Indirect-Acting Cholinergic Drugs

Lecture no.2

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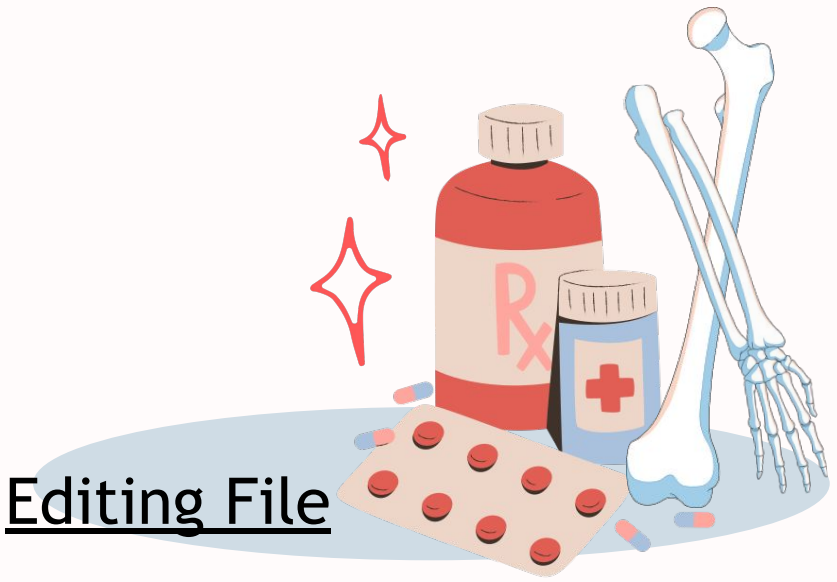

Editing File

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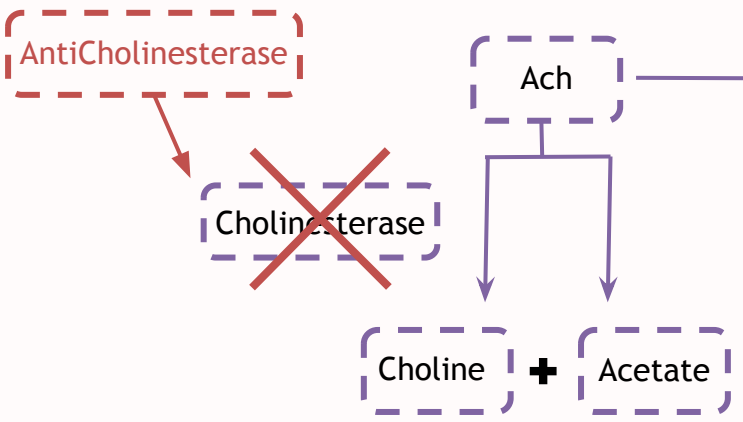
Objectives

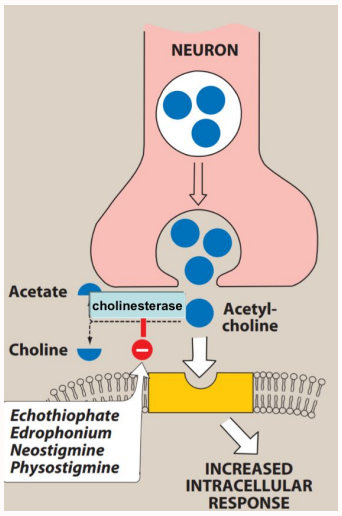
- To know the classification of indirect acting cholinomimetics.
- To know the mechanism of action, kinetics, dynamics and uses of anticholinesterases.
- To know the adverse effects & contraindications of anticholinesterases.
- To know the symptoms and treatment of organophosphates toxicity.

Indirect cholinomimetics /Anticholinesterases

Mechanism of action:

Anticholinesterases prevent hydrolysis of Ach by inhibiting acetylcholinesterase thus increase Ach concentrations and actions at the cholinergic receptors (both nicotinic and muscarinic).



