Pharmacology
Team 437

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Editing File

Direct Cholinergic Drugs

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 Notes Extra

Nervous System

Central Nervous System	Peripheral NS	
• Brain • Spinal Cord	• Afferent (Sensory)	• **Efferent (Motor):** Somatic; skeletal muscles Autonomic; Smooth muscles: Sympathetic Parasympathetic Enteric

Autonomic PNS

- It is subdivided into:

✓ Parasympathetic (Cholinergic)
✓ Sympathetic (Adrenergic)
✓ Enteric (For GIT)

Parasympathetic "our drugs will act here"

Preganglionic neurons:
- Long.
- Synapses with postganglionic at or near organ.
- Acetylcholine is neurotransmitter.
- Nicotinic receptor on postganglionic.

Postganglionic neurons:
- Short.
- Synapses on the organ.
- Acetylcholine is neurotransmitter.
- Muscarinic receptor on the organ.

*Cholinergic Fibers:
Fibers release Ach in ANS.

Cholinergic Transmission

- Half-life of Ach is very short.
- Targets for pharmacologic therapy (interventions):

1.Synthesis. 2.Storage. 3.Release. 4.Termination of action of the transmitter. 5.Receptor.

Cholinomimetics

M.O.A	Drugs that produce actions similar to stimulation of parasympathetic system or similar to Acetylcholine.	
Class	**Direct Cholinomimetics**	**Indirect Cholinomimetics**
Action	Cause direct stimulation of cholinergic receptors. Each receptor will give different effect.	Acts indirectly by inhibiting Acetyl cholinesterase thus prevent the hydrolysis of Ach. They are called Cholinesterase inhibitors or anticholinesterases
Site of Action	**Cholinergic drugs act upon two types of receptors:** • Nicotinic receptors • Muscarinic receptors	

Cholinergic or Parasympathetic receptors

Nicotinic receptors (N) "Central Receptors"	Muscarinic receptors (M) "Peripheral Receptors"
Type I receptors: Ion channel linked receptors (Na channels) Located in: Skeletal muscles (Neuromuscular junction) (Nm) Autonomic ganglia (Sympathetic and parasympathetic ganglia) (Nn) Adrenal Medulla(Nn) CNS(Nn) Subclasses: Nm: On muscles Nn: On nerves Stimulated by: Nicotine	**Type II receptors:** G-protein linked receptors Located at: All target organs that are innervated by parasympathetic fibers (Heart, CVS, Eye, Bladder, etc). Internal organs except ventricles Subclasses: M1,M3,M5 are excitatory or stimulatory in function. Smooth muscles and glands M2,M4 are inhibitory in function.Heart Stimulated by: Muscarine

Nicotinic Receptors VS Muscarinic:

Nicotinic receptors Central cholinoceptors	Muscarinic receptors Peripheral cholinoceptors
Almost excitatory	Excitatory or inhibitory
Autonomic ganglia Nn sympathetic & parasympathetic stimulation	On all peripheral organs innervated by postganglionic parasympathetic fibers
Adrenal medulla Nn release of catecholamines (adrenaline & noradrenaline)	Heart (bradycardia, M2) exocrine glands (secretion, M3)
Skeletal muscles Nm contraction	Smooth muscles (contraction, M3) (GIT, urinary tract, bronchial muscles, uterus)

Direct Acting Cholinergic drugs:

✓ EDRF stands for Endothelium Derived Relaxing Factor

Pharmacological actions

- Actions that are similar to the effects of parasympathetic system activation. And are classified according to the type of receptor acting on into: Actions means uses!

Nicotinic Actions	Muscarinic Actions
Drugs produce their effect on nicotinic receptors	Drugs produce their effect on Muscarinic receptors

Cont.

