

وَتَوَكَّلْ عَلَى اللَّهِ
وَكَفَى بِاللَّهِ وَكِيلًا

Indirect acting cholinomimetics

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1-what's the function of CH E?

2-what's the function of pseudo cholinesterase?

3-what're the classification of indirect drug?

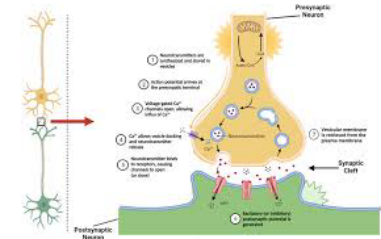
Cholinesterase enzymes

❖ CE is a protein

➤ In cholinergic synapses & RBC

➤ Metabolizes Ach into choline & acetate

➤ Specific for Ach in cholinergic synapses



❖ Pseudocholinesterase in plasma & liver

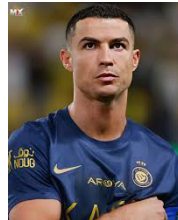
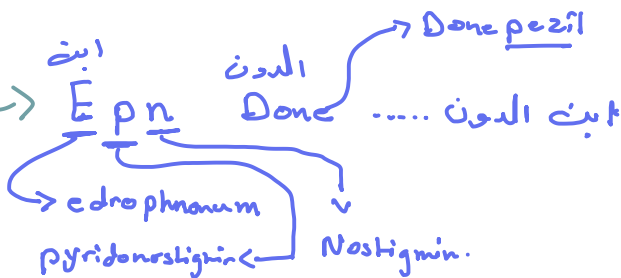
➤ Not specific to Ach ✓

➤ Metabolizes other drugs (suxamethonium, procaine)

Classification of indirect-acting cholinomimetics

Classified into:

- ❖ **Reversible** cholinesterase inhibitors ⇒ They act by carbamylation of enzyme.
- ❖ **Irreversible** cholinesterase inhibitors ⇒ " by phosphylation of enzyme.
→ not drug / may they're Toxics.



Uses of indirect-acting cholinomimetics

- ❖ Diagnosis of MG (Edrophonium)
- ❖ Treatment of MG (Pyridostigmine)
- ❖ Reversible NMB intoxication (Neostigmine)
- ❖ Alzheimer's disease (Donepezil)
- ❖ Irreversible CEI: insecticides

1- Describe the MG?

3- what's the treatment?

2- what're the receptor?

Myasthenia gravis (MG)

- genetic
- ❖ Autoimmune (autoantibodies to N_M in NMJ)
→ So ACh can't bind to it lead to perment relaxation.
 - ❖ Reduction in receptor number
 - ❖ Muscle weakness, fatigability, Ptosis, diplopia, difficult speaking & swallowing
① ② x ③ ④ ⑤
→ سقوفا الكفن
 - ❖ Treatment:
 - Reversible CEI
 - Thymectomy → Remove the Thymus.
 - Immunosuppressant (CS, cyclosporine)





1- what's the mechanism of them?

2- what does it involve?

Reversible ChE inhibitors

- ❖ Inhibit reversibly CE enzyme
- ❖ Accumulation of Ach
- ❖ Electrostatic bonds
- ❖ Stimulate nicotinic & muscarinic receptors
- ❖ Useful in myasthenia gravis

1- what're the feature of it? 2- what're the indications of it? 3- what's the note of it?

→ it given with ATropin β_1 to block the antidiiser muscarinic Receptor

Neostigmine



❖ Synthetic CEI, does not cross BBB

❖ Duration of action (4 hrs)

① ❖ Mainly in MG & also in: by increasing ACh → acting on Nm → Contraction.

② ➤ Antidote to competitive NM blocker tubocurarine poisoning

③ ➤ Paralytic ileus, urinary retention

❖ Given orally, SC

→ \uparrow ACh → action M
 ↳ open sphincter.
 ↳ indirect acting of Neostigmin.

⇒ during surgery a skeletal resting drug is given and causes block of nicotinic muscle receptor → but with over does

- have a :-
- ① muscarinic effect ✓
 - ② Nicotinic effect ✓
 - ③ No CNS effect ✓

this could causes paralysis → To treat that a Neostigmin is given to treat H₂'s poisoning.

Physostigmine

- Tertiary amine alkaloid.
- Lipid soluble
- well absorbed orally.
- Cross CNS and cornea.
Predominant effect on the Muscarinic receptors ,autonomic ganglia and CNS

Neostigmine

- Quaternary ammonium compound.
- Poorly absorbed orally
- doesn't cross CNS.
- Predominant effect on the skeletal muscles (direct & indirect action).

