PHARMACOLOGY OF ANS
part 1

General Pharmacology
M212

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Lecture 12 handout
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A. **Cholinergic agonists (parasympathomimetics)**

- ACh has both muscarinic and nicotinic activity. Its actions include:

➢ Decrease in heart rate and cardiac output

➢ Decrease in blood pressure (VASODILATION)? HOW?

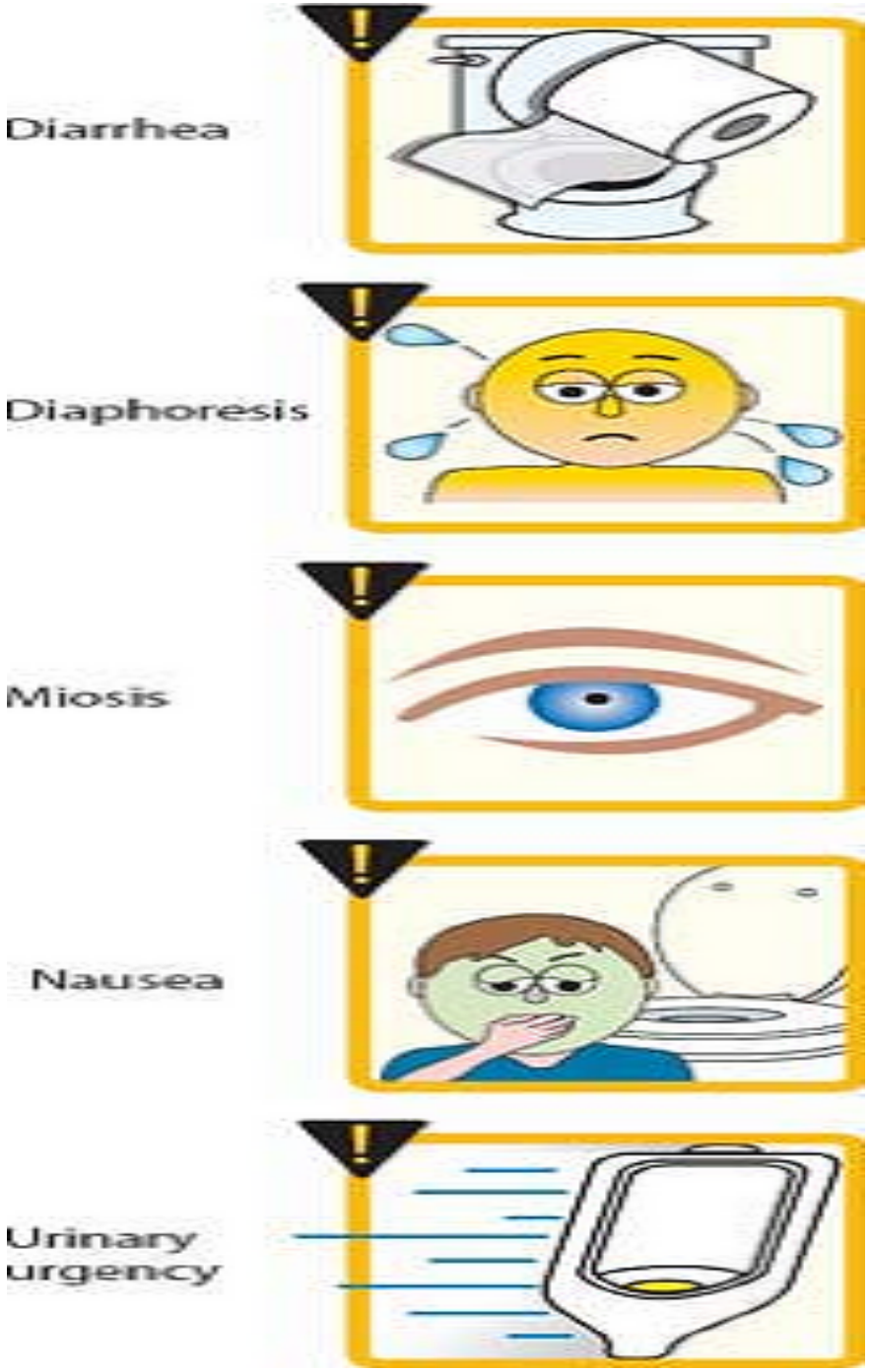
➢ Increases salivary secretion and intestinal secretions and motility.

➢ increases the tone of the detrusor urinae muscle, causing expulsion of urine.

➢ constriction of the pupillae sphincter muscle, causing miosis (marked constriction of the pupil).

Last time we talked about the ach and how it synthesis and release occur, keep in mind that any medicine that causes ach to be released from the vesicles where is it stored is called agonist (like botox) and the opposite it the antagonist (like sarin gas and spiders venom)
Working on ach actually has different ways, one of them being the release from storage of the neurotransmitter and the second way is working on the enzyme that gets rid of this neurotransmitter which it acytlecholinsterase enzyme
Now if we use the given information in a pharmacological way, inhibition of this enzyme means a longer duration for the ach which mimics an agonist.
This lecture is going to be all in one lecture
Lets talk a bit about the ach agonist also called parasympathomimetics and cholenergic agonist
The action of this on the heart
decreases the heart rate and contractility m2
M3 in smooth muscles and m1 in the GI
M3 receptors they do not bind with ach on smooth muscle and causes dilation
It works in an indirect way
By stimulating nitric oxide from arginine and the NO is a vasodilator
But how did they notice that ?
Under study they noticed that there are no ach in plasma which lead to the conclusion that this receptor does not work unless it is exogenous but in reality it works but in an indirect way and not by binding to the receptor so its his not even released in the post synaptic cleft !!
This is a very important mechanism in hypotension treatment

