No.6

Doctor 2022 - أثر - Medicine - MU

Pharmacology Sheet

DOCTOR:

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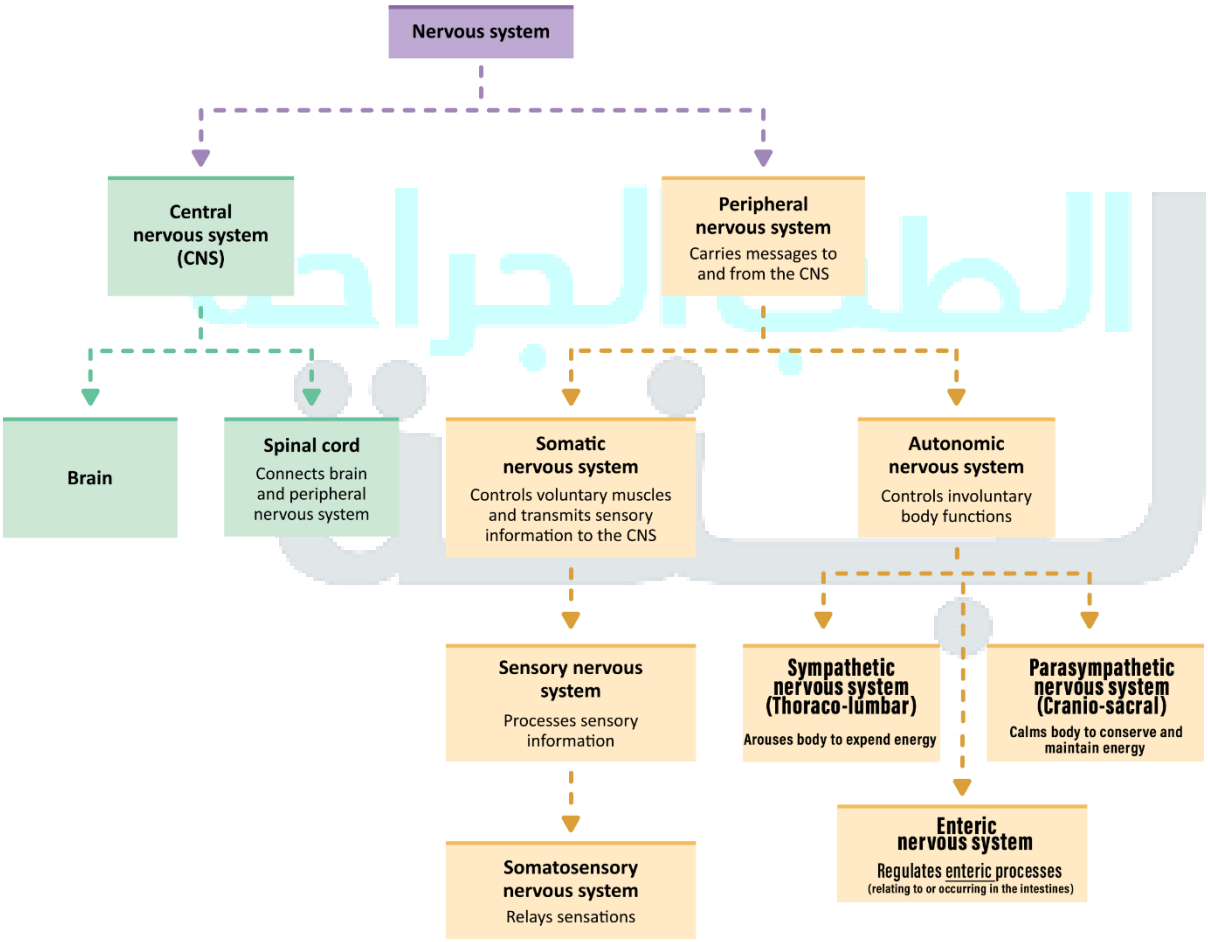
Autonomic Pharmacology and Direct-acting Cholinomimetics

Autonomic Pharmacology:

Intro:

- **Nervous system:**
  1. **CNS (central nervous system):**
     - **Brain**
     - **Spinal cord**
  2. **Peripheral NS:**
     - **Somatic nerves**
     - **ANS (autonomic nervous system)**

- **The diagram below is from an extra source.**



ANS:

- Autonomous:
  - Responsible for visceral involuntary functions.
  - Important to maintain life (unconscious control)
  - E.g. Smooth & Cardiac m. (muscles), exocrine glands.
  - Remember: Neurotransmitter (NT) -> binds receptor -> yields action.
- Consists of:
  - Sympathetic system (Thoraco-lumbar)
  - Parasympathetic system (Cranio- sacral)
  - Enteric nervous system
- Consists of:
  - Medullary centers.
  - Preganglionic fibers.
  - Ganglia.
  - Postganglionic fibers.
- Lacrimal gland, sweat gland, salivary gland and intestine all have PNS receptors. Depending on the location of the receptor(s) the action will be determined.