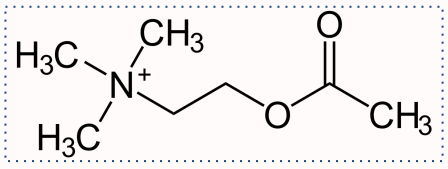


indirect cholinomimetics are drugs that act on the enzyme (cholinesterase) by blocking it

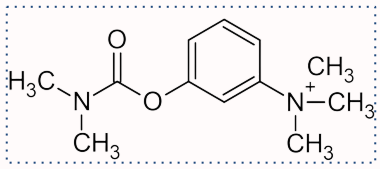
Team43: Anticholinesterases are nonspecific because they affect cholinesterases and not the receptors

Anticholinesterases:

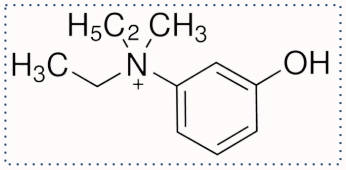
Anticholinesterases are similar in structure to Ach so combine with cholinesterase enzyme (two sites, anionic and esteratic sites) instead of Ach.



Acetylcholine



Neostigmine



Edrophonium

Pharmacological Effects of Anticholinesterases

All Anticholinesterases have muscarinic and nicotinic actions (M & N actions) and some have CNS effects (only lipid soluble drugs).

- Muscarinic actions → Similar to Ach (Miosis, Bradycardia, Bronchoconstriction, Increased motility, secretion of exocrine glands, sweating, lacrimation)
- Nicotinic actions
- CNS actions → (Excitation, convulsion, respiratory failure, coma) only for lipid soluble anticholinesterases e.g. physostigmine & all phosphate ester (except echothiophate that is polar).

	Site	Action
Nicotinic actions	Skeletal muscle Neuromuscular junction	-Therapeutic dose: muscle contraction -Toxic dose: persistent depolarization & relaxation, paralysis (depolarization block)
	Autonomic ganglia	Stimulation of Autonomic ganglia (sympathetic & parasympathetic)
	Adrenal medulla	Release of catecholamines (Adrenaline & Noradrenaline)
Muscarinic actions	**Eye**	-Contraction of circular muscle of iris (miosis) **(M3)** -Contraction of ciliary muscles for near vision **(M3)** -Decrease in intraocular pressure (IOP)
	Heart endothelium	-Bradycardia (decrease in heart rate) **(M2)** -Release of NO (EDRF, endothelium-derived relaxing factor)
	Lung	-Constriction of bronchial smooth muscles -Increase in bronchial secretion **(M3)**
	GIT	-Increased motility (peristalsis) -Increased secretion -Relaxation of sphincter - defecation **(M3)**
	Urinary Bladder	-Contraction of muscles -Relaxation of sphincter **(M3)** -Urination
	Exocrine glands	-Increase of secretions of exocrine glands -sweat, saliva, lacrimal, bronchial, intestinal secretions **(M3)**

Classification of Anticholinesterases

Anticholinesterases

Reversible

Irreversible

Alcohols
(Short acting)

Edrophonium

- it is an alcohol
- forms weak hydrogen bond with acetylcholinesterase enzyme (anionic site)
- e.g. edrophonium

Carbamate esters
(Intermediate acting)

-Physostigmine
-Neostigmine
-Pyridostigmine

- Carbamates esters
- binds to two sites of cholinesterase enzyme
- All polar (except physostigmine)
- e.g. -Physostigmine
  -Pyridostigmine
  -Neostigmine

Phosphate esters
(Long acting)
e.g. insecticides, gas war

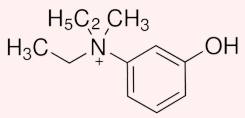
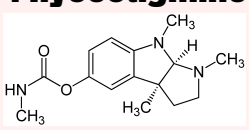
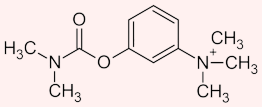
-Echothiophate
-Isoflurophate

- Phosphate esters
- Very long acting
- form very stable covalent bond with cholinesterase
- All phosphates are lipid soluble (except echothiophate which is polar)
- Used as insecticides and war gases
- e.g. -Echothiophate

  -Isoflurophate

P.K: Pharmacokinetics is what the body does to a drug.It refers to the movement of the drug into, through, and out of the body