Now lets talk about salivary secretions, when is it important to increase salivary and gi secretions as a medication ?
sojgren syndrome
Xerostomia secondry to radiation
Some cancer now are treated by radiation specially nasopharyngeal cancer, after radiation the salivary glands will be damaged and so will suffer from xerostomia (posy radiation xerostomia)which is a deficiency in saliva
And in this case chollinergic agonist can be given to increase the salivary secretions for a month or two
Now if a patient has an issue the stops them from urinating and I want to give him a medicine to make him urinate more what should I give him ?
This is given if the patient has unureia and this is an issue in the sphincter not in the urine production
This issue can be causes b y prostate hypertrophy but mostly for people with **postoperative urinary retention** and this is caused because of the anastesia that was given for the patient that lowers the motility of the GIT
Thats why the first question after the surgical round is, did you pass motion or urinate ?
Now lets talk about the eye, in the eye there is a canal that releases the aqueous humours of the eye, if this canal closes the IOP will increase and this high pressure will eventually cause glaucoma and glaucoma has 2 causes either this canal is closed or increased production from the eye it self
1 . If this drainage canal is closed (closed angle glaucoma) the best thing to do in this situation is to contract the ciliary muscles and cause miosis so it allows the fluid to leave the eye
2. the open angle glaucoma is a case which there is no blocking in the drainage canal but they eye produce way too much aqueous humor and we will talk about them in details later, they found out that the B receptors are responsible for synthesis of the AH so once you block them the IOP is less



Keep in mind that the effect caused by a drug can be either therapeutic or side effect depending on the patient
So lets say a patient with post urinary retention is a given a medicine that causes urinary urgency this is now considered a therapeutic effect not a side effect

CHOLINERGIC AGONISTS

DIRECT ACTING

- Acetylcholine
- *Bethanechol*
- *Carbachol*
- *Cevimeline*
- *Pilocarpine*

INDIRECT ACTING (reversible)

- *Ambenomium*
- *Demecarium*
- *Donezepil*
- *Edrophonium*
- *Galantamine*
- *Neostigmine*
- *Physostigmine*
- *Pyridostigmine*
- *Rivastigmine*
- *Tacrine*

REACTIVATION OF ACETYL-CHOLINE ESTERASE

- *Pralidoxime*

INDIRECT ACTING (irreversible)

- *Echothiophate*

1- Direct-acting Agonist Drugs

This means it works directly on the receptor and it mimics ach

- **Bethanechol:** used for urinary retention " binds with muscarine receptors"is considered the best for urinary retention
- **Carbachol:** as a miotic agent to treat glaucoma (decrease the IOP) they have noticed that carbachol is found in higher conc in the eye and has many side effects if taken orally so it is given in eyedrops
- **Pilocarpine:** *to treat glaucoma and lower IOP* of both narrow-angle (or closed-angle) and wide-angle (also called open-angle) glaucoma. This is am er drug for high IOP because sometimes glaucoma causes cataract
- It Is also the first medicine given after cancer treatment in al Husain treatment center
- **Also it is used for Xerostomia(dry mouth) and for sojgren syndrome which is a syndrome that antibodies attack salivary glands and lacrimal**

- **Notes : ach is not a medicine because the duration of it is very short but it is used in ophthalmic surgery because it gives a quick miotic action but does not last for more than 10 mins**

Two types of Glaucoma (for your knowledge)

Types of Glaucoma:

1. Open Angle Glaucoma – Excessive production of Aqueous Humour. Excessive β adrenergic receptor mediated production and secretion of aqueous humor from the *ciliary body epithelium*.

- Best treated with beta- blockers :Reduce (Production, Synthesis or Secretion, Acetazolamide, Timolol, Betoxolol

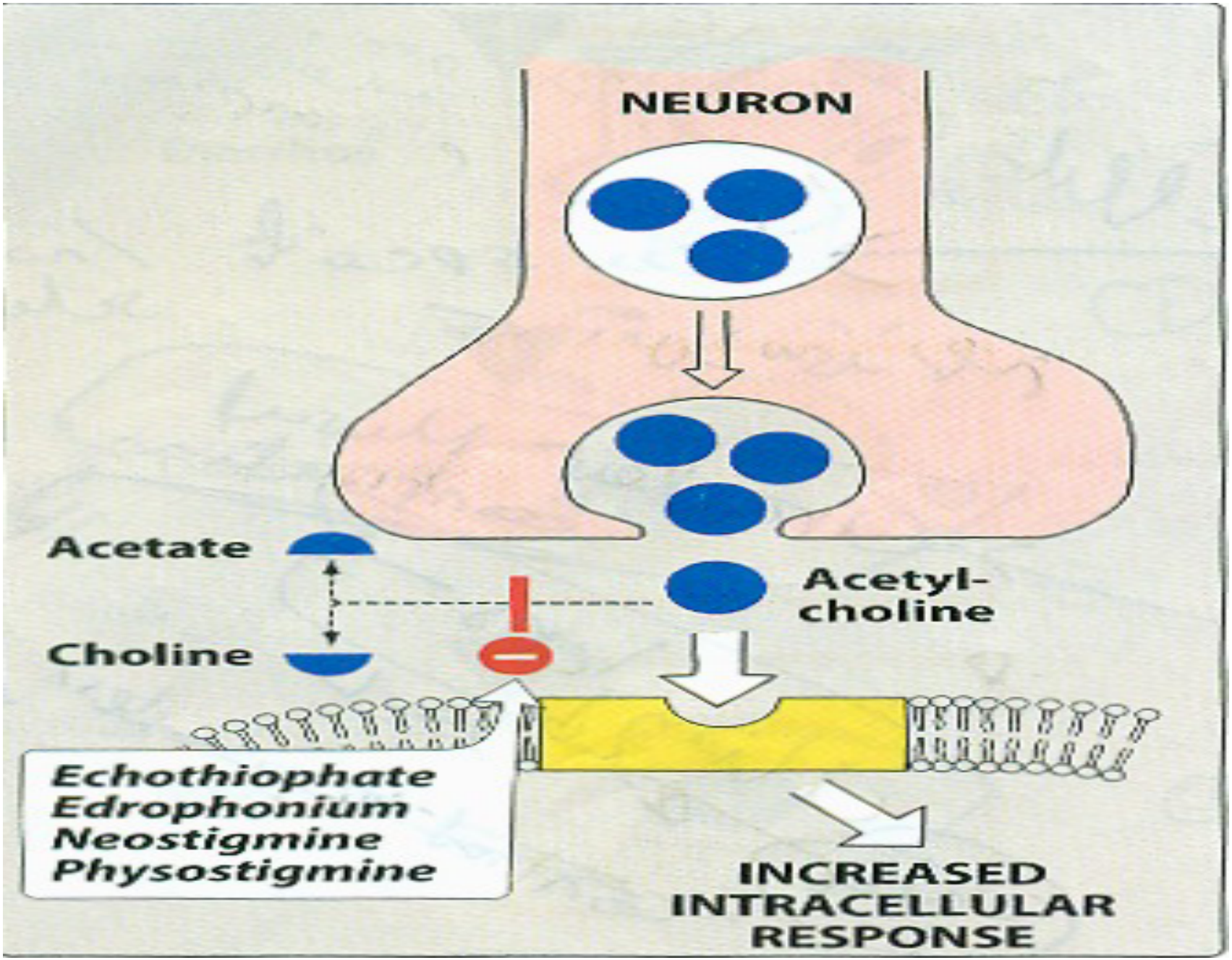
2. Closed Angle Glaucoma – Outflow obstruction of Aqueous Humour

