PHARMACOLOGY
433

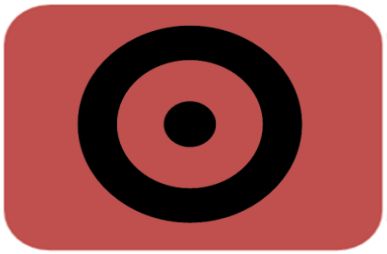
King Saud University
College of Medicine
1st Year, 2nd Block

Indirect acting cholinergic drugs

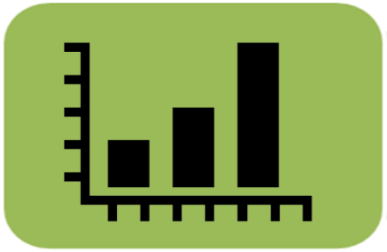
4

Musculoskeletal Block

OBJECTIVES

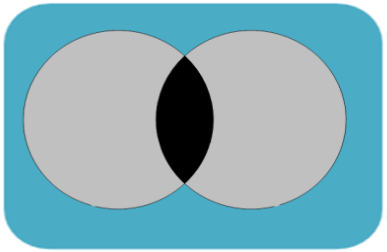


Classification of indirect acting cholinomimetics.

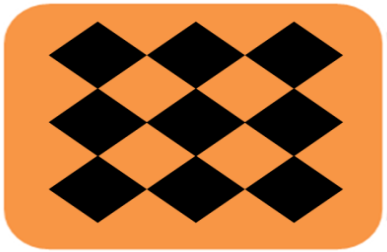


Mechanism of action, kinetics and dynamics.

Adverse effects & contraindications of anticholinesterases.



Symptoms and treatment of organophosphates toxicity.



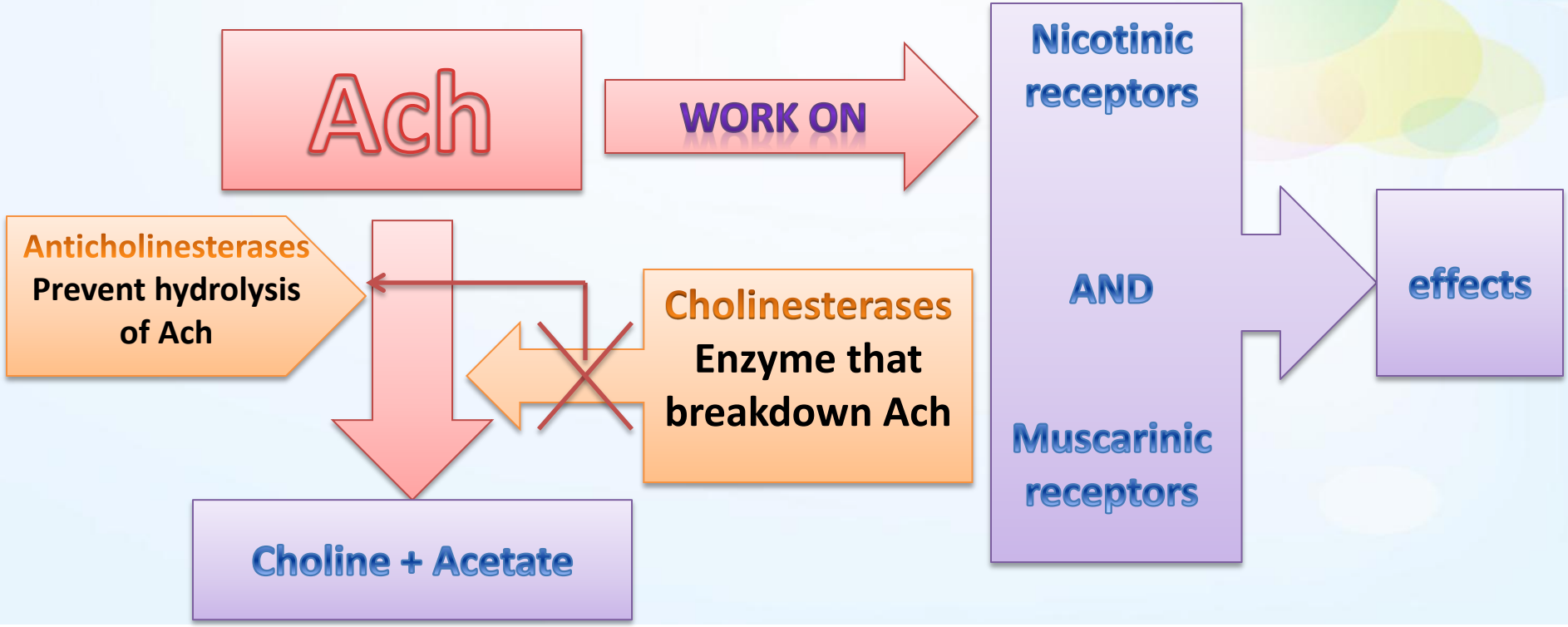
uses of anticholinesterases.