Reversible Anticholinesterases

	Action	P.K	Uses	Binding with Ach esterases	Chemical structures
Edrophonium (Tensilon) 	Muscarinic & nicotinic actions M, N	•Polar (alcohol) •NOT absorbed orally (must be given by injection) •short duration of action (5-15 min)	•Diagnosis of myasthenia gravis (not for treatment) •As an antidote for tubocurarine (neuromuscular blocking agent, skeletal muscle relaxant)	has sufficient affinity for the enzyme active site to similarly prevent access of acetylcholine, attach mainly to acetylcholinesterase by weak hydrogen bond	Quaternary ammonium compound
Physostigmine 	•Muscarinic and nicotinic actions •Has CNS effect M,N,CNS	•Non polar (lipid soluble) •Good oral absorption •Good lipid solubility—>Cross BBB (has CNS effects) •Intermediate duration of action (0.5-2hr)	•Glaucoma •Atropine toxicity (anticholinergic drug)	binds to two sites of cholinesterase enzyme (covalent bond)	Tertiary ammonium compound
Pyridostigmine	Muscarinic & nicotinic actions M,N	-Polar -Intermediate duration of action (3-6hr)	Treatment of myasthenia gravis	binds to two sites of cholinesterase enzyme (covalent bond)	Quaternary ammonium compound
Neostigmine 	•Muscarinic and nicotinic actions •(prominent on GIT & urinary tract) •No CNS effect M, N	•Polar compound—>No CNS effect •Intermediate duration of action (0.5-2hr) •can be used orally	•Treatment of myasthenia gravis •Paralytic ileus & Urinary retention •Competitive neuromuscular blockers intoxication—>Curare toxicity	binds to two sites of cholinesterase enzyme (covalent bond)	Quaternary ammonium compound
Ambenonium	Muscarinic & nicotinic actions M,N	•Polar •Long duration of action (4-8hr)	Treatment of myasthenia gravis		Quaternary ammonium compound
Donepezil	Is a centrally acting reversible acetylcholinesterase inhibitor M4,M5	•Lipid soluble •Given orally	Treatment of dementia of Alzheimer's disease		

Indirect Cholinomimetics (Organophosphorous compounds):

organo: highly lipid soluble

Echothiophate

Mechanism:

1. Irreversible anticholinesterase
2. Binds to cholinesterase by strong covalent bond.
3. Have very long duration of action (up to 100 hours)
4. Aging makes bond extremely stable
5. All are highly lipid soluble except echothiophate
6. Used for glaucoma

Team 443:
Aging means that the bond gets stronger over time to the point where drugs cannot reverse the bond

Organophosphates are used as insecticides

Symptoms of Organophosphate Toxicity

Team 443:
Increase organophosphate = very high depolarization = overstimulation of muscles (constant contraction) = muscles get tired and overworked = bradycardia etc...
Increase in organophosphate will increase the Ach due to inhibition of AchE (Acetylcholine esterase) thus increasing all the effects of the muscarinic and nicotinic receptors

The organ:

Mnemonic :
DUMBBELLS
Diarrhea - Urination - Miosis - Bradycardia - Bronchospasm - Emesis - Lacrimation - sweating - salivation

Heart	GIT	CNS	Muscles	Other symptoms
-severe bradycardia -hypotension	Increased GIT motility leading to cramps & diarrhea	-convulsion -coma -respiratory failure -cardiovascular collapse	initial twitching of skeletal muscles → weakness & paralysis	-bronchospasm -sweating -salivation -lacrimation

Treatment of Organophosphate Toxicity

1. Support respiration
2. Cholinesterase reactivators -oximes-
3. Atropine - to block Muscarinic actions & CNS effects
4. Diazepam is administered to reduce the persistent convulsion

Pralidoxime (PAM)

Actions

- Cholinesterase reactivator or regenerator
- Acts by regeneration of cholinesterase enzyme
- Reactivates recently inhabited enzymes before aging

Uses

I.V over 15-30 min for organophosphate intoxication

Adverse effects of cholinergic drugs:

- Bradycardia
- Hypotension
- Bronchospasm
- Diarrhea
- Sweating & Salivation

Contraindications of cholinergic drugs:

- Bronchial asthma
- Peptic ulcer
- Angina pectoris (chest pain or discomfort that keeps coming back)
- Intestinal Obstruction
- Urinary incontinence

Contraindication: reasons for a person to not receive a particular treatment or procedure because it may be harmful.

