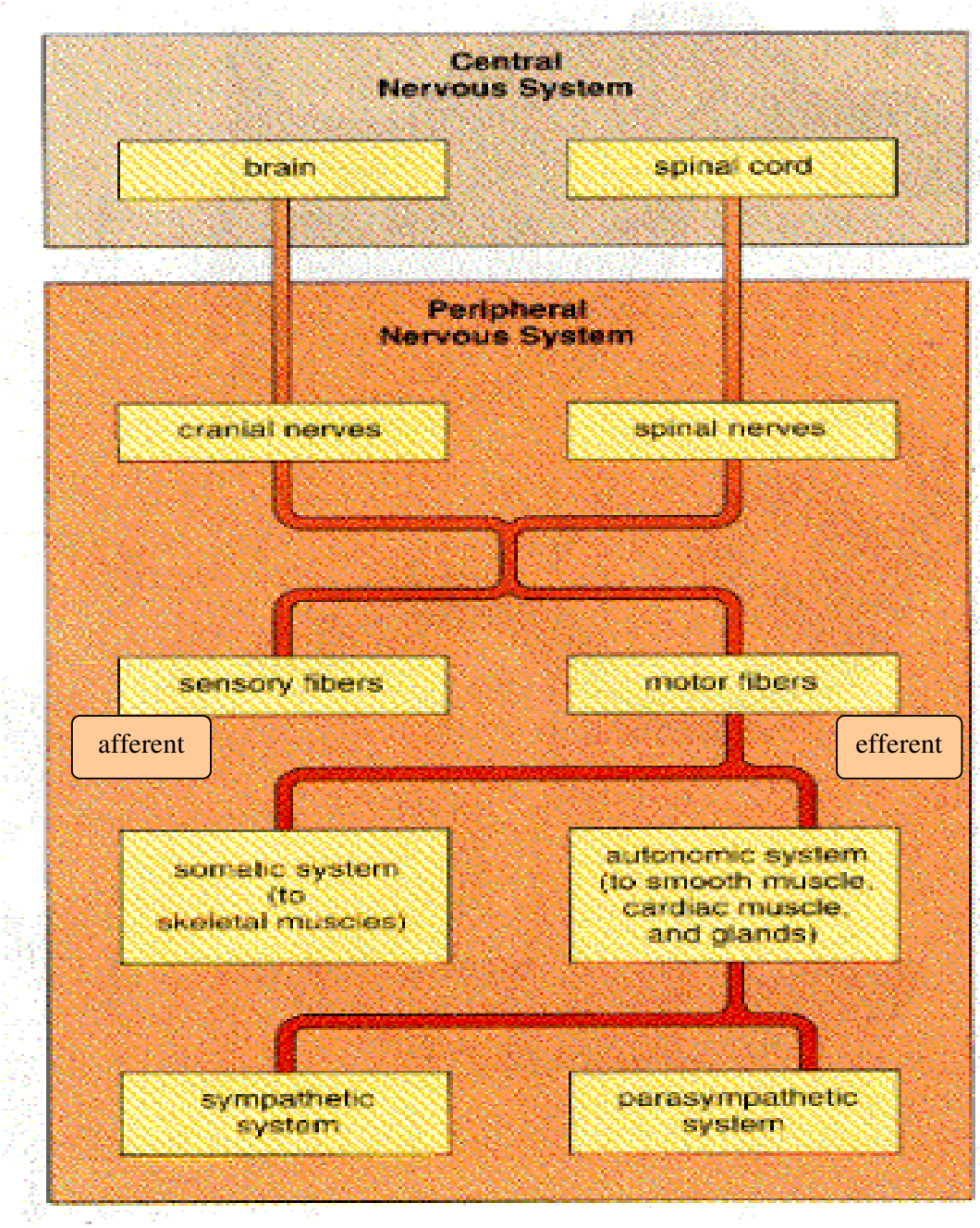
Introduction to the nervous system

nervous system is divided into :
central and peripheral nervous system



Human Nervous System

Central Nervous System (CNS)
Brain and spinal cord
Interneurons

Peripheral Nervous System (PNS)
Everything else
Sensory & motor neurons

Somatic Nervous System
Voluntary
Input from sense organs
Output to skeletal muscles