- Results from obstruction of *canal of Schlemm* through which aqueous humor was supposed to be filtrated out .
- Caused by
  1. Mydriatics : Anti-cholinergic drugs
  2. Antidepressants : SSRI drugs

  Treatment: *Pilocarpine*, *Carbachol* , *ecothiopate* and *physostigmine*

2. Indirect-acting Cholinergic Agonists: Acetylcholinesterase Inhibitors (Reversible)

- Drugs inhibit AChE the enzyme that cleaves ACh to acetate and choline and terminate ACh action this results in the accumulation of ACh in the synaptic space– so prolong ACh action side note they found that the ache conc is higher in NMJ so the nicotinic receptors will be the first to be affected, keep in mind that the ach causes depolarization and ca influx which causes actin myosin and contraction in the muscle, so more ach causes more contraction and this in normal patient causes flaccid paralysis
- Examples: keep in mind most of these medicines have almost the same structure they only differ in the duration of action
- **Physostigmine:** used to stimulate the bladder and GI tract.can be used for postoperative patient
- **Neostigmine, ambenonium** and **Pyridostigmine:** used to treat myasthenia gravis
- **Rivastigmine:** to delay the progression of Alzheimer disease (is a dementia that starts with aging or by toxicity of certain metals like caboric that causes toxicity in the recall memory center and it has no treatment but there are drugs that prevent prognosis like donezepil, also a study done 10 years ago related ach low conc to Alzheimer because they noticed that all alzheimer disease patient has lower conc of ach
- **Edrophonium** It is used in the diagnosis of myasthenia gravis (by giving an injection of edrophonium and measuring the muscle tone before and after if the muscle tone increased this means that the test is positive)which is an autoimmune disease caused by antibodies to the nicotinic receptor at NMJs. It is the first AChE found but it has a very short duration barely for few seconds.


NEURON
Acetate
Choline
Acetyl-
choline
Echothiophate
Edrophonium
Neostigmine
Physostigmine
INCREASED
INTRACELLULAR
RESPONSE

3. Indirect-acting cholinergic agonists: anticholinesterases (IRREVERSIBLE)

- **Echothiophate:** for the chronic treatment of open-angle glaucoma.
- Long duration of action (1 week)
- You may be curious about how does it just last for a week and not forever ? And that is because of feedback mechanism where the body starts hydrolyzing the substrate and it is given as an eyedrops not orally
- Side note that atropine could also be an antidote for sarin gas

