSCLE RELAXANTS, GANGLION STIMULANTS AND BLOCKERS, PROPERTIES OF GANGLION STIMULANTS AND BLOCKERS, STRUCTURE ACTIVITY RELATIONSHIP BETWEEN CHOLINERGIC AND ANTICHOLINERGICS.

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REVIEW OF ANATOMY/PHYSIOLOGY OF THE AUTONOMIC/SOMATIC NERVOUS SYSTEM

The Nervous system (NS) enables the body to react to continuous changes in its internal and external environment. For descriptive purposes, the NS is divided:

1.Structurally/Anatomically into;

1a.Central Nervous System (CNS)- Which consist of the brain and spinal cord. Its function is to integrate/coordinate incoming and outgoing neural signals and carry out higher mental functions such as thinking and learning.

1b.Peripheral Nervous System (PNS)-Which consist of cranial, spinal nerves fibers and cell bodies outside CNS that conduct impulses to or away from CNS.

2.Functionally/Physiologically into;

2a.Somatic Nervous System (SNS). It is largely concerned with consciously controlled functions such as movement, Respiration and posture. SNS consist of Somatic parts of the CNS and PNS, provides sensory/afferent and motor/efferent innervation to all parts of the body, except the viscera in the body cavities, smooth muscles (**m**) and glands. Somatic fibers are classified as follows: (a) General sensory (S afferent)- transmit impulses from the body to the spinal cord, which may be; conscious impulses (eg pain, pressure, touch, temperature) from skin or unconscious impulses from m, tendons and joints. (b) S motor (efferent)-transmit impulses to skeletal m, permitting voluntary and reflexive movement by causing contraction of skeletal m, such as occurs when one touches a hot cloth pressing iron.

2b.Autonomic Nervous System (ANS). It is largely independent (autonomous) in that its activities are not under direct conscious control. Visceral (autonomic) fibers are classified as follows: (a) Visceral sensory (visceral afferent)- transmit reflex or pain impulses from mucous membranes, glands and blood vessels to CNS. (b) Visceral motor (visceral efferent)-consist of a series of two variety of neurons (presynaptic and postsynaptic) that team up together to transmit impulses from CNS to viscera in the body cavities, smooth/involuntary m and glands. **ANS is classically described as the visceral motor system.** However, the visceral **motor/efferent fibers (leaving/coming out from CNS)** of ANS are accompanied by visceral **sensory/afferent fibers (going to the CNS)** to complete the autonomic reflexes and regulate visceral function. The motor/efferent neurons and ganglia of ANS are organised into two divisions, namely:

2bi- Sympathetic system, SS (functionally) or Thoracolumbar system (structurally)

2bii- Parasympathetic system, PS (functionally) or Craniosacral system (structurally)

The Enteric Nervous System (ENS) consist intestinal/enteric plexus of nerves which though receives inputs from both SS and PS of ANS, **function independently** to regulate secretion/absorption and integrate bowel movement. Consequently it is labelled as a distinct ENS, however some authors include it as a third division of the ANS.

Table 1.2. Functions of the Autonomic Nervous System (ANS)

Organ, Tract, or System		Effect of Sympathetic Stimulation ^a	Effect of Parasympathetic Stimulation ^b
Eyes	Pupil	Dilates pupil (admits more light for increased acuity at a distance)	Constricts pupil (protects pupil from excessively bright light)
	Ciliary body		Contracts ciliary muscle, allowing lens to thicken for near vision (accommodation)
Skin	Arrector muscle of hair	Causes hairs to "stand on end" ("gooseflesh or goose bumps")	No effect (does not reach) ^c
	Peripheral blood vessels	Vasoconstricts (blanching of skin, lips, and turning fingertips blue)	No effect (does not reach) ^c
	Sweat glands	Promotes sweating ^d	No effect (does not reach) ^c
Other glands	Lacrimal glands	Slightly decreases secretion ^e	Promotes secretion
	Salivary glands	Secretion decreases, becomes thicker, more viscous ^e	Promotes abundant, watery secretion
Heart		Increases the rate and strength of contraction; inhibits the effect of parasympathetic system on coronary vessels, allowing them to dilate ^e	Decreases the rate and strength of contraction (conserving energy); constricts coronary vessels in relation to reduced demand
Lungs		Inhibits effect of parasympathetic system, resulting in bronchodilation and reduced secretion, allowing for maximum air exchange	Constricts bronchi (conserving energy) and promotes bronchial secretion
Digestive tract		Inhibits peristalsis, and constricts blood vessels to digestive tract so that blood is available to skeletal muscle; contracts internal anal sphincter to aid fecal continence	Stimulates peristalsis and secretion of digestive juices Contracts rectum, inhibits internal anal sphincter to cause defecation
Liver and gallbladder		Promotes breakdown of glycogen to glucose (for increased energy)	Promotes building/conservation of glycogen; increases secretion of bile
Urinary tract		Vasoconstriction of renal vessels slows urine formation; internal sphincter of bladder contracted to maintain urinary continence	Inhibits contraction of internal sphincter of bladder, contracts detrusor muscle of the bladder wall causing urination
Genital system		Causes ejaculation and vasoconstriction resulting in remission of erection	Produces engorgement (erection) of erectile tissues of the external genitals
Suprarenal medulla		Release of adrenaline into blood	No effect (does not innervate)