Autonomic Nervous System
Involuntary
Input from internal receptors
Output to smooth muscles & glands

Sympathetic Motor System
"fight or flight" responses
Neurotransmitter: noradrenaline
"Adrenergic System"

Parasympathetic Motor System
relaxing responses
Neurotransmitter: acetylcholine
"Cholinergic System"

Sympathetic	Parasympathetic
Thoracolumbar Preganglionic fibers leave CNS through first thoracic to second lumbar segments of spinal nerves	**Craniosacral** Preganglionic fibers leave the CNS through cranial nerves (3,7,9,10) and 2,3,4 sacral segments of spinal cord
Preganglionic is **shorter** than postganglionic	**Longer**
Ganglia form **chain** near the SP cord	Ganglia present **near** the organ innervated or nearly **embedded** in it
Ergotropic system Energy expenditure (consumption)	**Trophotropic** system Growth

◙ Parasympathetic Nervous system consumes less energy than does the sympathetic system.

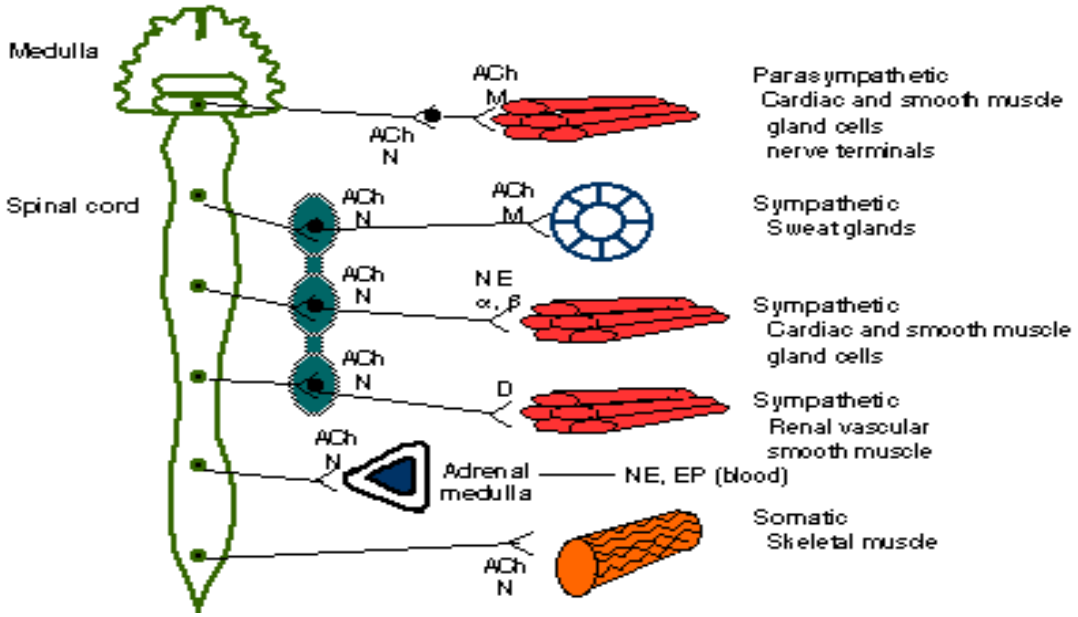
some notes u have to put them in your mind regarding the autonomic nervous system

◙ within the autonomic nervous system 2 neurons are required to reach a target organ preganglionc and postganglionic neuron .

◙ preganglionic neuron originate in the CNS. it forms a synapse with the postganglionic, the cell body of which is located in autonomic ganglia .

◙ all preganglionic neuron release Ach as their transmitter, the acetylcholine (Ach) binds to nicotinic receptors on the postganglionic cell .

◙ all of the parasympathetic postganglionic fibers release Ach . at the target organ Ach interact with muscarinic receptor .



◙ most of the sympathetic postganglionic fibers release NE (norepinephrin). at the target organ NE interacts with a variety of receptor.

◙ most of the <u>vascular smooth muscle</u> is innervated solely by the sympathetic nervous system . this means that blood pressure and peripheral resistance are ***controlled by the sympathetic nervous system .***

Cholinergic drugs

Cholinergic Transmission:

1- synthesis of acetylcholine (Ach)
2- storage
3- release
4- metabolism (fate)

Cholinergic Mechanisms:-
All process required for the Synthesis, Storage, Releases, Activation of the Receptors and then the termination of Acetylcholines's Action.