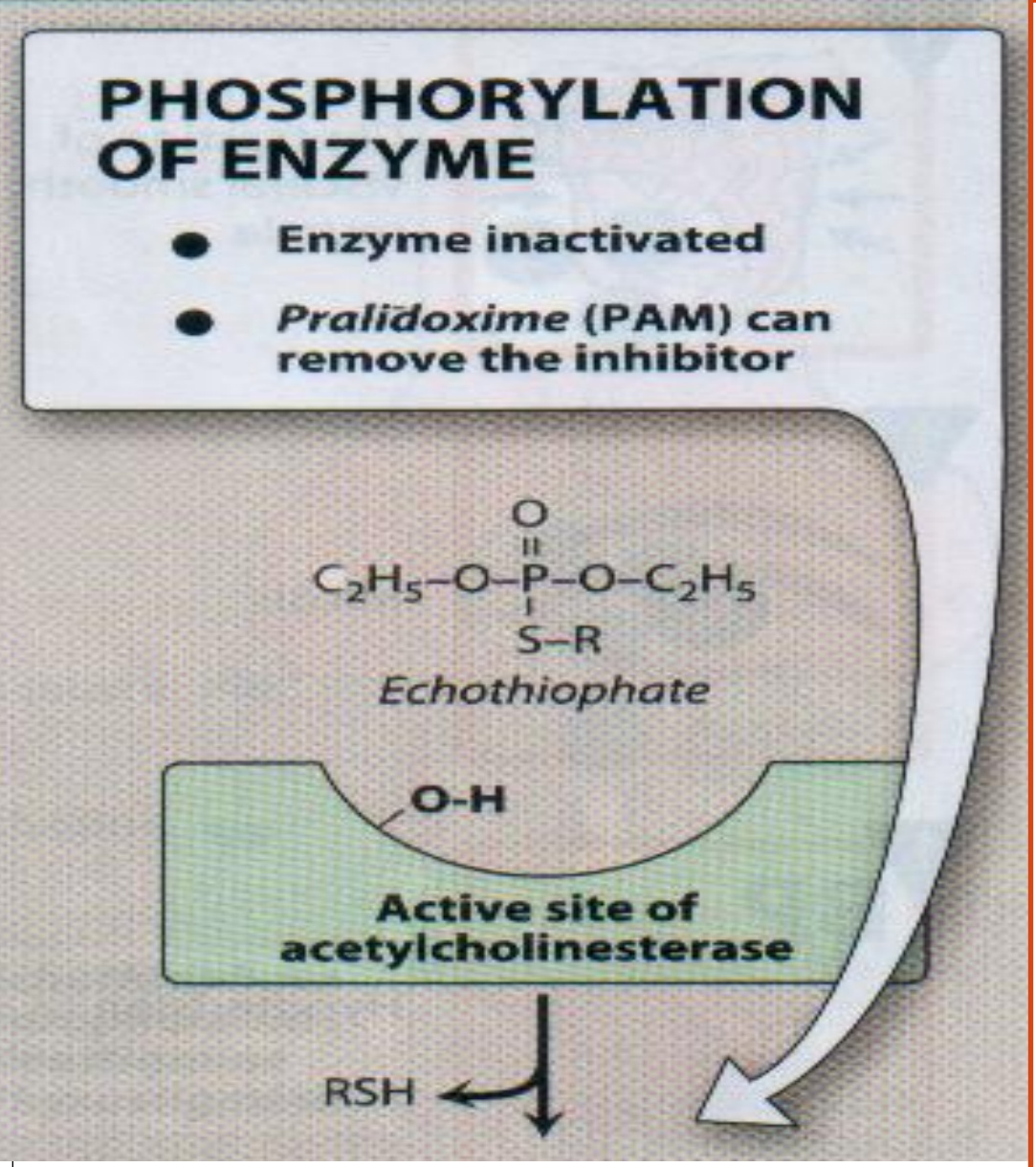
insecticides toxins usually happens to farmers and we should know that this is an cholinergic agonist and it cause hypotension emergency 🚨 so the patient will come to the hospital with the following issues
firstly bradycardia and hypotension and nausea and miotic vision as well as increased secretions of mucus in GI and saliva as well as shortness of breath

Toxicology of anticholinsterease agent

Reactivation of acetylcholinesterase (Antidote)

- Example: organophosphate (sarin gas) and insecticide poisoning
- Treatment:
  - **Pralidoxime (PAM) antidote :** can reactivate inhibited AChE: it displace phosphate group and regenerate the enzyme

- **Look at page 57 , fig 4.11**
- **Page 60 Fig 4.10**



keep in mind any enzyme starts out being reversible for a while before becoming irreversible

Each enzyme has a hydroxyl group that will bind with the substrate (echothiophate) and till now the enzyme is still reversible

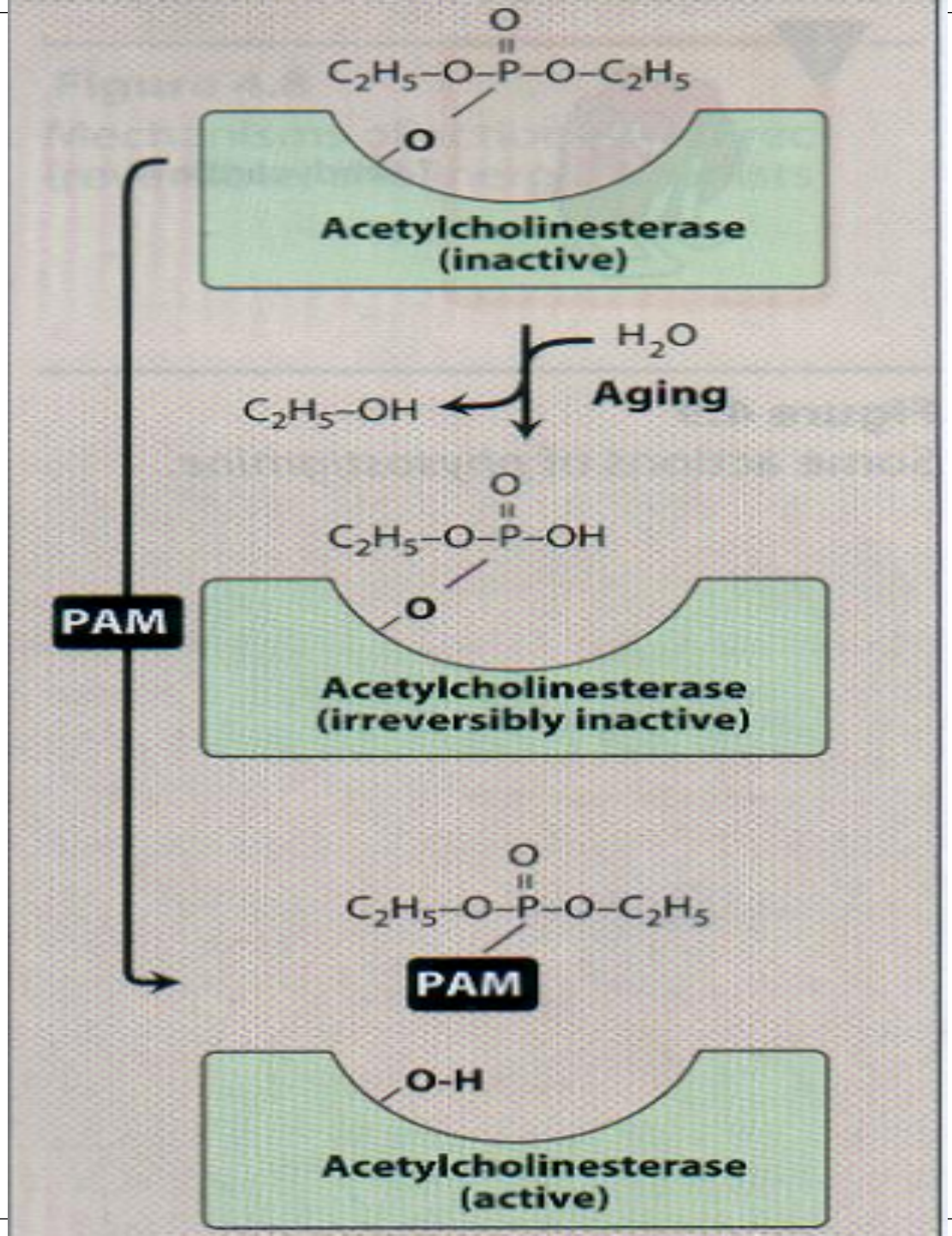
Now why is this so important ?

