PHARMACOLOGY
TEAM 439

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MED439
KING SAUD UNIVERSITY

Editing file

DIRECT CHOLINERGIC DRUGS

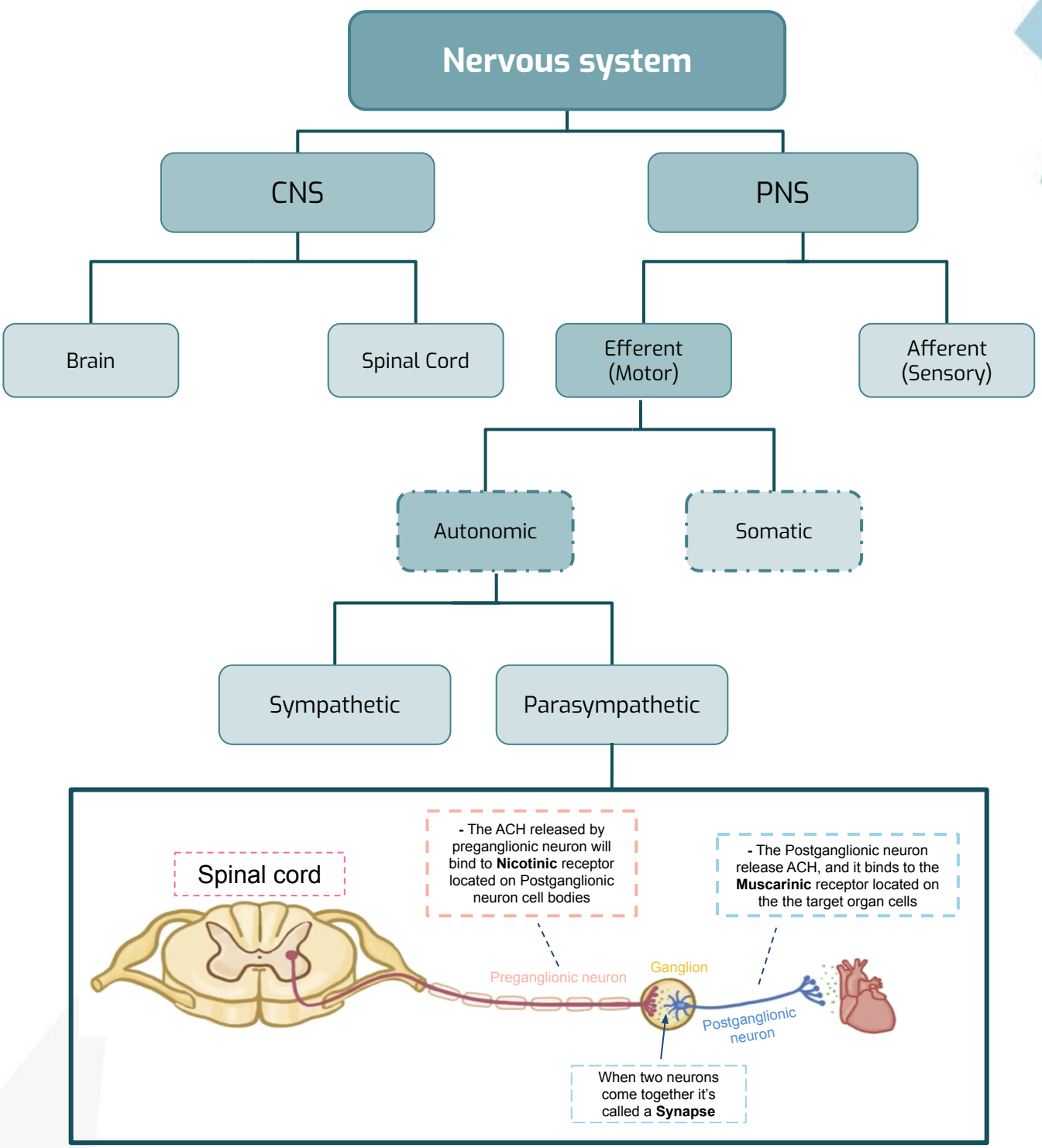
Lecture 3

OBJECTIVES:

- Mention the different types, locations and actions of cholinergic receptors.
- Identify the mechanism of action of direct acting cholinomimetics.
- Describe the pharmacokinetics of cholinergic drugs.
- Identify pharmacological actions and uses of cholinomimetics.