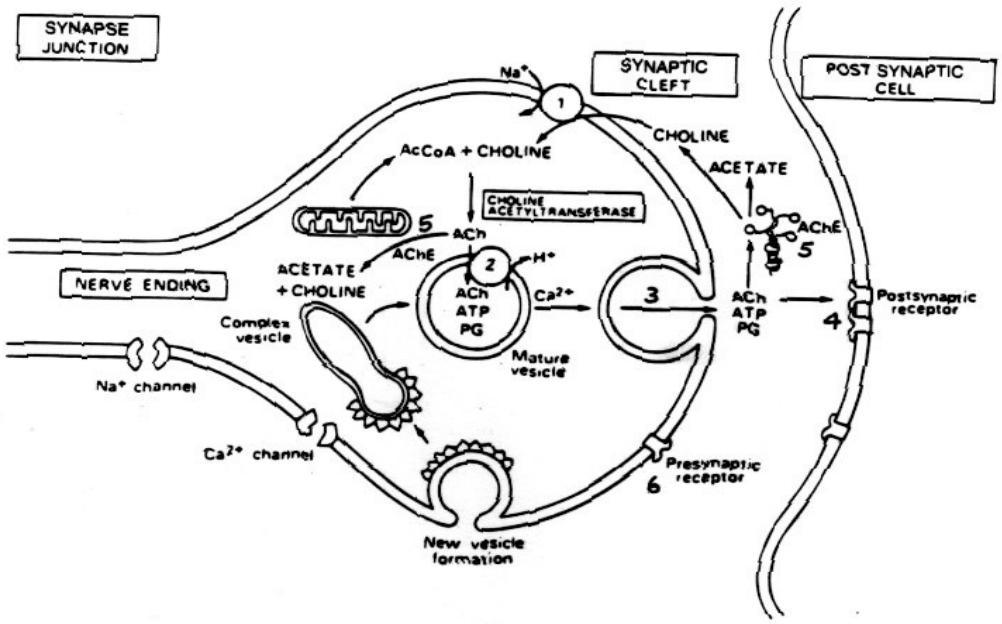


Fig. 17–2. General cholinergic nerve junction showing location of receptor sites and biosynthesis, storage, release, and hydrolysis of acetylcholine. (From B. G. Katzung, Introduction to autonomic pharmacology, in *Basic and Clinical Pharmacology*, B. G. Katzung, Ed., Norwalk, CT, Appleton & Lange, 1992.)

Synthesis:

- choline is transported into presynaptic nerve terminals by carrier (inhibition by: hemicholinium, triethylcholine).
- Formula of synthesis : Choline + acetyl CoA => Ach + CoA
- The enxyme required for catalyzing this reaction is Choline Acetyl Transferase.

- Choline either synthesized in the liver, uptaken from the ECM of the degradation of Acetylcholine, or is taken from diet is transferred to the cell body but then transported ACTIVELY to the axon terminal by axoplasmic flow.
- The choline molecules, are very hydrophilic so in order to transport them to the axon terminal, they are isolated in a vesicle then transported in it. (a carrier is required for getting them inside the vesicle)
- Sodium is also required to be co-transported with the choline to the Axon terminal.
- For Acetyl CoA, it is synthesized in the mitochondria then transported out of it in the form of citrate which is then reconverted into Acetyl CoA that can freely travel to the terminal.

- Drugs that can impair the Synthesis of Acetylcholine work on one of two pathways:-

- 1) in the process of transport of Acetylcholine to the nerve terminal:

- The drug is hemicholinium.

- It does not cause immediate failure of cholinergic fibers because the terminal has some stored amount of Acetylcholine that it can work on it for a while until it shows the signs of failure. But if the nerve was electrically stimulated, it will quickly discharge the stored Ach. And show the signs quicker.

2) the level of enzyme inhibition:
Examples of drugs that can inhibit Choline Acetyl Transferrase:-
e.g. Choroacetylcholine.
e.g. Bromoacetylcholine.
They are structural Analogs of Ach.
They have broad specificity (not specific)
e.g. NaphthylVinilPyridine which is a very specific inhibitor though NOT an analog of Ach.