Sympathetic Vs. Parasympathetic:

Sympathetic	Parasympathetic
Act at stress, trauma, hypoglycemia	Acts at rest
Cold & Exercise	Opposes sympathetic
Fight or flight response	Regulates digestion, bowel and urinary function

- Sympathetic -> adrenergic receptors -> fight or flight. On response to stimulation -> adrenaline and noradrenaline will be released.

Direct- acting Cholinomimetics:

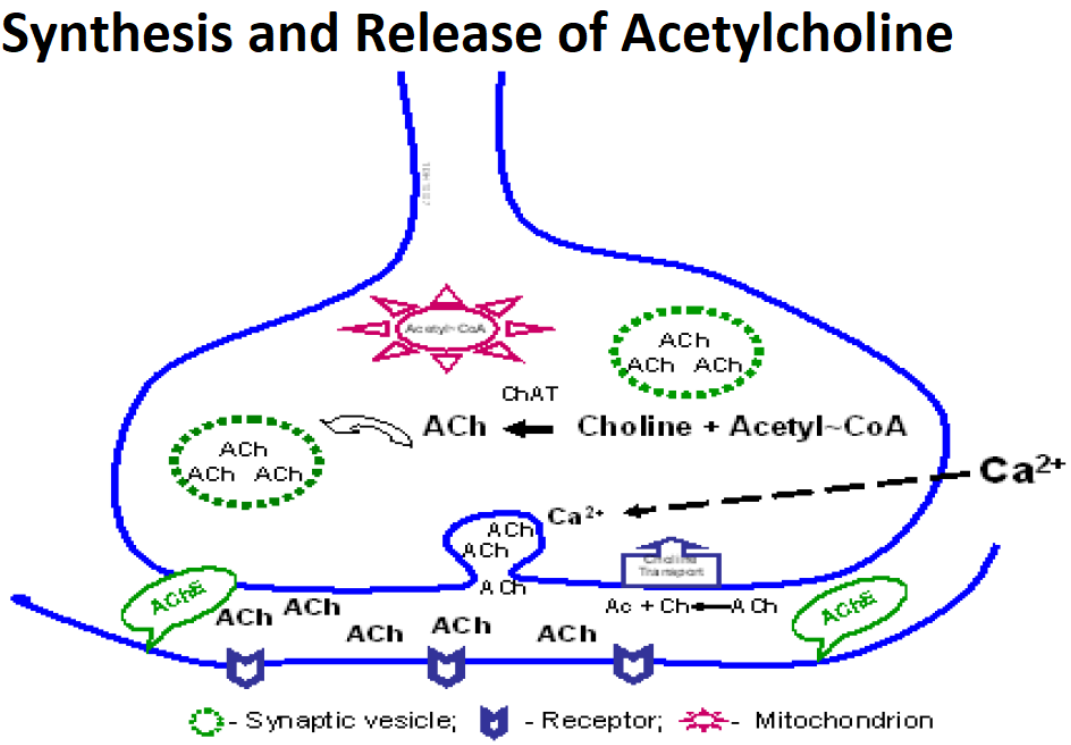
- Direct means it has an activity on muscarinic receptors.

Cholinomimetics:

- Agents that mimic or simulate actions of Ach (acetylcholine)
- Ach is neurotransmitter of cholinergic nerves acts on cholinoceptors (cholinergic receptors) in:
  - Ganglia
  - Postsynaptic endings of the parasympathetic sys (system)
  - Adrenal medulla
  - NMJ (neuromuscular junction) endplates (or motor endplates)

Pathway of Acetylcholine:

- **The main NT of PNS is Ach.**
- **Choline is the precursor needed to start synthesizing Ach. Choline is directly transported from cytoplasm to vesicles -> protective mechanism.**
- **Synthesized in the cytoplasm of cholinergic nerve terminals from Acetyl-CoA & choline:**
- **By the action of choline acetyl transferase enzyme (CAT).**
- $Acetyl - CoA + Choline \xrightarrow{CAT} Ach$
- **Storage in vesicles.**
- **Release**
  - **Action potential:**
  - **Depolarization:** ⟶
  - **Influx of Ca: Increase intraneuronal Ca:** ⟶
  - **Fusion of storage vesicles with membrane** ⟶
  - **Expulsion & release of Ach (exocytosis)**