Underlying general principles:

^a In general, the effects of sympathetic stimulation are catabolic—preparing body to "flee or fight."

^b In general, the effects of parasympathetic stimulation are anabolic—promoting normal function and conserving energy.

^c The parasympathetic system is restricted in its distribution to the head, neck, and body cavities (except for erectile tissues of genitalia); otherwise, parasympathetic fibers are never found in the body wall and limbs. Sympathetic fibers, by comparison, are distributed to all vascularized portions of the body.

^d With the exception of the sweat glands, glandular secretion is parasympathetically stimulated.

^e With the exception of the coronary arteries, vasoconstriction is sympathetically stimulated; the effects of sympathetic stimulation on glands (other than sweat glands) are the indirect effects of vasoconstriction.

Structure of the neuron and synaptic cleft: N tissues consist of two main types of cells; **Neurons** and **Neuroglia** (glia cells that support the neurons). The neuron is composed of a **cell body** (having a nucleus) and **two types of processes**, namely, **dendrites** (through which impulses **pass to** the cell body) and **axon or fiber** (through which impulses are **carried away from** cell body). Neurons communicate with each other at **synapses (synaptic cleft)** by means of **neurotransmitters**.

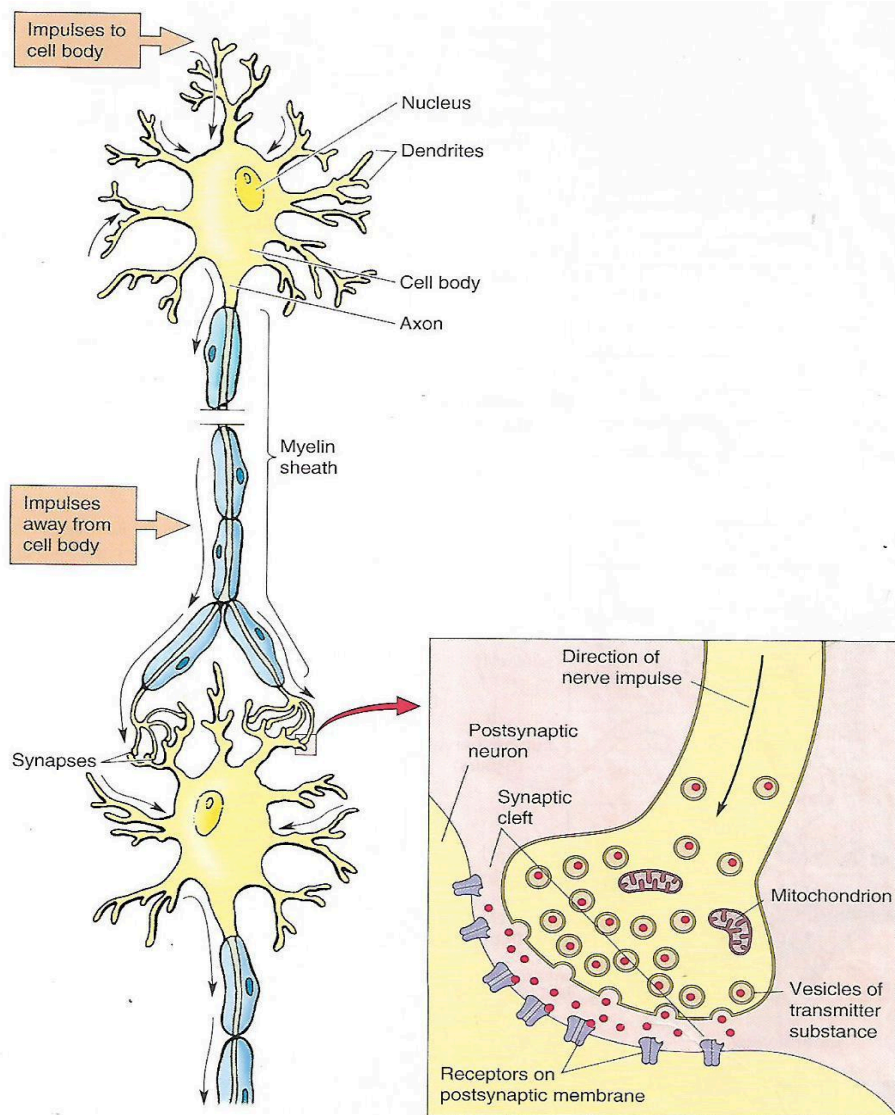


Figure 1.23. Structure of a motor neuron. A neuron or nerve cell is composed of a cell body having a nucleus and two types of processes—dendrites and axons. Impulses pass to the cell body through the dendrites (*upper black arrows*) and the axon carries impulses away from the cell body (*lower black arrows*). A neuron influences other neurons at junctional points or synapses. The detailed structure of an *axodendritic synapse* is illustrated (*inset*); neurotransmitter substances diffuse across the narrow space (synaptic cleft) between the two cells and become bound to receptors.