Storage :

- Ach is transported into the storage vesicles by second carrier (inhibited by: vesamicol).

Release:

- Ach is released upon stimulation.
- Stimulation => influx of Ca => exocytosis of Ach (inhibited by: Mg, aminoglycosides).

- depolarization of nerve axon by nerve impulse triggers Ca++ influx .
- vesicles contain ATP , protein & Ach .

**** drugs affecting Ach release :***

- 1) Botulium toxin from C.botulium .
- it cleaves SNAp25 .
- poisoning by the toxin is called botulism .
- its because prevention of transmission at all peripheral cholinergic Junction & agglutination of RBCs .
- lethal effect >>>>> paralysis of respiratory muscle .

2) aminoglycosides : affect the Ca++ influx so it will cause skeletal Muscle relaxation .

3) Ca++ is substituted by mg++ .
4) morphine , catecholamine & B-bungartoxin .

**** Clinical application :***

- botulium toxin relaxes the underlying muscle of expression leading to the Reduction to the formation of skin creases .
- over time regular maintenance treatment can lead to the disappearance of These creases .
- e,g,: botox .

Fate:

- acetylcholinesterase enzyme (degrades it).
- acetylcholinesterase enzyme is inhibited by neostigmine .

MCQ :
Which ONE of the following statements is UNTRUE with regard to synthesis and release of acetylcholine from cholinergic nerve ending?

a. Uptake of choline is the rate limiting step in the synthesis of acetylcholine.
b. Botulinum toxin inhibits the release of ACh from the nerve ending
c. Vesamicol causes release of ACh into synaptic cleft
d. Hemicholinium competes with choline for uptake into the neuron and inhibits the synthesis of ACh.

Sites of Ach Release:

1- Neuromuscular junction (motor end plate).
2- Autonomic ganglia: all preganglionic nerve fibers of both sympathetic and parasympathetic nerves.
3- Parasympathetic post ganglionic fibers.
4- Sympathetic post-ganglionic fibers to sweat glands.
5- Preganglionic sympathetic nerve to adrenal medulla.

Note :

- adrenal medulla has no post ganglionic fibers (it acts as ganglia) & it is stimulated by adrenalin and noradrenalin .

Acetylcholinesterase:

found on both presynaptic and post synaptic membrane

True	Pseudocholinesterase
Specific cholinergic fiber	Non-specific
RBC,s , CSF ,nervous tissue ,striated muscle	Plasma, liver, skin, intestine.
Slow turnover, 120 days	Rapid turnover
Ach, methacholine	Succinylcholine. Butyryl-choline, bezoylcholine (they act on ACH)

- pseudocholinestrase is not found in choline fibers & it breaks any esters rather than ACH .
- pseudocholinestrase is also called (plasmacholinestrase)
- cholinestrase has two active sites .

Cholinergic receptor :

1- Central cholinergic receptors (nicotinic – since they are stimulated by low nicotinic concentration-).
2- Peripheral cholinergic receptors (muscarinic).

NOTE : (central) is found in ganglia & (peripheral) is found in organ .

Nicotinic Receptors:

It is cation channels- linked receptors (fast). Remember that ion channel act in millisecond

When nicotinic receptor are stimulated Na channels will open causing depolarization (that's why we said that the nicotinic receptors are cation channels linked receptors)

it's classified into 2 subtypes
1- *Nm (muscle) :* found at site of neuromuscular junction
2- *Nn (nerve)* : found at autonomic ganglion–sympathetic or parasympathetic ,brain and Adrenal medulla

autonomic ganglia :
* Agonist : epibatidine .
* Antagonist : mecamylamine .
Neuromuscular junction.
* Agonist : decamethonium .
*Antagonist : alpha – bungarotoxin
**** Do you remember what B – bungarotoxin do ?????

Peripheral Cholinergic Receptors (Muscarinic)

- M_1 => M_5 : $M_{1,3,5}$ => excitatory (odd). (activate phospholipase)
  $M_{2,4}$ => inhibitory (even). (inhibit adenylatecyclase)
- is G-protein linked receptors.
- **Found at:**

CNS, exocrine glands, smooth muscle (GIT, UT, RT) , vascular endothelial .