- **Binding and activation of cholinoceptors.**
  - **Actions**
- **Degradation:**
  - $Ach \xrightarrow{Cholinesterase} Choline + Acetate$
  - **Cholinesterase is specific to Ach (or true cholinesterase enzymes= only for Ach).**
  - **Pseudocholinesterase (PCE) in plasma and liver is not specific (binds many substances and has various locations); acts on others as suxamethonium and succinylcholine.**

- ♦ $Genetic\ absence\ PCE \rightarrow Prolonged\ apneoa$

- **Recycling:**
  - **Recycling of choline back into neurons.**
  - **Inhibitors of Ach pathway:**
    - ♦ **Release: Botulinum toxins.**
    - ♦ **Binding of Ach: Anti-cholinergic drugs.**

Locations and Function of Cholinoceptors:

- **Cholinoceptors are of two types: Muscarinic (where muscarine [a natural substance found in mushrooms] or muscarine- like substances bind) and Nicotine (where nicotine or nicotine- like substances bind).**
- **Depending on 1) the type of the receptor and 2) its location -> different actions -> specific treatments as well as routes of administration.**

- **Muscarinic receptors:**

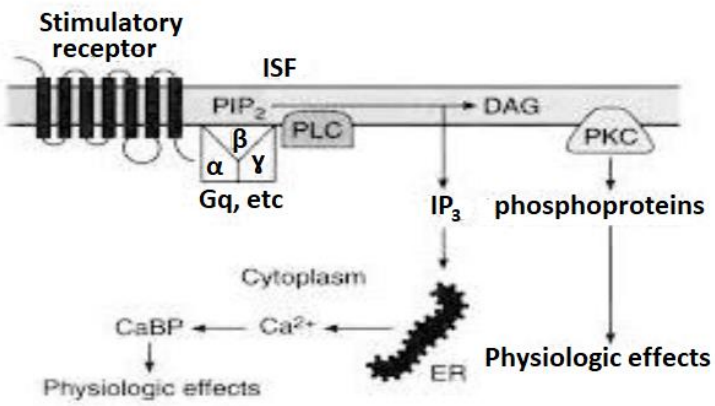
Receptor:	*Location:*	*Function:*
M_1	CNS	Excitatory
	Parietal cells on stomach, a good choice for constipation Tx.	↑ Gastric secretion
M_2	Myocardium	↓ Rate, contractility. So, on ↑ doses -> hypotension
M_3	Vascular SM (smooth muscles)	Relaxation
	Endothelium	Nitric oxide production
	Circular M (muscle) of iris	Miosis
	Exocrine, GIT	↑Secretions
	GIT& Bladder wall	Contraction
	Sphincters (intestine and urinary bladder)	Relaxation
	Bronchi	Constriction, contraindicated in asthmatic patients.

- **Muscarinic receptors are found in corpora cavernosa of penis where:**
  - ♦ **Through release of nitric oxide**
  - ♦ **And vasodilatation**
  - ♦ **Leads to erection**

- Nicotinic receptors:

Receptor:	*Location:*	*Function:*
Nicotinic N_N (Nerve with Nerve)	Ganglia	Stimulation
	Adrenal medulla	Adrenaline& NA (noradrenaline) release
Nicotinic N_M (Nerve with Muscle)	NMJ endplates	Muscle contraction

Mechanism of Ach signal transduction:



- Muscarinic receptors:
  - G- protein coupled receptors (GPCR).
  - Second messengers (as DAG, IP3, cGMP)
- Nicotinic receptors:
  - Ion channel receptors

Acetylcholine:

- Has little therapeutic value. Why? 1) short duration and 2) rapidly degraded by cholinesterase(s).
  - Multiple actions:
    - ♦ Binds & activates muscarinic & nicotinic receptors
    - ♦ Short t ½

○ ***Pharmacodynamics of Ach:***

- Muscarinic stimulation on the CVS (cardiovascular system)
  - Decrease SV (stroke volume) & CO (cardiac output)
    - ♦ By -ve (negative= decreases) (chronotropic [related to heart rate], inotropic [related muscle contractility] & dromotropic [related to rate of conduction through AV node])
  - Decrease ABP: (arterial blood pressure)= hypotension; we have 2 causes:
    - ♦ 1) Stimulation of vascular M_3 receptors in endothelium -> Increase nitric oxide -> Vasodilation (VD) -> hypotension
    - ♦ 2) Stimulation of M_2 receptors in heart -> VD -> hypotension.
  - Cardiac arrest usually results from either poor diagnosis or dosage adjustments -> people die while sleeping.