Structural/functional arrangement of neurons in ANS and SNS: In ANS- conduction of impulses from **afferent organs** (eg mucous membranes) to CNS is through **the visceral afferent neuron**. In contrast, conduction of impulses from CNS back to effector organs involves **visceral efferent neurons (presynaptic or preganglionic and postsynaptic or postganglionic between which there is ganglia and synapse)**. The cell body of the 1st neuron (presynaptic) is located in the **gray matter of the CNS** (brain and spinal cord) and its fibers synapses only on the cell bodies of the 2nd neuron (postsynaptic) in the series which are located in the **autonomic ganglia**. The fibers of the postsynaptic neuron terminate on the **effector organs** and a synapse is located between these fibers and effector organs. In SNS- conduction of impulses from **afferent organs** (eg skin) to CNS is through **a single variety of general sensory (general s afferent) neuron**. Similarly, conduction of impulses from CNS back to effector organs (skeletal m) is through **a single variety of s motor (s efferent) neurons**. **Consequently there no ganglia in the SNS.**

INTRODUCTION TO PARASYMPATHETIC (CHOLINERGIC) DRUGS AND SKELETAL MUSCLE RELAXANTS

Types of Neurotransmitters, Neurons and Receptors in ANS (PS, SS) and SNS: A functional distinction between SS and PS of ANS, pharmacologically important in medical practice is that the **postsynaptic neurons of SS and PS generally release different neurotransmitter substances**, namely; **Norepinephrine/Noradrenaline by the SS** (except in the case of sweat glands) but **Acetylcholine (ACh) by the PS**. Similarly; (a). **All preganglionic motor ANS (SS and PS) fibers release ACh** at the synapse with postganglionic neuron/nerve cell bodies-called **ganglionic neurotransmitter**. (b). **All SNS motor fibers to skeletal m at neuromuscular junction (Nmj) release ACh**- called **neuromuscular neurotransmitter**. Summarily: The neurons/nerve fibers that function by synthesizing/releasing ACh neurotransmitter are referred to as **cholinergic neurons/fibers**, namely; (1) Postganglionic PS fibers. (2) The few postganglionic SS fibers innervating sweat glands. (3) All preganglionic motor ANS (SS and PS) fibers (4) All SNS motor fibers to skeletal m. **Acetylcholin-esterase (AChE)**, an enzyme breaks down ACh in the synapse. Similarly, the neurons/nerve fibers that function by synthesizing/releasing Noradrenaline are referred to as Noradrenergic or **Adrenergic neurons** namely; Postganglionic SS fibers except those innervating sweat glands.