Lets say that you Are in the ER section and a person with this case (the farmer case) comes in, we have to know when is it still possible to give antidote

If it has been only 4 to 6 hours since the insecticide poison it is still reversible so I can still give the patient PAM and also this is applicable for the sarin gas

But how does this work ? If the antidote is given in 4 to 6 hours the pam will bing with the phosphate and thus regenerate the enzyme

But if has been more than 6 hours what will happen? The substrate will loose an ethanol and the bond will turn into a permanent bond and now it would be too late to give antidote and it would cause no effect if given


O
C2H5–O–P–O–C2H5
O
Acetylcholinesterase
(inactive)
H2O
Aging
C2H5–OH
O
C2H5–O–P–OH
O
PAM
Acetylcholinesterase
(irreversibly inactive)
O
C2H5–O–P–O–C2H5
PAM
O-H
Acetylcholinesterase
(active)

These drugs bind preferentially at muscarinic receptors; other drugs act directly or indirectly at both muscarinic and nicotinic receptors

Drug	Therapeutic uses
Acetylcholine	None
Bethanechol	Treatment of urinary retention
Carbachol	Miosis during ocular surgery Topically to reduce intraocular pressure in open-angle or narrow-angle glaucoma, particularly in patients who have become tolerant to pilocarpine
Pilocarpine	Reduce intraocular pressure in open-angle and narrow-angle glaucoma

These drugs are uncharged, tertiary amines that can penetrate the CNS

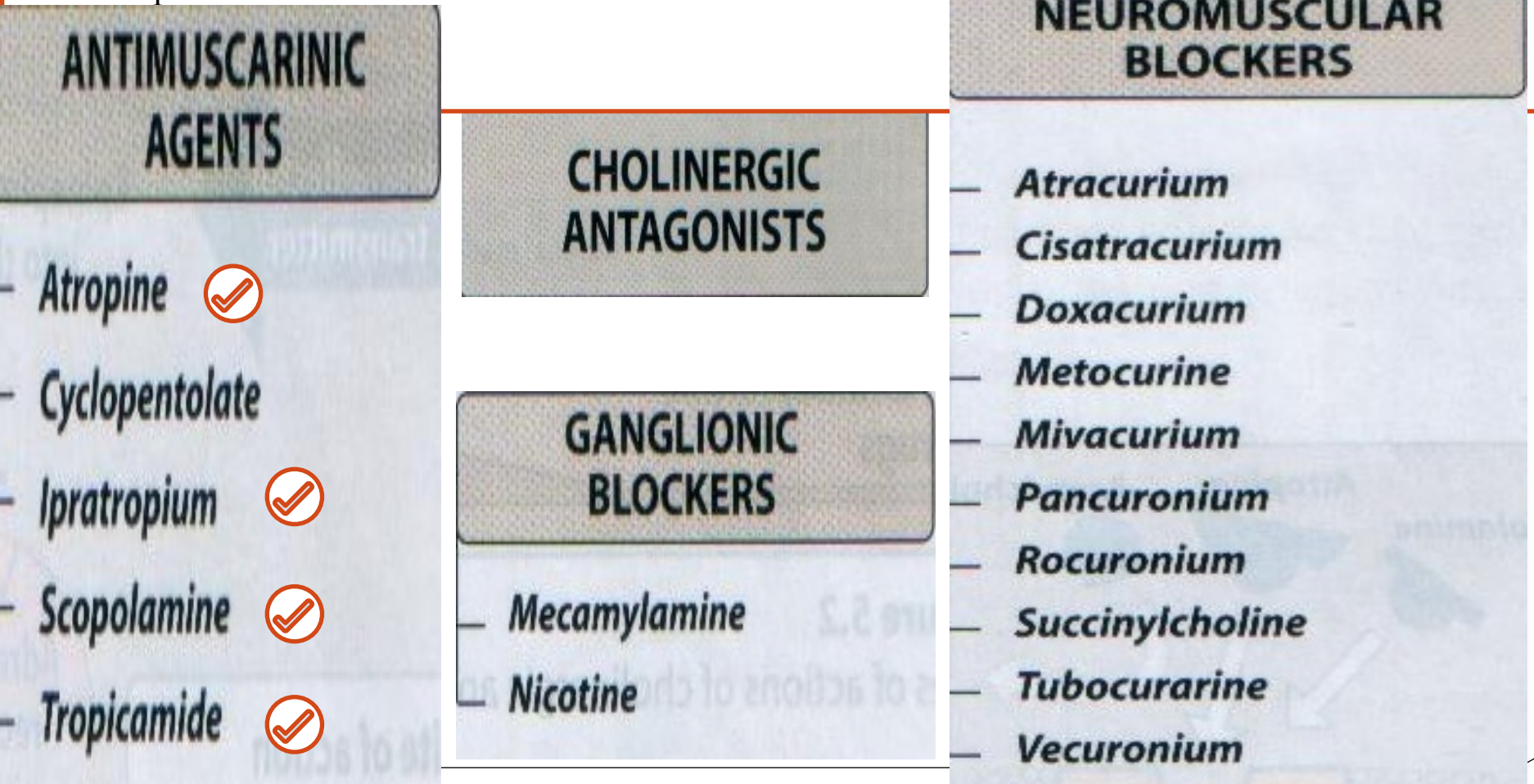
Pilocarpine	Reduce intraocular pressure in open-angle and narrow-angle glaucoma
Physostigmine	Increase intestinal and bladder motility Reduce intraocular pressure in glaucoma Reverse CNS and cardiac effects of tricyclic antidepressants Reverse CNS effects of atropine
Neostigmine	Prevent postoperative abdominal distention and urinary retention Treat myasthenia gravis As antidote for tubocurarine