Important
In male and female slides
Only in male slides
Only in female slides
Extra information

Helpful video



Comparison of Autonomic and Somatic Motor Systems

	Cell bodies in central nervous system	Peripheral nervous system	Neurotransmitter at effector	Effector organs	Effect
SOMATIC NERVOUS SYSTEM		Single neuron from CNS to effector organs; Heavily myelinated axon	ACh	Skeletal muscle	+ Stimulatory
AUTONOMIC NERVOUS SYSTEM — SYMPATHETIC		Two-neuron chain from CNS to effector organs; Lightly myelinated preganglionic axons; ACh; Ganglion; Unmyelinated postganglionic axon; Epinephrine and norepinephrine; Adrenal medulla; Blood vessel	NE	Smooth muscle (e.g., in gut), glands, cardiac muscle	+ — Stimulatory or inhibitory, depending on neuro-transmitter and receptors on effector organs
AUTONOMIC NERVOUS SYSTEM — PARASYMPATHETIC		Lightly myelinated preganglionic axon; ACh; Ganglion; Unmyelinated postganglionic axon	ACh		

Acetylcholine (ACh) Norepinephrine (NE)

Cholinomimetics

Are drugs that produce actions similar to stimulation of parasympathetic system or similar to Acetylcholine, **and It's divided into two types:**

Direct Cholinomimetics:
It causes direct stimulation of cholinergic receptors (Nicotinic, Muscarinic receptors). The Cholinergic drug will directly bind with cholinergic receptors.

Indirect Cholinomimetics:
Acts indirectly by inhibiting Acetylcholinesterase, thus prevent the hydrolysis of Ach. They are called (cholinesterase inhibitors or anticholinesterases).

Acetylcholinesterase is an enzyme that break down ACH to stop muscle contraction.

Cholinergic (Parasympathetic) receptors

They open when they bind to ACH

Nicotinic receptors

- It's a **type I receptor:** Ion channel linked receptor.
- **Location and Action:**

skeletal Muscles (Neuromuscular junction,Nm):
- Low concentration (Therapeutic dose) → muscle contraction.
- High concentration (Toxic dose) → Persistent depolarization & relaxation (Blocking of depolarization) Constant contraction of muscles means there is no repolarization which is essential for muscle relaxation, leading to muscle paralysis.

Autonomic ganglia (Nn) → Sympathetic and Parasympathetic stimulation.

Adrenal Medulla (Nn) → Release of Catecholamines (Adrenaline & noradrenaline)

CNS (Ns)

- **Subclasses:** Nn: Nerve to Nerve.
  Nm: Nerve to Muscle.
- **Pharmacological Action:** Almost excitatory (Cause excitation)

Muscarinic receptors

- It's a **type II receptor:** G-Protein linked receptor..
- **Location:**
  Located at all organs that are innervated by parasympathetic fibers (e.g., Heart, CVS, Eye, Bladder, etc..)
- **Action:**
  Heart → Bradycardia
  Exocrine glands → Secretion
  Smooth muscle → Contraction
  The actions are explained in details in the next slide
- **Subclasses:**
  M1, M3, M5,: Excitatory.الاعداد الفردية
  M2, M4: Inhibitory. الاعداد الزوجية
- **Pharmacological Action:** excitatory or Inhibitory.

Muscarinic Receptor	Location	Action
M1 Excitatory	CNS	CNS excitation
	Gastric parietal cells	Gastric acid secretion (Leading to peptic ulcer)
M2 Inhibitory	Heart endothelium	Bradycardia (cardiac inhibition: decrease in heart rate)
M3 Excitatory	Exocrine glands	Increase of exocrine glands secretion: sweat,, saliva, lacrimal, bronchial, nasopharyngeal and intestinal glands.
	smooth muscle	- Smooth muscle contraction - Uterus is not sensitive to muscarinic agonist.
	GIT	- Smooth muscle contraction - Increase in motility of GIT (peristalsis), may lead to diarrhea. - Relaxation of sphincter causing defecation.
	Urinary tract	Relaxation of sphincter leading to urination.
	Lung	- Constriction of bronchial smooth muscle - Increase bronchial secretion - **Contraindication: Asthma**
	Vascular endothelium	Vasodilation via Nitric Oxide
	Eye	- Contraction of circular muscle iris (Miosis) - Contraction of ciliary muscles for near vision - When these two contractions happen, a decrease in intraocular pressure happens.
M4&M5	CNS	Memory, arousal, attention and analgesia.