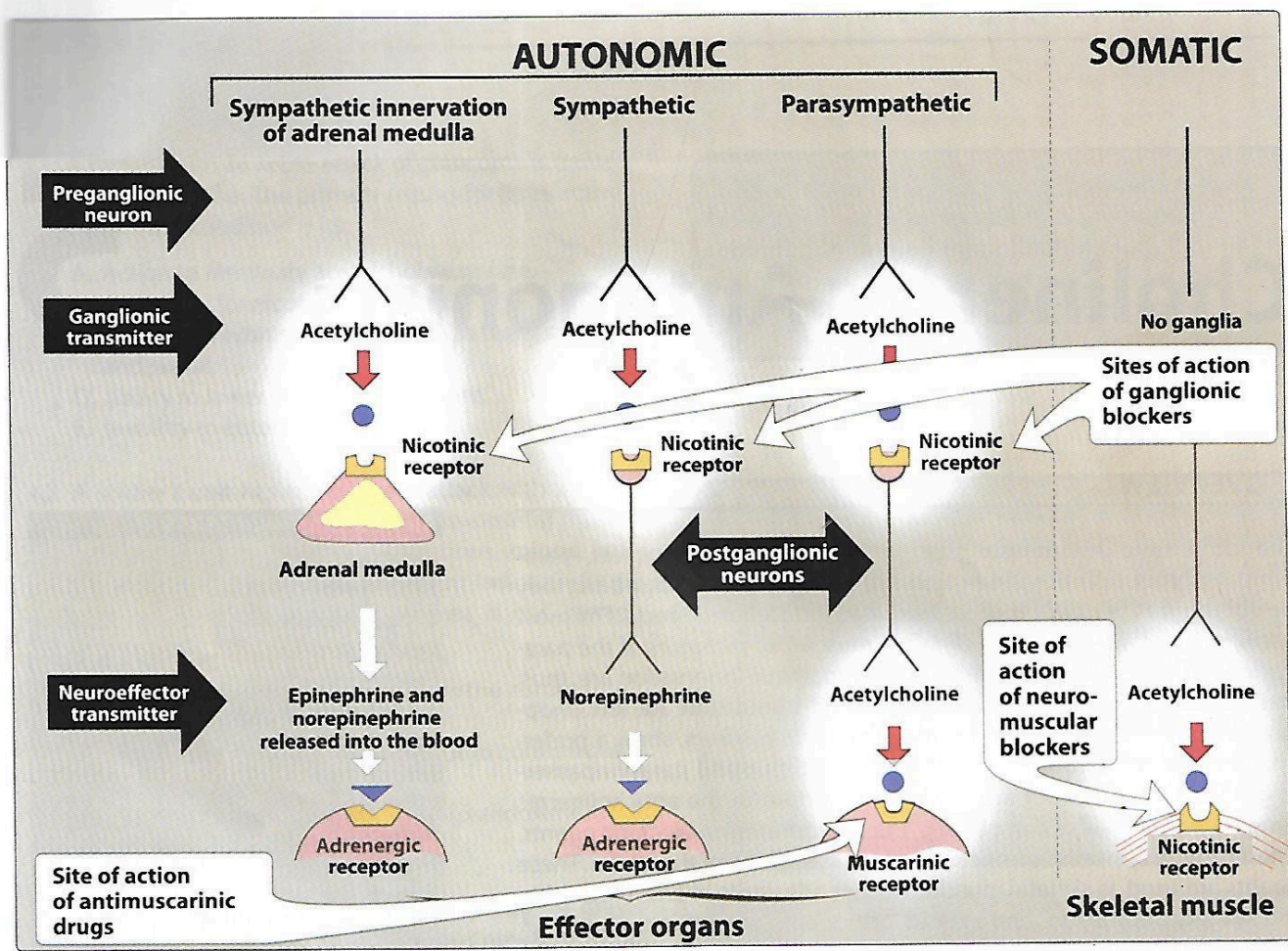


Diagram to show the types of neurotransmitters/receptors in ANS and SNS and sites of actions of drugs.

Cholinergic receptors (Cholinoceptors):

The two classes of ACh receptors (**cholinoceptors**) are;

- 1) **Muscarinic(M) receptors** (G protein coupled receptor) and
- 2) **Nicotinic(N) receptors** (a ligand gated cation channel)

The

two receptors can be distinguished from each other on the basis of their different affinities for **agents that mimic the action of ACh**- referred to as **cholinergic or cholinomimetic or parasympathetic or parasympathomimetic agents**.

Muscarinic receptors (G-protein coupled receptor):- In addition to binding to ACh, **M r** are selectively stimulated by muscarine and blocked by atropine, show weak affinity for nicotine **M r are located** primarily on the autonomic effector cell in heart, blood vessels, eye, smooth muscles and glands of GIT, respiratory and urinary tracts, sweat glands etc and in the CNS. There are 5 subtypes of M r, namely; M1, M2, M3, M4, M5, however only the first 3 have been functionally characterised.