Long duration of action (2 to 4 hrs)

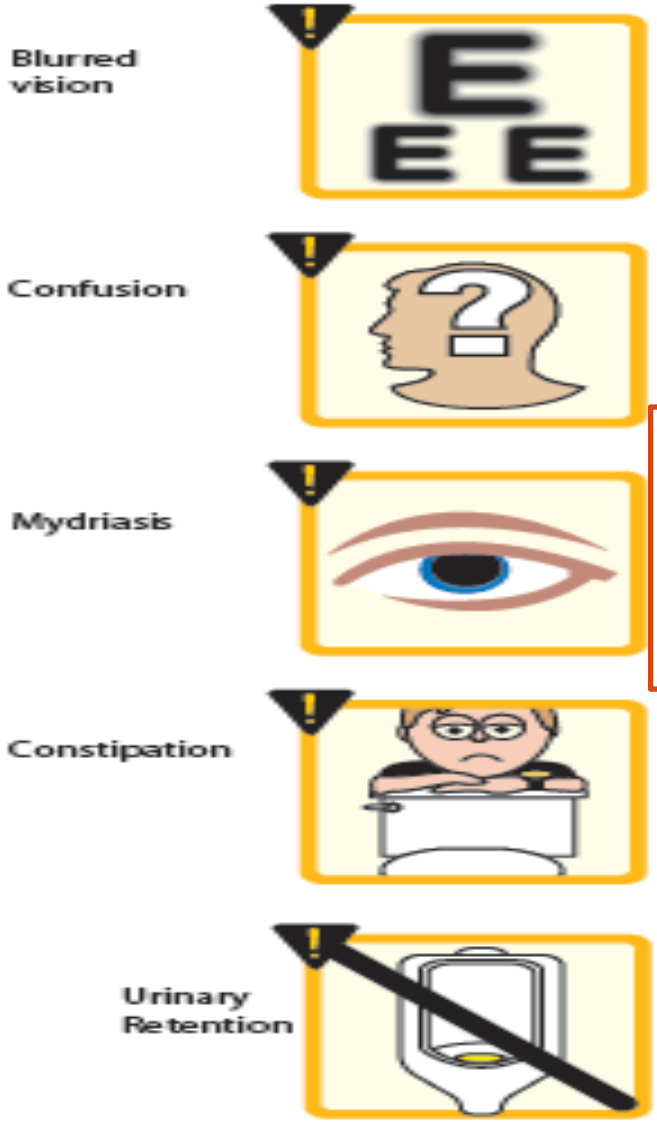
Short duration of action (10 to 20 min)	*Edrophonium*	For diagnosis of myasthenia gravis As antidote for tubocurarine
Alzheimer's disease	*Donepezil* *Galantamine* *Rivastigmine*	Although their benefit is modest, these cholinesterase inhibitors remain first-line treatment for Alzheimer's disease. There is no consistent evidence to suggest treatment reduces health care costs or prolongs time until institutionalization. When Alzheimer's disease becomes moderate to severe, *memantine*, an N-methyl-D-aspartate antagonist, sometimes is added to therapy.
Long duration of action (1 week)	*Echothiophate*	Treatment of open-angle glaucoma

Whenever a case is admitted to the hospital with cholinergic drug agonist toxicity the first question that the physician should ask is, is it a muscarinic agonist like bethanocol and pilocarpine in this case the antidote is atropine " kind of similar to adrenaline" because adrenaline is sympathomimetics and atropine is a cholinergic antagonist so it will cause similar effects and atropine is a M2 receptor blocker and it will increase the heart rate and contraction and also will cause bronchodilation and will cause vasoconstriction and increase the blood pressure(but only a bit) and this was first used in greek where it was a way of looking more beautiful because it causes mydriasis