Pyridostigmine

- ❖ Similar to neostigmine
- ❖ Has longer duration of action (6 hrs) and ^① selective drug to endplate for increasing ACh.
- ❖ Useful orally in myasthenia gravis

1- what're the pk ?

2- what's the indication?

Edrophonium

❖ Similar to neostigmine / Highly selective

❖ ^④ IV, ^② short duration of action (10-20 min)

Tensilon Test

❖ Useful in diagnosis of MG by given it IV lead to increase Act

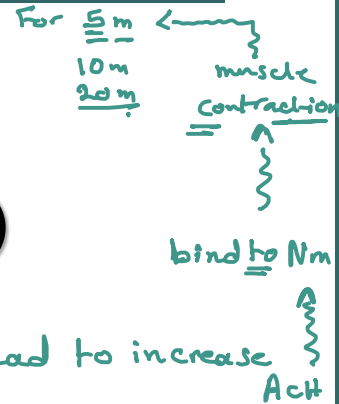
❖ To differentiate between weakness due to myasthenic crisis or cholinergic crisis:

➤ Myasthenic crisis → improvement

➤ Cholinergic crisis → aggravated

↪ over dose of MG drug → ↑↑ Act over increase.

→ Given the ① edrophonium IV, wait 10 m ②
→ if the patient get better, the diagnosis is my crisis
→ if the patient get worse, the diagnosis is ch crisis



Adverse effects of CEI

- ❖ Excessive salivation ✓
- ❖ Flushing and hypotension ✓
- ❖ Abdominal colic and diarrhoea ✓
- ❖ Bronchospasm ✓

1- what's the adverse effect of Tacrine?

2- what's the PKs of Donepezil and indication?

CEI useful in Alzheimer's disease

Tacrine is used to treat the symptoms of mild to moderate Alzheimer's disease. Tacrine will not cure Alzheimer's disease, and it will not stop the disease from

❖ Tacrine

- Reversible CEI used in treatment of Alzheimer's disease; hepatotoxic

❖ Donepezil → central effect No peripheral effect.

- New selective CEI
- Once daily ✓
- Lacks hepatotoxicity of tacrine
- Useful in Alzheimer's disease

1- Describe the chemical structure?

2- what's the mechanism of action of them?

3- what're the indication of it-?

Irreversible CE Inhibitors

- ❖ Organophosphorous compounds \Rightarrow Insecticide مبيدات حشرية
- ❖ Irreversibly inhibit CE by phosphorylation. very very Rapid absorption.
- ❖ Covalent bond in Enzyme-inhibitor complex
 \rightarrow irreversibly binding. / with Time this bond become strong irreversible (Aging enzyme)
- ❖ Used as insecticides:
 - Parathion, malathion
- ❖ As nerve gases in chemical warfare: STS
 - Tabun, Sarin, Soman



1-what's the mechanism of it?

2-what's the adverse effect of it?

3-what're the indications?

Isoflurophate (DFP)

- ❖ OP compound
- ❖ Irreversibly inhibits CE 31
- ❖ Insecticide
- ❖ Toxicity: excessive cholinergic stimulation
- ❖ May be used topically in glaucoma
- ❖ Duration of action about a week

Echothiophate

- ❖ New agent ⇒ used *Topically* in glaucoma as eye drop.
- ❖ Similar to isofluorophate
- ❖ Long duration of action (week)

Differences between direct & indirect-acting cholinomimetics

- ❖ Actions on receptors:
 - Direct
 - Indirect

- ❖ Pharmacodynamic effects:
 - Similar

- ❖ Central effects with indirect:
 - Cross BBB

Organophosphorous Insecticide Poisoning

- ❖ Agricultural or industrial accidents
- ❖ Excessive cholinergic manifestations
- ❖ GIT (diarrhoea, colic)
- ❖ Respiratory (dyspnoea, bronchospasm)
- ❖ CV (bradycardia, hypotension)
- ❖ Micturition, excessive sweating, M. paralysis
- ❖ Miosis (pin-point pupil), convulsions & death

Treatment of OPI Poisoning

- ❖ General measures → block all muscarinic Receptor
- ❖ High doses atropine IV or IM ⇒
 - ① pules مع متابعة ال
 - ② Bp و
 - توقف }
 - P > 80
 - Bp > 80Atropin
- ❖ Mechanical ventilation
- ❖ Diazepam for convulsions مهادى
- ❖ Enzyme reactivation by pralidoxime IM → break the bond by dephosphorylation.