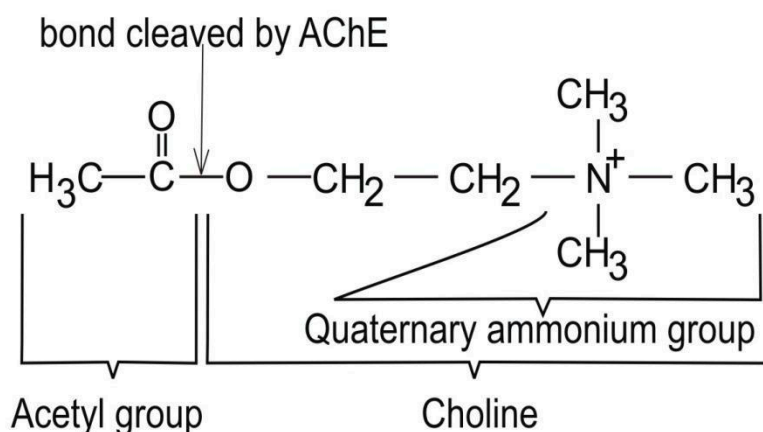
Nicotinic receptors (ligand gated ion channel):- In addition to binding ACh, Nr are selectively stimulated by nicotine alkaloid but blocked by tubocurarine or hexamethonium. Nr shows weak affinity for muscarine alkaloid. Nr are located on the CNS, Adrenal medulla, Autonomic ganglia and Neuro-muscular junction (Nmj). There are two types of nicotinic receptors Nm and NN.

STRUCTURE ACTIVITY RELATIONSHIP AMONG CHOLINERGICS AND ANTICHOLINERGICS

Structure Activity Relationship (SAR). SAR is defined as the relationship between the chemical structure (three-dimensional structure and chemical groups) of a drug molecule and its biological activity. SAR of a drug is the structural parameters of a drug that is responsible for evoking a target biological effect.

SAR among Cholinergics-

Structure of Acetylcholine (ACh)-acetic acid ester of choline



The key feature of ACh molecule that is important for its activities is the quaternary ammonium group, which bears a partial positive charge and is susceptible to rapid

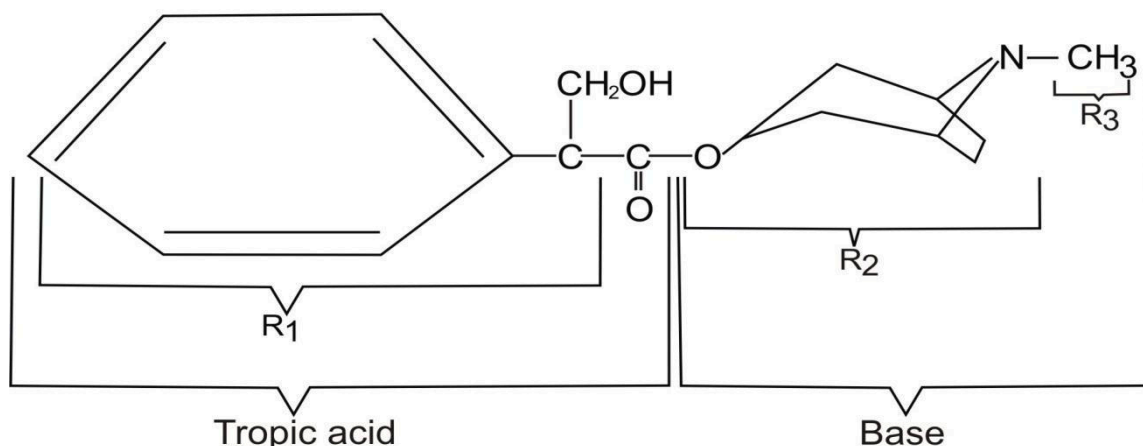
hydrolysis by AChE. Variants of the choline ester (Cholinergics) structure have the effect of reducing the susceptibility of the compound/drug to hydrolysis by AChE and altering the relative activity on M r and N r. For Cholinergic drugs/ACh agonist (with chemical structure described as small N-quaternary compounds), the following criteria with reference to ACh structure describe the SAR (Ing's Rule of 5);

1. There should be no more than five atoms between nitrogen and the terminal hydrogen for cholinergic/muscarinic activity.
2. The drug molecule must possess a nitrogen atom capable of bearing a positive charge, preferably a quaternary ammonium salt.
3. For maximum potency, the size of the alkyl groups substituted on the nitrogen should not exceed the size of a methyl group.
4. The drug molecule should have an oxygen atom, preferably an ester-like oxygen capable of participating in a hydrogen bond.
5. There should be a two-carbon unit between the oxygen atom and the nitrogen atom.