And atropine is herbal



Action of anticholinergic

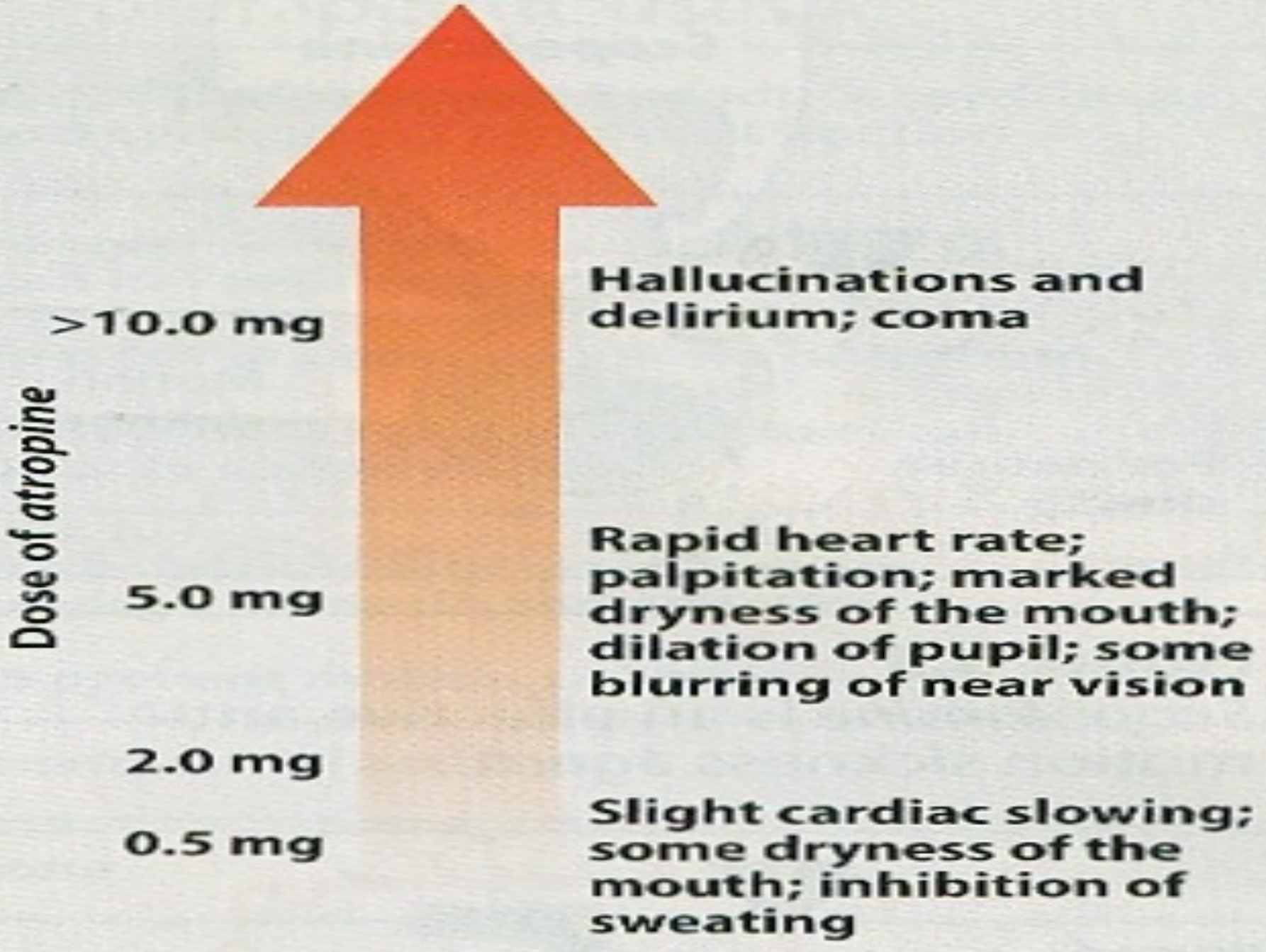


Scopinal
الميرميه فيها اتروبين و الاتروبين بقلل من gi motility

1. mydriasis (dilation of the pupil) so it is not given for glaucoma patient (contra indicated)
2. antispasmodic (reduce motility of the GI tract)
3. Reduce Hypermotility states of the urinary bladder.given for patient with relaxation in the sphincter
4. blocks the salivary glands secretion (cause xerostomia).side effect

I. **Antimuscarinic Agents**

- 1. Atropine:
- used as an antispasmodic to reduce activity of the GI tract
- used to reduce hypermotility states of the urinary bladder.
- Used as antidote for cholinergic agonist
- Antisecretory before surgary.
- **Contraindicated on narrow angle glucoma**


Dose of atropine
>10.0 mg
Hallucinations and delirium; coma
5.0 mg
Rapid heart rate; palpitation; marked dryness of the mouth; dilation of pupil; some blurring of near vision
2.0 mg
0.5 mg
Slight cardiac slowing; some dryness of the mouth; inhibition of sweating

I. Antimuscarinic Agents

- **2. Scopalamine**
- used for motion sickness

- 3. **Ipratropium**
- as bronchodilators for maintenance treatment of chronic obstructive pulmonary disease (COPD)

- 4. **Benztropine**
- treatment of Parkinson disease

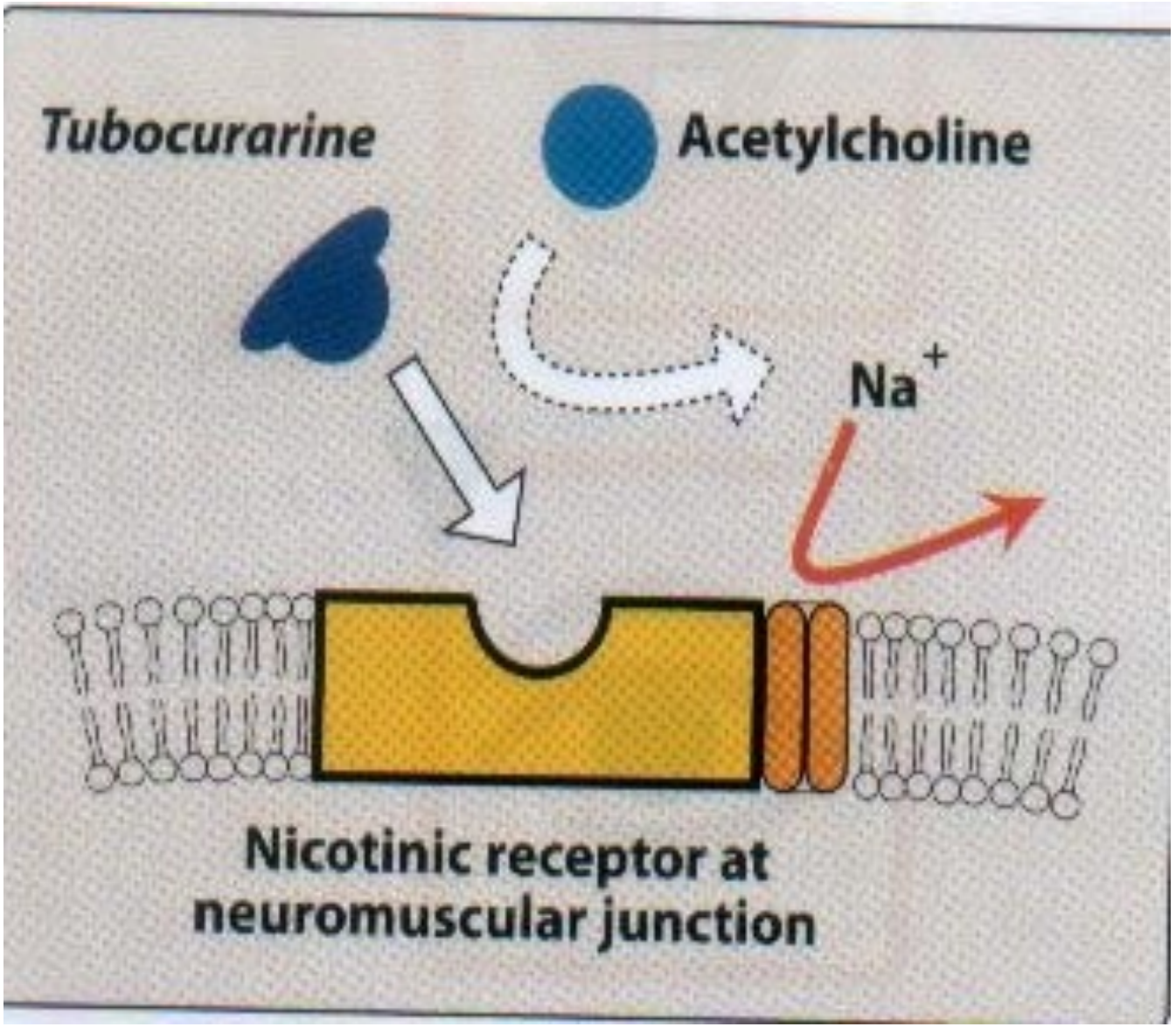
II. Neuromuscular-blocking drugs nicotinic receptors antagonist