◙ note : in CNS we found both muscarinic and nicotinic receptors

Receptor	Location	Effect
M1 (neural) Excitatory (by deacrease K conductance so membrane depolarization)	CNS Autonomic ganglia Gastric parietal cell	CNS excitation Gastric acid secretion Activation of phospholipase C increase IP3 & DAG → ↑ Ca **Antagonist : pirenzepine** (treat peptic ulcer by block M1 so reduce HCL secretion)
M2 (cardiac) Inhibitory (by increase K conductance So decrease Ca conductance)	Heart Presynaptic terminal of peripheral & central cholinergic fiber	Cardiac inhibition Presynaptic inhibition Inhibition of adenylcyclase (↓cAMP) Opening of K channels causes hyperpolarization =>increase the negativity so no propagation of impulses => Bradycardia **Antagonist : gallamine**
M3 (glandular) Excitatory mainly but is inhibitory in vascular smooth muscle	Exocrine glands Smooth muscles Vascular endothelium	Secretion Smooth muscle contraction Vasodilation (via nitric oxide NO) Activation of phopholipase C increase IP3 & DAG **Antagonist : hexahydrosiladifenol (HHSD)**

◙ **Note :** ALL Muscarinic receptors are coupled to G-protien receptor
» activation of M1, M3, M5 lead to → increase inisitol triphosphate (Ip3) which lead to increase Ca+ (Excitatory effect)
» activation of M2, M4 lead to → decrease adenylate cyclase (Inhibitory effect)

Note :M4 (in brain & autonomic ganglion) & M5 (in CNS) , there effect Are Unknown .

Note :
In the endothelium we have M3 receptor (how Ach causes dilation of blood vessels ?)
Answer : Ach cause increase Ca++ => activate No synthase enzyme (which convert L-arginine to citrullin & NO >>>>=> NO go to the smooth muscle cell and activate Granulate cyclase (which convert CTP to CGMP => cause relaxation)

Pharmacological Actions of Ach:

- Nicotinic action.
- CNS action.
- Muscarinic action.

Nicotinic actions:

1- **Neuromuscular junction :**
   - ✓ stimulation => muscle contraction (twitching).
   - ✓ High concentration => persistant depolarization and spastic paralysis.

2- **Ganglia:**
   - ✓ stimulation of sympathetic and parasympathetic ganglia.

3- **Adrenal medulla:**
   - ✓ release of catecholamines (A+ NA).

CNS Actions:

1- **Nicotinic actions:**
   - ✓ anti-diuretic hormone secretion from hypothalamus.
   - ✓ Activation of renshaw cells.
   - ✓ Inhibition of motor fibers.

2- **Muscarinic actions:**
   - ✓ Ach is involved in memory and arousal.
   - ✓ Parkinsonism. (↓ in **dopamine** and ↑ in **Ach**)
   - ✓ Dementia of Alzheimer: loss of cholinergic neurons (decreased Ach)

Organs	Response
Eye: - sphincter muscle of iris. - ciliary muscle	- contraction (miosis). - contraction for near vision.
Heart: - S.A. node. - Atria. - A.V.node. - Ventricles.	- ↓ decrease in rate (negative chronotropy). - ↓ Contractile strength (-chronotropy) + ↓ refractory periord. - ↓ Conduction velocity(-dromotropy)+ ↑ refractory period. - Small in contractile strength.
Blood vessels: - artery. - vein.	} Dilation via EDRF (endothelium derived relaxing factor) } Constriction (high dose direct effect).
Lung: - bronchial muscle. - bronchial glands.	- constriction (bronchconstrictor). - stmulation
GIT: - motility. - sphincters. - secretion	- increase. - relaxation. - stimulation. * increase motor activity . * in smooth muscle of GIT M3 is found but in the parietal cells Of stomach M1 is found .
Urinary bladder: - detrusor. - trigone +sphicter	- contraction. - relaxation. * uterus is not sensitive to muscarinic agonist .
Glands: Sweat, salivary, lacrimal, nasopharyngeal glands.	Secretion

- nicotine & labe line => alerting action .
- High level of nicotine => convulsion & coma .