Indirect cholinomimetics

(Also called anticholinesterases)

Mechanism of action: Anticholinesterases prevent hydrolysis of Ach by antagonizing cholinesterase thus increase Ach concentrations and actions at the cholinergic receptors (both nicotinic and muscarinic).

Anticholinesterases are similar in structure to Ach so combine with cholinesterase instead of Ach.



Classification of anticholinesterases

Reversible anticholinesterases

1- short action:-
- Drugs as Edrophonium.
- *Alcohol.*
- forms weak hydrogen bond with cholinesterase.

2- Intermediate action:-
- Carbamates esters.
- binds to two sites of cholinesterase enzyme.
- *All polar except* physostigmine
  - -Physostigmine.
  - -Pyridostigmine.
  - -Neostigmine.

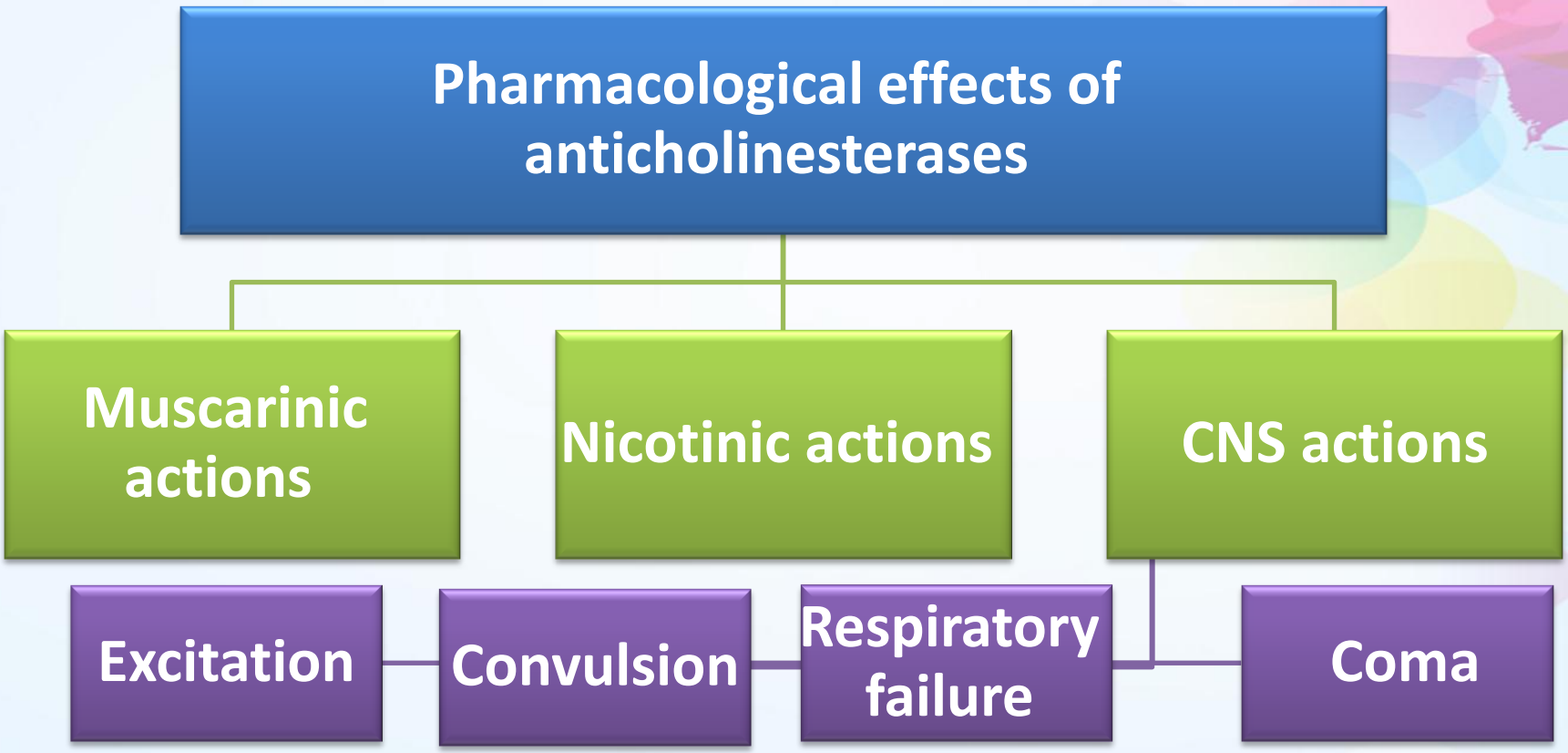
Irreversible anticholinesterases

Very long action :- (phospat esters e.g. insecticides, gas war)