1. **A. Nondepolarizing blockers**

- ***Tubocurarine*** *is* the prototype agent in this class
- interact with the nicotinic receptors to prevent the binding of Ach --- inhibit muscular contraction
- Therapeutic uses:
- as adjuvant drugs in anesthesia during surgery to relax skeletal muscle and to facilitate intubation

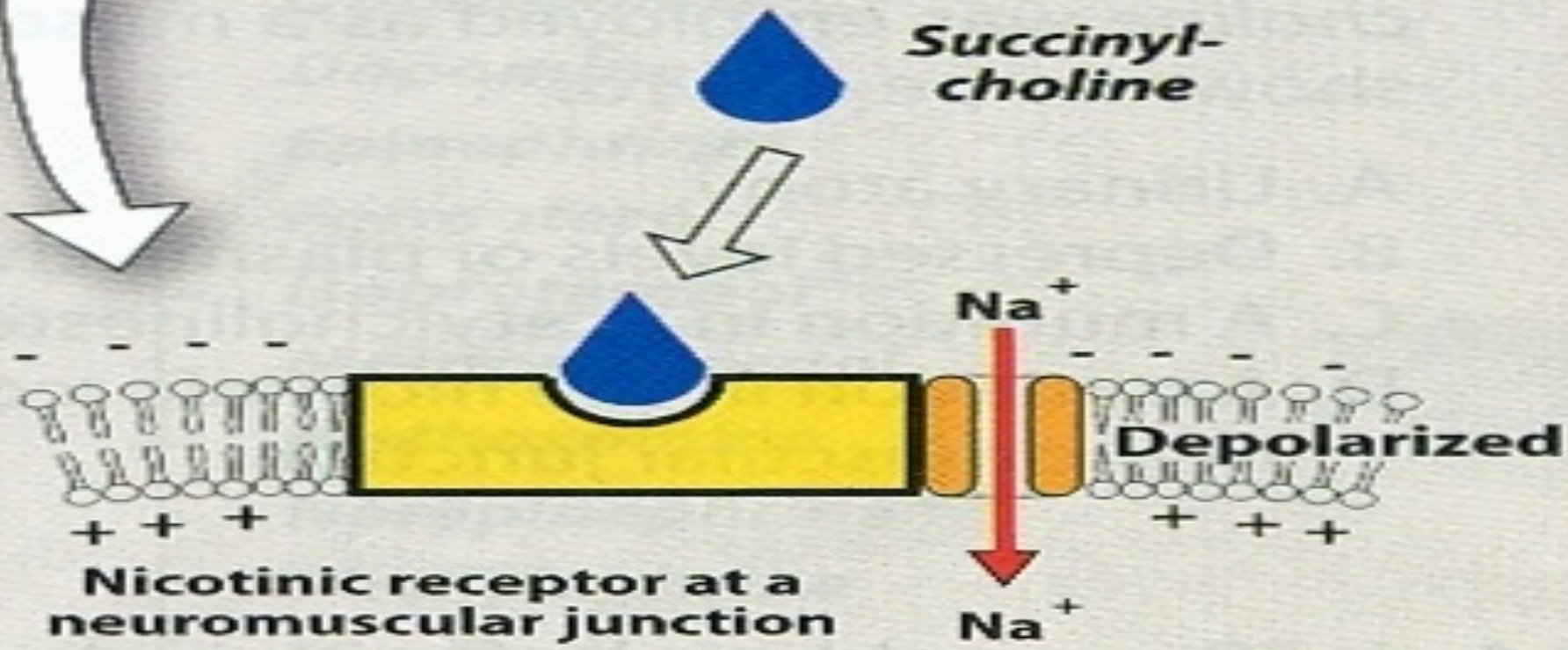
2. **Depolarizing agents**

- ***Succinylcholine***
- rapid onset and short duration of action, *useful when rapid endotracheal intubation* is required


Tubocurarine
Acetylcholine
Na+
Nicotinic receptor at
neuromuscular junction

PHASE I

Membrane depolarizes, resulting in an initial discharge that produces transient fasciculations followed by flaccid paralysis.



PHASE II

Membrane repolarizes, but receptor is desensitized to the effect of acetylcholine.