NOTE :
Ach cause contraction of ciliary muscle forward & inward relaxing the tension of the suspensory ligament of the lens , the lens bulge more , decrease focal length.
- the parasympathetic reflex is essential to accommodate for near vision .
- Aqueous humour : secreted by cells of the epithelium covering the ciliary body , is removed continuously by drainage into the canal of Schlemm .
- Normal intraocular pressure is 10 -15 mm Hg above atmospheric pressure .
- Abnormally raised pressure => retinal detachmentment
e.g, glaucoma .

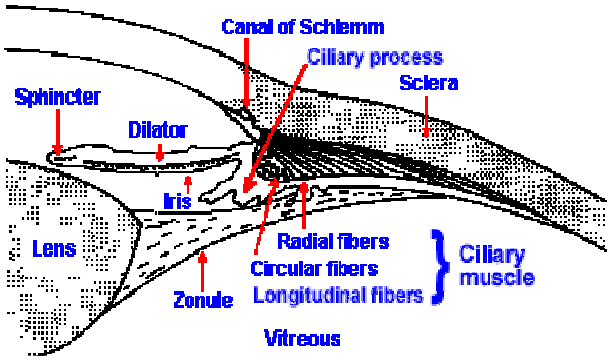
- Relaxation (dilation) of the iris => many folding of the iris => slow of aquous Humour flow => increase intraocular pressure , & vice versa .

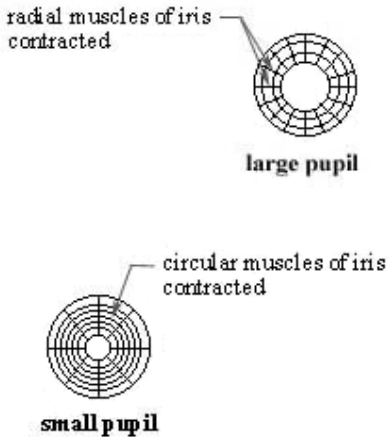
some notes regarding the responses of the eye :

» the responses in the eye can trip up . so there's one way to remember these responses is to recognize that radial muscle causes dilatation (mydriasis) and the circular muscle causes constriction (miosis). that is , there are no d's in any of the words relating to constriction.

» note there are two muscle of the iris one is the radial the another is the circular . the one that concerned with the mydriasis is the radial as we mention before and it look as a radiation from the pupil (look at the pictures)

now imagine how each muscle do its action





Cholinomimetic drug (cholinergic drugs):

► we can call it ***Parasympathomimetics*** because it produce effect like the parasympathetic.

► in fact, cholinergic drug (agonist) considers all the drug that ↑ activity in cholinergic neurons.

► cholinomimetric is called so, because they mimic the action of Ach (does what Ach does).

Types:

1- **Direct cholinomimetic** (act on the receptors directly):
   - ✓ act by direct stimulation of nicotinic or muscarinic receptors.

Activation of muscarinic receptors results in the following responses:

Eye	Miosis (constriction of pupil)
Cardiovascular	Decrease in heart rate
Respiratory	Bronchial constriction and increased secretions
Gastrointestinal (GI)	Increased motility, relaxation of sphincters
Genitourinary (GU)	Relaxation of sphincters and bladder wall contraction
Glands	Increased secretions

Activation of nicotinic receptors results in muscle contraction (fasciculations and weakness).

2- **Indirect cholinomimetic:**
   - ✓ act indirectly by inhibiting Achesterase thus prevent the degradation of Ach (prolong action of Ach).

Direct cholinomimetic:

a. **Natural occurring alkaloid**, e.g. pilocarpine. note most of the drugs end with the suffix -ine ,it will be alkaloids (plant derivative)
b. **Choline ester (not natural),** e.g.:
   - ✓ Ach.
   - ✓ Methacholine.
   - ✓ Carbachol.
   - ✓ Bethanichol.

Indirect Cholinomimetics (anti-cholinesterase):

a. Reversible:

◙ **note :** also called cholinesterase inhibitors : they compete with Ach for the active site on cholinesterase enzyme .