- Eye:
  - Miosis:
    - ♦ Contraction of the circular muscle of the iris

- Accommodation to near vision:
  - Contraction of the ciliary muscle
- Decrease IOP (Intraocular pressure).

- Exocrine glands:
  - Increase secretion

- Increase intestine movement with relaxation of sphincter: ⟶ defecation

- Contraction of urinary bladder wall with relaxation of the sphincter: ⟶ urination

- Bronchi:
  - Broncho- constriction
  - Mucosal hypersecretion

- Stimulation of nicotinic cholinoceptors:
  - Effects on ganglia
  - Adrenal medulla
  - NM Junction transmission

Direct- acting Cholinomimetics:

1. Choline esters:
- Prototype is Ach (acetylcholine)
- Bethanechol, Carbachol, Methacholine
  - Resist degradation by cholinesterase(s)
  - Have longer duration of action than Ach
  - Can be summed in MBC
2. Natural alkaloid:
- Prototype is muscarine
- Pilocarpine:
  - Acts directly on the eye
- Can be summed in PM

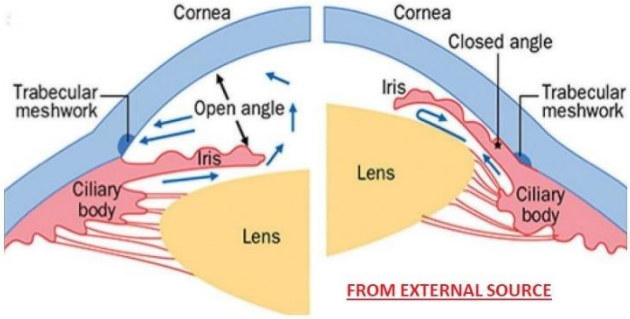
- To sum up all the direct- acting cholinomimetics: Watch MBC @ PM:
  - MBC @: Methacholine, Bethanechol, Carbachol and Ach are choline esters.
  - PM: Pilocarpine and Muscarine are natural alkaloids.

- ***Bethanechol:***

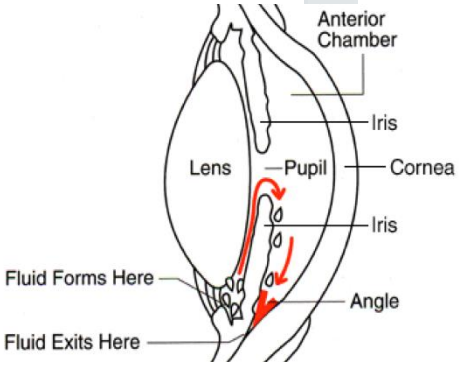
- Derivative of Ach which has little or no nicotinic effect
  - Good muscarinic activity on bladder & GIT
- Prokinetic agent (promote the passage of ingested material in the gastrointestinal tract).
- Leads to easier urination and defecation
- Used in treatment of:
  - Postoperative (Postop) or post- labour urinary retention or paralytic ileus (prokinetic).

- ***Carbachol:***
- **Derivative of Ach**
- **Has muscarinic & nicotinic actions**
- **Limited systemic uses because of its nicotinic stimulatory effects on ganglia & adrenal medulla with consequent changes in the CVS & other systems. -> activating both M and N at the same time will lead to overlapping between functions of different tissues -> a huge problem.**
- **Glaucoma: increased intraocular pressure (IOP) leading to optic nerve damage. One of the main causes of this high IOP is the buildup of vitreous humor which is linked to ciliary muscles weakness.**
- **Used topically as miotic agent to decrease high IOP in glaucoma.**

- ***Pilocarpine:***
- **Natural alkaloid**
- **Resistant to cholinesterase**
- **Its muscarinic action in eye result in miosis & contraction of ciliary muscle**
- **Used topically in glaucoma:**
  - **To lower high IOP in glaucoma**
  - **In open (the drainage angle formed by the iris and cornea remains open) or close- (drainage angle formed by the iris and the cornea closes or becomes obstructed) angle glaucoma.**