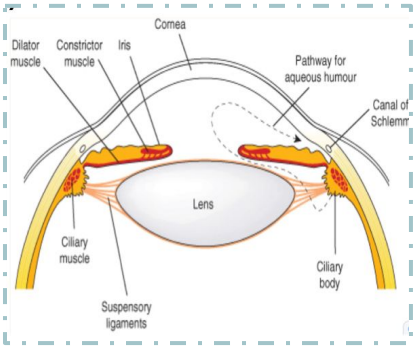
M1 in the 1st (most) important organ (Brain)
M2 in the 2nd (most) important organ (Heart)

Botox:

Is a Botulinum toxin that is produced by Clostridium botulinum

Parasympathetic Action On Eye

- It innervates the **constructor pupillae** (circular muscle of iris) which is important for adjusting the pupil in response to **change in light intensity and regulating the intraocular pressure**
- **Aqueous humor** secreted by **ciliary body** is removed continuously by drainage into the **canal of schlemm**
- **Normal intraocular pressure: 10-15 mmHg** above atmospheric pressure, abnormally raised pressure (glaucoma) leads to retinal detachment.
- **Cholinergic drugs leads to miosis which decreases the intraocular pressure in glaucoma by increasing the filtration angle**
- When the ciliary muscle contracts, the lens **bulges** more, this parasympathetic reflex is essential to **accommodate for near vision**



If the ciliary body is contracted the canal of Schliemann will open allowing the drainage of fluids

Direct Acting Cholinergic Drugs	Natural Alkaloids	Synthetic Choline Esters
Features	• Are lipid soluble nitrogen nonpolar compound found in nature • Tertiary amines • Common suffix (ine) which means natural and basic	• Polar (contains N ion) • quaternary ammonium compounds • Muscarinic quaternary amine not well absorbed in the GIT (orally) but still toxic when ingested in mushrooms
Examples	• Pilocarp**ine** • Nicot**ine** • Lobe**line** Nicotine & lobeline have alerting actions on the CNS and high levels of nicotine leads to convulsions(تشنجات) and coma	• Acetylcholine • Carbachol • Bethanechol • Cevimeline • Methacholine (3x more resistant to hydrolysis)
Pharmacokinetics	• Non-polar , lipid soluble • Well absorbed by the skin	• Poor distribution • Cannot cross BBB so no CNS effects • Not metabolized by cholinesterase **except** Ach • All of them have longer duration of action than Ach • Never given I.V. or I.M. But S.C. Why ? Because it may cause cardiac arrest but if you have to inject it that way then do it slowly
Contra-indications	• Bronchial asthma • Peptic ulcer • Angina pectoris (الذبحة الصدرية) (M3) • Urinary incontinence (inability to hold in urine, increase urination) • Intestinal obstruction (it will increase motility which will lead to perforation with this obstruction)	

Natural Alkaloids

Pilocarpine

It is not a derivative of Ach

It is not ester it is amine

M.O.A Mechanism Of Action	• Direct muscarinic agonist • Acts mainly on eye and secretion
P.K Pharmaco kinetics	• Non-polar (lipophilic) tertiary amine • Well absorbed, good distribution • Cross BBB, so has CNS effects • Cross placenta • Not metabolized by cholinesterase • Long duration of action • Excretion is enhanced by acidification of urine Because basic drugs are best excreted in acidic medium
Uses	• Xerostomia (dry mouth) • Drug of choice in emergency glaucoma (applied as eye drops)
Side effects	• Profuse sweating • Salivation (but it is desirable in dry mouth) • Bronchoconstriction (never given to patients with asthma) • Diarrhea • CNS effects

Synthetic Choline Esters

	M.O.A	P.K	Uses	Side effects
Acetylcholine	Muscarinic and nicotinic agonist	—-	Not used clinically. (Why ?) Because it's not as selective as it acts on both muscarinic and nicotinic receptors. Has short duration of action (Why ?) due to rapid metabolism by acetylcholinesterase	—-
Carbachol (carbamoylcholine)	Muscarinic action on the eyes GIT, UT Has nicotinic action (side effects)	Resistant to hydrolysis by acetylcholinesterase ⇩ Longer duration than Ach	**Treatment of glaucoma** as eye drops only	Nicotinic side effect
Bethanechol (Carbamoyl-β -methylcholine)	Prominent muscarinic action on GI,UT No nicotinic actions due to the presence of methyl group which reduce its potency at nicotinic junction	Resistant to hydrolysis by acetylcholinesterase ⇩ Longer duration than Ach	Drug of choice in **paralytic ileus** (Which is a failure of intestinal motility) **Urinary retentions** in case of postoperative atony and neurogenic bladder	—-
Cevimeline	Direct acting muscarinic agonist (M3)	—-	**Treatment of the dry mouth symptom associated with Sjogren's syndrome** Sjogren's syndrome: autoimmune disease characterized by formation of antibodies leading to dryness of mouth and eye **Patient who have cancer in (head ,neck) and treated by radiation ; that will lead to dry mouth**	—-