The permanently charged quaternary ammonium group of the choline esters directly-acting cholinergic agonist renders them relatively insoluble in lipids.

SAR among Anticholinergics-

Structure of Atropine-Tertiary amine alkaloid ester of tropic acid



Antimuscarinics/Anticholinergics chemical structures (compared to ACh chemical structure) usually contain ester and basic groups in the same relationship as ACh, but they have a bulky aromatic group in place of the acetyl group of ACh. Two naturally occurring antimuscarinic/anticholinergic compounds; Atropine and Hyoscine (scopolamine) are tertiary amine/ammonium plant alkaloid ester of tropic acid, are lipid-soluble and penetrate the blood brain barrier. For Anticholinergics/ACh antagonist (with chemical structure described as larger N-quaternary compound), with reference to their acid moiety, the following SAR are found:

1. As R₃ is increased from methyl to higher alkyl groups (or becomes hydrogen, alkenyl Amino or aminoalkyl), the psychotropic potency diminishes without much effect on the peripheral anticholinergic action.
2. R₂ should be an unsubstituted phenyl group whereas R₁ must be either a cycloalkyl, alkynyl, thienyl or unsubstituted phenyl group.

3. Alkyl, aryl, halide or hydroxyl substituents on the Phenyl rings diminishes anticholinergic potency and abolishes its central/CNS action.

4. The Position of ester side chain affects central but not peripheral action.

PARASYMPATHETIC DRUGS (CHOLINERGIC AGONIST)

These are drugs which produce actions similar to that of ACh, either by directly interacting with cholinergic receptors (cholinergic agonist) or by increasing the availability of ACh at these sites (anticholinesterase). Drugs that mimic the action of ACh are referred to as Parasympathetic or Parasympathomimetic or Cholinergic or Cholinomimetic agonist/drugs.

Classification of Cholinergic agonist: They are classified based on whether their agonist action on the cholinergic receptors are direct or indirect

1. Direct-acting Cholinergic agonist- act directly, binding to cholinergic receptors. Based on their chemical structure, they are further divided into two types, namely;

1a. Choline esters:- Eg, ACh, Bethanechol, Carbachol, Methacholine

1b. Alkaloid:- Eg, Muscarine, Pilocarpine, Arecoline.

2. Indirect-acting Cholinergic agonist (Anticholinesterases)- They are agent which inhibit ChE, protect ACh from hydrolysis thereby producing cholinergic effects. They are divided into two types based on reversibility of their action

2a. Reversible indirect-acting cholinergic agonist- They prevent the hydrolysis of ACh, hence increase the endogenous ACh concentration in synapses (neuro-effector junctions), the excess ACh in turn stimulate cholinergic receptors to evoke increased responses. Eg, Physostigmine, Neostigmine, Edrophonium, Rivastigmine, Galantamine.

2b. Irreversible indirect-acting cholinergic agonist- They bind covalently to AChE, resulting in long lasting increase in ACh. They are mainly synthetic organophosphate compounds that are extremely toxic and were developed by the military as nerve agents. Eg, Echothiophate, Deflofos. Related compounds such as Parathion and Malathion are used as agricultural insecticides.

ANTICHOLINERGIC DRUGS (CHOLINERGIC ANTAGONIST)

They are drugs that bind to cholinergic receptors but do not trigger the usual agonist effect. They are referred to as **Anticholinergic drugs or Cholinergic antagonist or Cholinergic blockers or Parasympatholytics.**

Classification of Anticholinergic drugs with examples: Based on their specific receptor affinities, (Muscarinic M, or Nicotinic N, receptors) that is antagonised, they are divided into two broad types, namely;

1. Antimuscarinic drugs- They selectively block M_r at the neuro-effector organ of PS, hence effect of PS are antagonised/interrupted while effect of SS left uninterrupted. Conventionally the term Anticholinergic drugs is used to mean (restricted to) Antimuscarinic drugs, though ideally should include Antinicotinic drugs (ie ganglionic and neuromuscular blockers). All Antimuscarinic drugs are competitive antagonist and are further divided into three subtypes, namely;