- e.g. Ecothiophate Isoflurophate
- very long duration of action
- form very stable covalent bond with cholinesterase.
- All phosphates are lipid soluble except ecothiophate which is polar.
- Some of them are used as pesticides.

Pharmacological effects of anticholinesterases

ALL Anticholinesterases have muscarinic and nicotinic actions. (M&N actions)
& some have CNS effects (only lipid soluble drugs like: Physostigmine).



- **CNS actions: only for <u>lipid soluble</u> anticholinesterases:**
  Physostigmine & Phosphate ester except Ecothiophate that is polar.

Edrophonium	Physostigmine	Neostigmine	Other drugs
• Reversible. • Polar . • Only given by injection . • attach mainly to anionic site of cholinesterase. • has weak hydrogen bond . • duration 5-15 min. • Uses: -for diagnosis of MG .	• Reversible . • Tertiary . • has CNS effect (cross BBB). • Non polar (lipid soluble). • oral absorption. • has N,M action. • duration 0.5-2hr. • Uses: -glaucoma. -atropine toxicity. (atropine is anticholinergic drug).	• Reversible. • Quaternary. • Polar. •No CNS effect. • can be used oral. • has N,M action. •(prominent on GIT & urinary tract). • duration 0.5-2 hr. •Uses: -treat of MG. -Paralytic ileus. -curare toxicity. -Urinary retention. -Competitive neuromuscular blockers intoxication.	❖ **Pyridostigmine:** • has N,M action. • duration 3-6 hr. • Polar. • Treat of MG. ❖ **Ambenonium:** • has N,M action. • Polar. • duration 4-8 hr. • Treat of MG. ❖ **Ecothiophate:** • Irreversible . • Treat of glaucoma. •Aging make bond extremely stable and can lead to organophosphate toxicity. ❖ **Donepezil:** • has N,M action . •Anticholinesterase drugs. • given oral. • treat of dementia الخرف of Alzheimer's disease.