This slide was Found in Male's slides only

Glaucoma (in the eye)

1- Primary

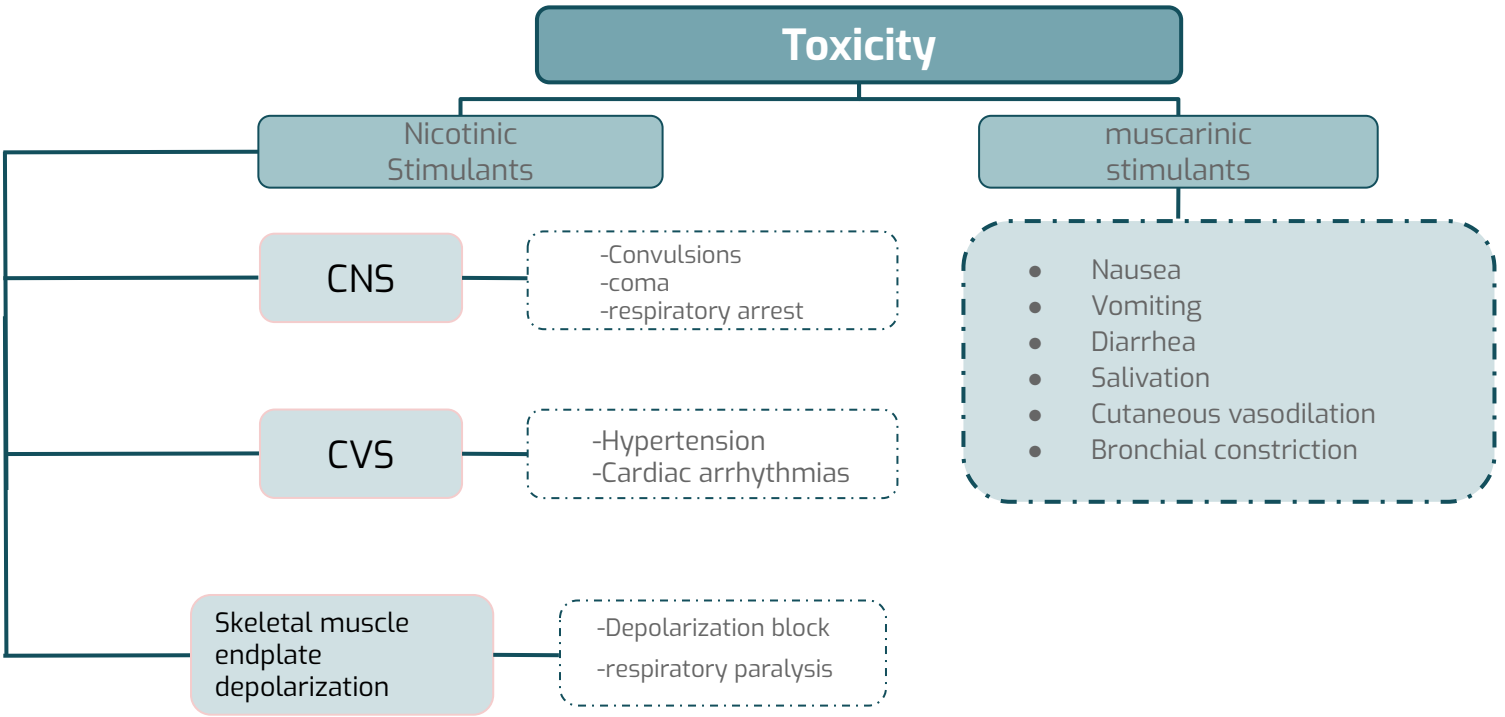
- Angle closure
- Open angle (Blockage of trabecular meshwork)

2- Secondary

- Trauma, inflammation, surgery.