- 1a. Natural alkaloids- Eg, Atropine and Hyoscine (Scopolamine)
- 1b. Semisynthetic derivatives- Eg, Ipratropium bromide and Tiotropium bromide etc.
- 1c. Synthetic compounds- Eg Oxybutynin (vesicoselective) and Trihexyphenidyl (antiparkinsonian), Cyclopentolate, Tropicamide(mydriatics) Propantheline etc.
2. Anticholinergic drugs- They block N_A, they are divided into two types;
 - 2a. Ganglionic blockers- They block N_A of both SS and PS at the ganglia. Eg, Nicotine, Mecamylamine. Clinically they are the least important of the Anticholinergic drugs.
 - 2b. Neuromuscular blockers- They block N_A of SNS at the neuromuscular junction, hence block the transmission of efferent impulses to skeletal muscle. Eg Atracurium, Pancuronium, Succinylcholine (Suxamethonium).

PHARMACOLOGY OF SOME THERAPEUTICALLY USEFUL PARASYMPATHETIC DRUGS.

PHARMACOLOGY OF PILOCARPINE (P).

Definition/MOA; Pilocarpine(P) is an alkaloid-direct acting cholinergic agonist. It is a tertiary amine and is stable to hydrolysis by AChE. Compared to ACh and its derivatives, it is far less potent but is uncharged and will penetrate the CNS at therapeutic doses. Pilocarpine exhibits muscarinic activity and is used primarily in ophthalmology.

Effects of Pilocarpine; The effect of Pilocarpine is basically due to its stimulation of cholinergic receptors of the Parasympathetic (P) system (S).

On the Eye- Applied topically on the eye, it penetrates the cornea and produces;

1. constriction of ciliary muscle, allowing the lens to thicken/focus for near vision (accommodation).
2. It constricts the pupil (Miosis), hence protecting the pupil from excessive bright light.
3. More importantly, it also causes a fall in the intra-ocular pressure in the eye, lasting 4-8 hours. While Pilocarpine causes miosis (contraction of the pupil), Atropine, a cholinergic/muscarinic antagonist has an opposite effect by causing mydriasis (dilatation of the pupil).

On Sweat/Salivary/Lacrimal gland.- Pilocarpine is one of the potent stimulators of secretion (secretagogue or sialogogue), causing marked sweating, salivation and tears. However its use for producing these effects is limited due to its lack of selectivity.

Therapeutic uses; In glaucoma- P (0.5% - 4% eyedrops) is used to treat glaucoma and it is the drug of choice in the emergency lowering of intraocular pressure of both narrow-angle (closed-angle) and wide-angle (open-angle) glaucoma. P is extremely effective in opening the trabecular meshwork around the canal of Schlemm, causing an immediate drop in intraocular pressure as a result of increased drainage of aqueous humour. Carbonic anhydrase inhibitors such as Acetazolamide and Timolol (a beta adrenergic blocker) are effective in treating chronic glaucoma but not used for emergency lowering of intraocular pressure.

Adverse effect; P can enter the brain and cause CNS disturbances. Poisoning with P is characterised by exaggeration of Parasympathetic effects such as sweating and salivation.

GANGLIONIC STIMULANTS AND BLOCKERS PROPERTIES

Ganglionic(G) Stimulants and Properties- They are Nicotinic receptor agonist which act like ACh but stimulate mainly the N_r at ANS (SS and PS) ganglia (ie N_N) than N_r at Nm_j (N_m) and other receptors located elsewhere in human body. The drugs which act on **N_N are more selective**, mediating the **primary** rapid depolarization of G cells. However, there are subsidiary receptors (M₁, M₂, adrenergic, dopaminergic and peptidergic) which mediate **secondary** changes (slowly developing but longer lasting) in membrane potential that modulate the primary response. Therefore ANS ganglia is not merely a one transmitter to one cell synapse, but a complex system capable of local adjustments in the level of excitability.

Ganglionic stimulants are classified as follows;

1. Selective Nicotinic agonist- Eg, Nicotine (small dose), Lobeline, Dimethyl phenyl etc.
2. Nonselective/Muscarinic agonists- Eg, ACh, Carbachol, Pilocarpine.

Ganglionic Blockers and Properties- They specifically act as nicotinic receptor antagonist of both sympathetic and parasympathetic autonomic ganglia, which competitively block the action of ACh and similar agents. They show no selectivity towards the SS or PS ganglia and are not effective as Neuromuscular antagonist, hence they block the entire output of ANS at **N_N**. Consequently the effect of these non-depolarising (competitive, antagonistic) blockers are complex with intolerable adverse effect, therefore Ganglionic blockers are rarely used therapeutically (clinically the least important anticholinergics) but serve as a tool in experimental pharmacology.