Summary for cholinomimetics and their uses

Xerostomia: the salivary glands in your mouth don't make enough saliva to keep your mouth wet

Eye: treatment of glaucoma

1- Pilocarpine (direct muscarinic agonist)

2- Physostigmine

3- Echothiophate (indirect cholinomimetic)

4- Carbachol

Urinary retention and paralytic ileus

1- Bethanechol (direct)

2- Neostigmine (indirect)

Myasthenia gravis(Only indirect cholinomimetics)

1- Pyridostigmine

2- Neostigmine

3- Ambenonium

Xerostomia

1- Pilocarpine

2- Cevimeline (Sjogren's syndrome)

Alzheimer disease

Donepezil

Indirect Cholinomimetics

Males' Slides:

Edrophonium M,N	-Very Short 5-15 min -Polar	Diagnosis of Myasthenia gravis
Neostigmine M,N	-Short 0.5-2hr -polar	Myasthenia gravis treatment Paralytic ileus Urinary retention Curare toxicity
Physostigmine M,N,CNS	-Short 0.5-2hr -Lipid soluble	Glaucoma Atropine toxicity
Ambenonium **Pyridostigmine** M,N	-Short 3-6hr -polar	Myasthenia gravis treatment
Echothiophate M,N	-Long 100hr -polar	Glaucoma
Donepezil M,N	Lipid soluble	Dementia of Alzheimer's disease

Extra Info.

➔ **How to differentiate between cholinergic crisis and myasthenic crisis?**

Because cholinergic crisis can result in muscle weakness like myasthenic crisis, distinguishing the 2 conditions may be difficult. Administration of a short-acting cholinomimetic, such as edrophonium, will improve muscle strength in myasthenic crisis but weaken it in cholinergic crisis.

➔ **How to differentiate between overdose and myasthenia gravis?**

By Edrophonium.Edrophonium is used to diagnose myasthenia gravis, if the patient had a positive effect after having Edrophonium, this means the patient has myasthenia gravis. The drug acts for a short time so it is used only for diagnosis not as a treatment.

MCQs

Q1. A patient develops paralytic ileus after a surgery.What can be used to treat his condition?			
a) Neostigmine	b) Physostigmine	c) Edrophonium	d) Tubocurarine

Q2. What drug should we use to treat atropine toxicity ?			
a) Pyridostigmine	b) Physostigmine	c) Edrophonium	d) Donepezil

Q3. A patient has eyelid drop, what can be used to treat this condition?			
a) Physostigmine	b) Isoflurophate	c) Donepezil	d) Pyridostigmine

Q4. Alzheimer disease can be treated using which drug?			
a) Donepezil	b) Pyridostigmine	c) Cevimeline	d) Neostigmine

Q5. Which one of the following can be used in the treatment of organophosphate toxicity ?			
a)Neostigmine	b)Pralidoxime	c)Carbachol	d)Physostigmine

Answers:1)A 2)B 3)D 4)A 5)B

SAQs

1 **If your patient is taking atracurium drug but after a while he had curare toxicity which drug would you give him?**

Neostigmine

2 **Describe the mechanism of action of indirect acting cholinergic drugs:**

Prevent hydrolysis of Ach by inhibiting acetylcholinesterase thus increase Ach concentrations and actions at the cholinergic receptors (both nicotinic and muscarinic)

3 **What drug is used to diagnose myasthenia gravis?**

Edrophonium.

4 **List 3 contraindications of cholinergic drugs :**

- Bronchial asthma
- Peptic ulcer chest pain or discomfort
- Angina pectoris

Team Leaders:

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- Shoug Albattah

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- Waleed Alanazi
- Ali Al-Abdulazem
- Saleh Alotaibi
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