Acute angle closure:

- medical emergency, initially treated by drugs
- Permanent correction is by surgery (**iridectomy**)
- Muscarinic stimulants (**Methacholine, Carbachol, Pilocarpine**) decrease Intraocular pressure by:
  - Facilitating outflow of aqueous humor
  - Decrease rate of secretion



Treatment

- Muscarinic excess —> Atropine
- CNS stimulation —> central anticonvulsants e.g. Diazepam
- Neuromuscular block —> mechanical respiration

Chronic Nicotine Toxicity

- 30% of death due to cancer and coronary heart disease are due to smoking
- Nicotinic contributes to increase the risk of vascular diseases sudden coronary death and ulcers

Next slide is a summary

Drug	Acetylcholine	Carbachol	Bethanechol	Pilocarpine	Cevimeline
Chemistry	Quaternary polar	Quaternary polar	Quaternary polar	Tertiary Non polar	—
Absorption	Not	Better absorbed than Ach		Complete	—
Metabolism	Metabolized by cholinesterase	Not metabolized by cholinesterase			—
Duration	Very short	Long			—
Administration	I.V eye drops	Oral, eye drops, S.C	Oral, S.C	Oral, eye drops	—
Receptor	Muscarinic & Nicotinic	Muscarinic & Nicotinic	Muscarinic	Muscarinic	Muscarinic
Muscarinic	All				
Nicotinic	Yes		No		
Selectivity	Not	Eyes, GIT, Urinary bladder	GIT,Urinary bladder	More in eyes, Exocrine glands	Exocrine glands
Uses	No	Glaucoma	Paralytic ileus, Urinary bladder	Glaucoma, Xerostomia. dryness of mouth	Sjogren's syndrome

MCQ

MQ team made some Questions for you to solve!! **Check them out here**

1- Which one of the following is an inhibitory in function			
A- M1	B- M3	C- M2	D- M5

2- A class of nicotinic receptor found in CNS and Adrenal medulla			
A- Nn	B- Nm	C- Nb	D- Nc

3- Muscarinic receptors are found in ?			
A- Heart	B- Eye	C- CVS	D- All of them

4- which one of the following is used in Sjogren's syndrome			
A- Pilocarpine	B- Cevimeline	C- Carbachol	D- Bethanechol

5- Which on of the following can cross BBB ?			
A- Pilocarpine	B- Bethanechol	C- Cevimeline	D- Acetylcholine

6- Which one of the following is an example of Natural Alkaloids ?			
A- Acetylcholine	B- Methacholine	C- Nicotine	D- Carbachol

7- The normal intraocular pressure is ?			
A- 10-15 mmHg	B- 10-20 mmHg	C- 20-30mmHg	D- 30-35 mmHg

8- Which one of these has the shortest duration of action ?			
A - Carbachol	B- Acetylcholine	C- Bethanechol	D- pilocarpine

ANSWERS

1	2	3	4	5	6	7	8
C	A	D	B	A	C	A	B

SAQ

A quick quiz is waiting for you! Just click here

1) What is the muscarinic action in smooth muscle ?

2) In which receptors the cholinergic drugs act on ?

3) what is the function of Adrenal medulla ?

4) Why we don't use Ach clinically ?

5) If we used a drug that acts on M3 receptor at the eye, what are the expected reactions ?

6) A dentist would like to reduce salivation in a patient in preparation for an oral surgical procedure, which receptor will he block to reduce salivation ?

7) What are Cholinomimetics drugs ?

8) What are the targets for both direct Cholinomimetics & Indirect Cholinomimetics ?

ANSWERS

A1) ~~Urinary bladder : contraction of muscles relaxation of sphincter leading to urination / smooth muscle: contraction~~

A2) ~~Nicotinic receptor and Muscarinic receptor~~

A3) ~~Release of Catecholamine (Adrenaline and Noradrenaline)~~

A4) ~~1- Because it's not selective as it acts on both muscarinic and nicotinic / 2- It has short duration of action~~

A5) ~~Contraction of circular muscle iris (Miosis), Contraction of ciliary muscles for near vision, a decrease in intraocular pressure happens.~~

A6) ~~He will block muscarinic receptor (M3) located in the salivary gland.~~

A7) ~~drugs that produce action similar to stimulation of parasympathetic system or similar to Acetylcholine~~

A4) ~~Direct: cholinergic receptors (Nicotinic, Muscarinic receptors) - Indirect: Acetylcholinesterase~~

GOOD LUCK!

LIVE AS IF YOU WERE TO DIE TOMORROW. LEARN AS IF YOU WERE TO LIVE FOREVER.

- MAHATMA GANDHI

Team leaders

طرفة الشريدي

حمود القاضب

Girls team members

منيرة السدحان

لينا المزيد

سديم الحازمي

نورة المسعد

وسام ال حويس

رانيا المطيري

الجوهرة البنيان

شادن العبيد

سديم آل زايد

روان باقادر

ميس العجمي

نورة السالم

نوف السبيعي

ندى بابللي

دانه نائب الحرم

Boys team members

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ماجد العسكر

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