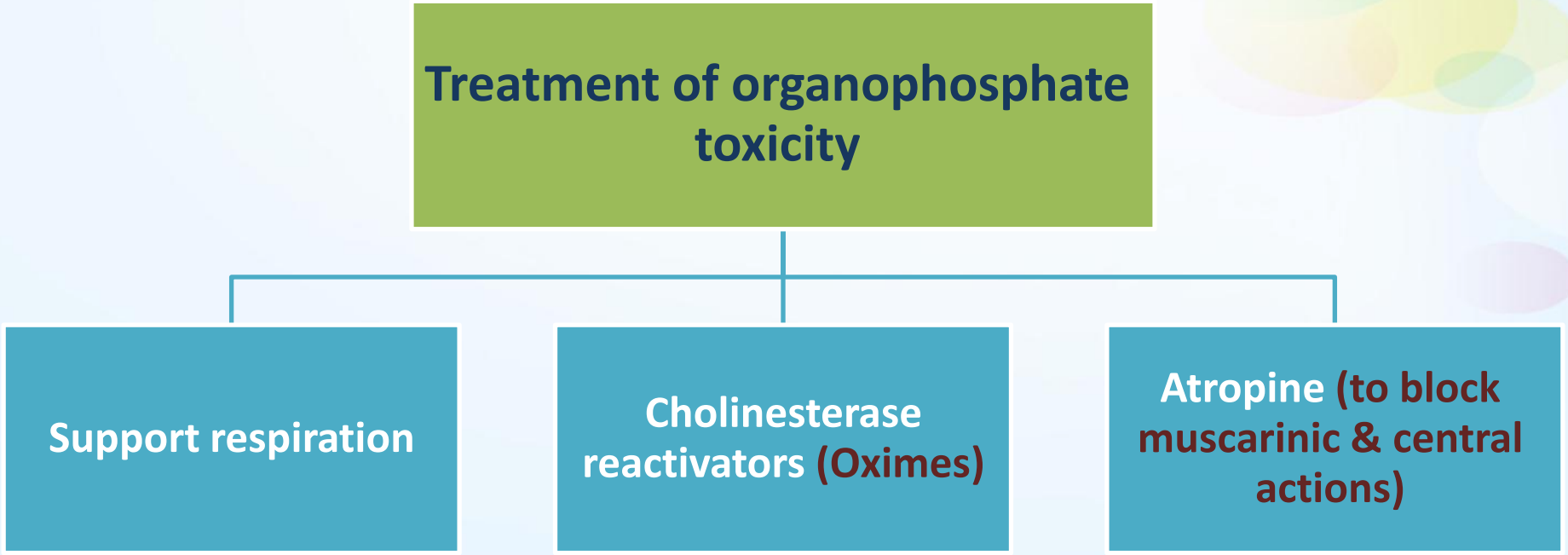
MG : **Myasthenia gravis**

Organophosphates toxicity:

*It is an anticholinesterase → increase Ach

Mainly Ach present at **nicotinic Receptors** then it will cause :

- Sever bradycardia, hypotension and bronchospasm.
- Increased GIT motility → cramps & diarrhea.
- CNS effects → convulsion, coma and respiratory failure.
- Initial twitching of skeletal muscles → muscle weakness & paralysis. (as succinylcholine which is muscle relaxant)



OXIMES

Pralidoxime (PAM) → cholinesterase reactivator

Acts by regeneration of cholinesterase enzyme.

Reactivates recently inhibited enzymes before aging.

cholinesterase يعيد تصنيع أو تجديد الـ

Uses:

Given I.V. → over 15-30 min for organophosphate intoxication.

Summary

- Indirect cholinomimetics (anticholinesterases) inhibit the enzyme cholinesterase
- They are similar structures to Ach, so combine with cholinesterase instead of Ach .
- All the reversible Intermediate acting anticholinesterase are polar except physostigmine.
- The irreversible very long acting are phosphate esters (or Organophosphates) and all of them are lipid soluble except ecothiophate which is polar.
- Only lipid soluble drugs will have affect on the CNS e.g. Physostigmine.
- Their actions can be either therapeutic (muscle contraction) or toxic (relaxation or paralysis)
- Edrophonium (given by injection) is used for diagnosis of myasthenia gravis. Also called (Tensilon test)
- Physostigmine is Tertiary ammonium compound that can cross BBB and used for glaucoma
- Neostigmine is used for treatment of Myasthenia gravis and it causes urinary retention
- Organophosphates toxicity causes severe bradychardia and hypotension, effects on CNS manifest as coma and convulsion, it causes diarrhea due to increased GIT motility.
- Treatment of Organophosphates toxicity by : Oximes (IV) & Donepezil (orally).

Summary for cholinomimetics (direct , indirect) & their uses

***Eye : treatment of glaucoma**
Pilocarpine (direct muscarinic agonist)
Physostigmine -Ecothiophate (indirect cholinomimetics)

***Urinary retention and paralytic ileus**
Bethanechol (direct)
Neostigmine (indirect)

***Myasthenia gravis (only indirect cholinomimetics)**
Pyridostigmine, Neostigmine, Ambenonium

***Xerostomia** (dryness of the moth)
Pilocarpine –Cevimeline (Sjogren's syndrome)

***Alzheimer's disease: Donepezil**

M.C.Q.s

1- what is Mechanism of Anticholinesterase:
A- prevent hydrolysis of Ach.
B- Allows hydrolysis of Ach.
C- prevent Hydrogenation of Ach.
D-A and C.

2- Anticholinesterases are: :
A- non similar in structure to Ach .
B- similar in function to Ach .
C- All of the above.
D- similar in structure to Ach.

3- which of the following is Irreversible anticholinesterases:
A- Ecothiophate.
B- Physostigmine.
C- Neostigmine.
D- Pyridostigmine.

4- which of the following it has Short acting and reversible :
A- Physostigmine.
B- Edrophonium.
C- Neostigmine.
D- Pyridostigmine.

5- which of the following it has lipid soluble :
A- physostigmine.
B- Pyridostigmine.
C- Neostigmine.
D- A and B

6- glaucoma treated by:

A- Physostigmine .
B- Pilocarpine .
C- Neostigmine
D- A and B

7- Which of the following drug used for treatment of dementia of Alzheimer's disease :
A- Physostigmine
B- Edrophonium
C- Donepezil
D- A and C

8- Which of the following drug Used only for diagnosis of myasthenia gravis:
A- Physostigmine
B- Edrophonium
C- Neostigmine
D- Pilocarpine

1-A 2-D 3-A 4-B

5-A 6-D 7-C 8-B

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We hope that we made this lecture easier for you
Good Luck !