- ***Mechanism of Pilocarpine action:***
- **Improves outflow of aqueous humor**
- **Opens fluid pathways**
- **Enhances aqueous flow through canal of Schlemm:**
  - **Contraction of ciliary muscle upon stimulating M_3 receptor & circular muscle of iris -> the built-up fluids will exit -> reduction of IOP.**
- **Stimulates salivation and sweating**



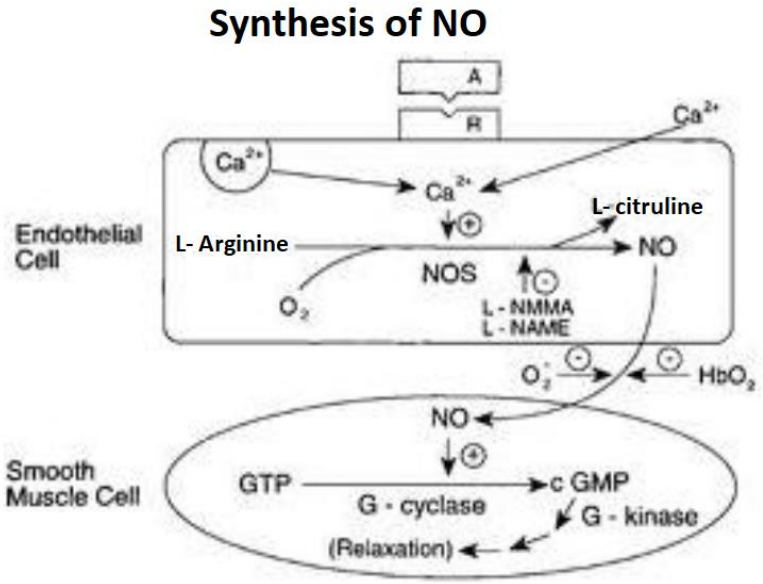
Indications of Direct Cholinomimetics:

- **Stimulate bladder & bowel function after surgery or labor (Bethanechol)**
- **Glaucoma (Pilocarpine & Carbachol)**
- **Pilocarpine orally to treat xerostomia (excessively dry mouth) of Sjogren's (pronounced Show-grin's) syndrome.**

Adverse effects of Direct Cholinomimetics:

- Exocrine glands -> increased stimulation -> Excessive sweating, salivation
- Abdominal colic, diarrhoea
- To treat the two above, give anti-M_1 and anti-M_3 medications.
- Flushing, hypotension
- Bronchospasm
- Pilocarpine: impaired accommodation to far vision & darkness (also carbachol)

Synthesis of NO:



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Summary of direct- acting cholinomimetics: EXTRA

Class:	Drug Name:	Origin:	Activity:	Effect(s):	Used in: (Treatment for)	Adverse Effects:	Notes:
Choline Esters	Acetylcholine	Acetylcholine	M & N	1.Muscarinic stimulation on CVS: ↓ SV & CO (-ve chronotropic, inotropic and dromotropic) ↓ ABP (vascular M_3 receptors and ↑ NO) 2. Eye: miosis, accommodation to near vision and ↓ IOP. 3. ↑ exocrine glands secretions. 4. defecation 5. urination 6. Broncho-constriction and mucosal hypersecretion. 7. Nicotinic stimulation: effects on ganglia, adrenal medulla and NMJ transmission.	- Of a little therapeutic value.	1. Excessive sweating, salivation. 2. Flushing, hypotension. 3. Abdominal colic, diarrhoea. 4. Bronchospasm. 5. Pilocarpine and Carbachol: impaired accommodation to far vision and darkness.	- short t ½
	Bethanechol		M (little or no N)	1.Good muscarinic activity on bladder and GIT→ Prokinetic agent → urination and defecation.	- Postop/ post labor urinary retention or paralytic ileus → stimulates bladder and bowel function.		1.Resist degradation by cholinesterase and 2. Have longer t ½ than Ach
	Carbachol		M & N	1.Limited systemic use → stimulatory nicotinic effects on ganglia and adrenal medulla → CVS and other systems effects. 2. Topically: miotic agent to ↓ IOP in glaucoma.	-Glaucoma		
	Methacholine						
Natural Alkaloid	Muscarine	Muscarine					
	Pilocarpine		Eye M action & others	1.Eye muscarinic action→miosis and contraction of ciliary muscle.	-Topically in glaucoma: to ↓ high IOP in glaucoma and in open or close- angle glaucoma. -Orally: xerostomia of Sjogren's syndrome.		Special MOA