Ganglionic blockers are classified as follows:

1. Competitive blockers (non-depolarising);
 - 1a. Quaternary ammonium compounds- Eg, Hexamethonium.
 - 1b. Tertiary/Secondary ammonium compounds- Eg, Mecamylamine.
 - 1c. Monosulfonium compound- Eg, Trimethaphan, camforsulfonate
2. Persistent depolarising blockers- Eg, Nicotine (large dose), Anticholinesterases (large dose)

SKELETAL MUSCLE RELAXANTS

Skeletal muscle relaxants (SMR) are drugs that act peripherally at neuromuscular junction fibre or centrally in the cerebrospinal axis to reduce muscle tone or cause paralysis. They are used primarily in conjunction with general anaesthetics to provide muscle relaxation in surgery while the centrally acting muscle relaxants are used mainly for painful muscle spasms and spastic neurological conditions.

Classification: There are two basic types,

1. Neuromuscular blocking drugs;
 - 1ai. Nondepolarising (Competitive) Neuromuscular blockers- They are structural analogues of ACh which act as **antagonist**(competitively) without causing depolarisation at

the nicotinic receptor on the motor endplate of Nmj. Eg Tubocurarine (long acting), Vencuronium (intermediate acting) and Mivacurium (short acting)

1bii. Depolarising (Non-competitive) Neuromuscular blockers- Eg, Succinylcholine (Suxamethonium).

1c. Directly acting muscle relaxants- . Eg Dantrolene and Quinine. Dantrolene, though a spasmolytic agent has no significant central effect and is used primarily to treat 'malignant hyperthermia' (a rare anesthetic-related complication).

2. Centrally acting muscle relaxants- They reduce skeletal muscle tone (spasticity) by a selective action in the cerebrospinal axis, without altering consciousness. Eg, Diazepam, Baclofen, and Tizanidine, methocarbamol, chlorzoxazone etc.

PHARMACOLOGY OF SUCCINYLCHOLINE (SUXAMETHONIUM) AS A SKELETAL MUSCLE RELAXANT (NEUROMUSCULAR BLOCKER).

SUCCINYLCHOLINE (SUXAMETHONIUM), S:

Definition/Mech Of Action- S is a depolarising neuromuscular blocking drug. Like ACh, it binds the N r on motor endplate of Neuromuscular junction (Nmj), acting as **agonist** (non-Competitive) to cause depolarisation of plasma membrane of skeletal muscle. S is the only clinically useful depolarising muscle relaxant/blocker in use. However unlike ACh which is instantly destroyed by AChE, S persist at high concentration in the Nmj (synaptic cleft), remaining attached to N r for a relatively longer time and providing constant stimulation of N r. The duration of action of S is independent on diffusion from the motor endplate and hydrolysis by plasma pseudo-cholinesterase. S first causes the opening of the sodium channel associated with N r, which results in depolarisation (**called phase 1 block**). This leads to a transient twitching of the muscle (fasciculation). Continued binding of S renders the N r incapable of transmitting further impulses. With time, continuous depolarisation gives way to gradual repolarisation as the sodium channel closes or is blocked. This causes a resistance to depolarisation, ie desensitization (**called phase 2 block**) or flaccid paralysis.

Effects- admin of IV S, cause muscle weakness followed by flaccid paralysis.

Pharmacokinetics- All the Neuromuscular blocking drugs including S are highly polar compounds and inactive orally, hence they must be administered parenterally (IV). S is rapidly broken down by plasma pseudo-cholinesterase, consequently its duration of action is normally very short and therapeutic benefit last only a few minutes. (It induces rapid, complete and predictable paralysis with spontaneous recovery in 5-10 minutes). However S that gets to the Nmj is not broken down by AChE, allowing it to bind to N r and redistribution to plasma is necessary for breakdown/metabolism.

Therapeutic uses; Endotracheal intubation, Treatment of convulsion

Adverse effect; Hyperkalemia, Hyperthermia- When halothane is used as an anaesthetic, admin of S has occasionally caused malignant hyperthermia (with muscular rigidity, metabolic acidosis, tachycardia and hyperpyrexia) in genetically susceptible people. This is treated with Dantrolene.