Nicotinic actions	
Skeletal Muscles	• **Low concentration (Therapeutic dose) of Nicotine:** Muscle Contraction • **High concentration (Toxic dose) of Nicotine:** Persistent depolarization and relaxation (Blocking of depolarization). Constant contraction of muscle means there is no repolarization which is essential for muscle relaxation leading to muscle paralysis. Succinylcholine has similar effect.
Autonomic Ganglia	✓ By stimulating it. This happens by both sympathetic and parasympathetic stimulation. Secretion of Neurotransmitters
Adrenal Gland	✓ By stimulation which leads to the release of Catecholamine (Adrenaline and Noradrenaline). Over stimulation leads Adrenergic crisis

Muscarinic Actions	
Eye (M3)	Contraction of circular muscle of iris (miosis) Contraction of ciliary muscles for near vision Decrease in intraocular pressure (IOP)
Heart endothelium (M2)	Bradycardia (decrease in heart rate) Release of Nitric oxide(NO) (EDRF) Affects blood vessels
Lung (M3)	Constriction of bronchial smooth muscles and increase bronchial secretion
GIT (M3)	Increase in motility(peristalsis) ↑ Increase in secretion Postsurgical Relaxation of sphincter causes defecation No with diarrhea
Urinary Bladder (M3)	Contraction of muscles Relaxation of sphincter causes urination
Exocrine glands (M3)	Increase in exocrine glands secretions which are: Sweat, Saliva, Lacrimal, Bronchial, intestinal glands

Parasympathetic actions on Eye

- It innervates the constrictor pupillae (Circular muscle of iris) which is important adjusting the pupil in response to change in light intensity and regulating the intraocular pressure
- Aqueous humour secreted by ciliary body is removed continuously by drainage into the canal of Schlemm
- Normal ocular pressure is 10-15 mmHg above atmospheric pressure. Abnormal raised pressure (Glaucoma) leads to retinal detachment
- Miosis decreases the IOP in Glaucoma by increasing the filtration angle through ciliary muscles contraction
- When the ciliary muscle contracts, the lens bulge more and this parasympathetic reflex is essential to accommodate for near vision

Cont.

Type of Drug	Natural Alkaloids	Synthetic Choline Esters
Features	• Alkaloids are lipid soluble nitrogen non polar compound found in nature • Tertiary amines • Common suffix (ine) which means natural and base	• Polar (contains N ion) Quaternary ammonium compounds that change the acidity of the medium it acts on • β-methyl group :Selectivity to M receptor
Examples	• Pilocarpine • Nicotine • Muscarine	• Acetylcholine found in our body naturally • Carbachol • Bethanechol • Cevimeline
P.K	• Non polar, lipid soluble • Well absorbed except Muscarine, Excreted by the kidneys.	• Poor distribution • Can not cross BBB so no CNS effects • Not metabolized by Cholinesterase (Why?) • 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
Contraindications of Direct cholinomimetics	❖ Bronchial asthma ❖ Peptic ulcer ❖ Angina pectoris (الذبحة الصدرية)(M3) ❖ Urinary incontinence (increases urination) ❖ Intestinal obstruction (it'll increase motility which will lead to perforation with this obstruction)	

Natural Alkaloids:

Drug	Pilocarpine It is not a derivative of Ach
M.O.A	• Direct muscarinic agonist • **Acts mainly on eye and secretion**
P.K	• **Nonpolar (Lipophilic)** tertiary amine • Well absorbed and good distribution • Cross BBB so it has CNS effects • Cross placenta • Not metabolized by Cholinesterase • Long duration of action • **Excretion is enhanced by acidification of urine**
Uses	✓ Xerostomia (Dry mouth) ✓ Drug of choice in emergency Glaucoma (applied as eye drops) Local effect
ADRs	❖ Profuse sweating ❖ Salivation but it is desirable in dry mouth ❖ Bronchoconstriction NEVER given to patients with asthma ❖ Diarrhea ❖ CNS effects due to its solubility and this raises ADRs

Synthetic Choline Esters:

Drug	Acetylcholine
M.O.A	• Muscarinic and Nicotinic agonist
Uses	**Not used clinically because:** • Is not selective as it acts on both nicotinic and muscarinic receptors • Has short duration of action. Why? Due to rapid metabolism by acetylcholinesterase

Cont.

Drug	Carbachol (Carbamoylcholine)	Bethanechol (Carbamoyl-β-methylcholine)	Cevimeline
M.O.A	• Muscarinic actions on the eyes, GIT, UT. More selective • Has nicotinic actions (side effects) • First drug in this class	• Prominent muscarinic actions on GI, UT. No eye • No nicotinic actions	• Direct acting muscarinic agonist (M3)
P.K	• Resistant to hydrolysis by acetylcholinesterase • Longer duration than Ach	• Resistant to hydrolysis by acetylcholinesterase • Longer duration than Ach	-
Uses	• Treatment of Glaucoma as an eye drops only • Decreased motility of GI • Decreased urination (But not anymore is used for the last two problems)	Drug of choice in: • Paralytic (Relaxation) ileus • Urinary retention in case of post-operative atony (No contraction) and bladder	• Dry mouth symptom associated with Sjogren's syndrome
ADRs	• Nicotinic side effects	-	-

Sjogren's Syndrome:

✓ Autoimmune disease characterized by Formation of antibodies leading to dryness of mouth and eye.

Next slide is a summary!

Drug	ACh	Carbachol	Bethanechol	Pilocarpine
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	Longer (++)		
administration	I.V. eye drops	Oral, eye drops S.C.	Oral, S.C.	Oral, eye drops

Drug	ACh	Carbachol	Bethanechol	Pilocarpine	Cevimeline
Receptors	Muscarinic Nicotinic	Muscarinic Nicotinic	Muscarinic	Muscarinic	Muscarinic
Muscarinic	+++				
Selectivity	NOT	Eye, GIT Urinary bladder	GIT, Urinary bladder	More on eye, exocrine glands	More on eye, exocrine glands
Nicotinic	+++		NO		
Uses	NO	Glaucoma	Paralytic ileus Urinary retention	Glaucoma Xerostomia	Sjogren's syndrome

Questions

MCQs:

1-Which of the following is the primary receptor for organs supplied by autonomic system?

A. A) Acetylcholine receptors. B) Nicotinic receptors.

B. C) Epinephrine. D) Muscarinic.

2-Nicotinic receptors are found in:

A) Parasympathetic Ganglia. B) CNS.

C) Adrenal Medulla. D) All the above

3-In the ligand-gated ion channel, Ach binds to:

A) Alpha subunits. B) Beta subunits.

C) Gamma subunits. D) A&B.

4- Which one of the following drugs are used to treat dry mouth symptom that associated with Sjogren's syndrome?

A) Carbachol. B) Bethanechol.

C) Acetylcholine (Ach). D) Cevimeline.

5-Which one of the following has the shortest duration of action?

A) Cevimeline. B) Acetylcholine (Ach).

C) Pilocarpine . D) Carbachol.

6-Which one of the following can cross BBB?

A) Bethanechol. B) Cevimeline

C) Pilocarpine. D) Acetylcholine (Ach).

Answers:

1-D

2-D

3-A

4-D

5-B

6-C

Cont..

SAQ:

How many acetylcholine bind with ligand-gated ion (N+) channel?

2 acetylcholine molecules

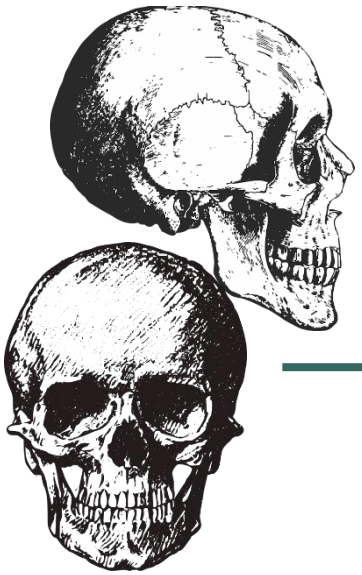
What's the function of Adrenal medulla?

Release catecholamines (adrenaline & noradrenaline)

Why we don't use Ach clinically?

1. It is not selective as it acts on both nicotinic and muscarinic receptors.

2. It has short duration of action.



"It is not hard, you just made it to the end!"

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Yazeed Alharbi & Aseel Badukhon

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References:

- ✓ Team436
- ✓ Doctors' notes and slides

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