- ✓ edrophonium.
- ✓ Ambenonium.
- ✓ Physostigmine.
- ✓ Pyridostigmine.
- ✓ Neostigmine.

b. Irreversible:

◙ **note :** phosphorylate the enzyme and inactivate it

- ✓ ecothiophate.
- ✓ Isoflurophate.

Mechanism of Action of Cholinomimetic:

Muscarinic agonist: (G-protein linked receptor)

- activation of phospholipase C => increases IP_3 + DAG => contraction of smooth muscles.
- Increase cGMP => NO (nitric oxide) release => relaxation.
- Inhibition of adenyl cyclase => hyperpolarization.

Nicotinic agonist: (ion channel linked receptor)

- opening of ion channels => depolarization (because of Na influx).

◙ **note :** the muscarinic type uses G protein , whereas the nicotinic type uses the Na/K ion channel.

before we starting the drugs there are rules or notes u have to read them to understand the next pages

» Ach and cholinergic drugs affect the urinary bladder by : destrusor contraction , sphincter relaxation
thus → cholinergic drugs enhance the urination
» any drug that block the action of cholinergic , produce urinary retention .
» cholinergic drugs increase salivation, secretions in the body and sweating.

» **drugs may have quaternary structure or tertiary structure :**
a- quaternary
it's a nitrogen with 4 carbon atoms (NC4+) so, it contains positive charge , therefore, it's polar
e.g. Ach (natural product) , methacholine , carbachol , bethanechol (non-natural product)
b- tertiary
they are all natural product (uncharged) ,non-polar (lipid soluble) e.g. pilocarpine , nicotine , lobeline .

pharmacokinetics
quaternary group
►**Ach**
▫ low-lipid solubility because it's polar, therefore , poorly absorbed and poorly distributed in the CNS
▫ it is hydrolyzed in the GIT becoming not active
▫ it's ***not suitable by giving in oral route*** because of 3 reasons
i- poorly absorbed
ii- if it's absorbed it hydrolysed very rapidly by esterases in plasma (becuase very sensitive to esterases 2-3 seconds)
iii- it digested by intestinal enzymes
methacholine is 3 times more resistant to hydrolyzed by cholinesterase
►**other compounds**
carbamic are completely resistance to be hydrolyzed by cholinesterase such as carbachol , bethanechol
presence of methyl group on bethanechol reduce it potency at nicotinic junction , so it's muscarinic

tertiary cholinomimetics
they are well-absobed from site of administration because it's non-polar compound
▫ **nicotin** is lipid-soluble, it's absorbed across the skin
▫ excretion by kidney . the clearence of tertiary amines can be enhance by acidification of urine
▫ pilocarpine is pure muscarinic & completely resistant to cholinesterase , and it's rapidly absorbed by the corona of the eye & it can cross blood-brain barrier
▫ Muscarinic quaternary amines is less absorbed in GIT but still toxic when ingested the mushroom.

◙ **note :**
► the *action of the direct drugs* is mostly **muscarinic receptors**
► the *action of the indirect drugs* is mostly **on both kinds of the receptors**.

Pilocarpine: -MCQ-(doctor said that it always come in exams):

- Direct cholinomimetic drugs => direct (+) the receptors.
- Natural occurring alkaloid.

Chemistry:

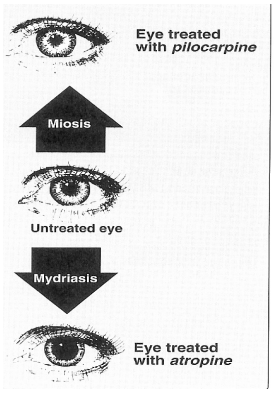
- tertiary amine.
- Non-polar (non-ionized).

Pharmacokinetics:

- well absorbed orally.
- Cross BBB.
- Good distribution.
- Not metabolized by cholinesterase. (because its not an ester)
- Long duration of action.
- Excreted unchanged in urine (acidification => increased excretion).

NOTE :

- unchanged means that it does not enter phase one and only undergoes Conjugation (to transform it from non polar to polar form) in order to Be excreted by the kidney .



Pharmacodynamics:

- direct muscarinic agonist mainly on eye and secretion.
- No nicotinic action.
- CNS action (can cross BBB).

Uses:

- glaucoma
- Xerostomia (dry mouth) => increase secretion of saliva.
- To counteract mydriasis after fundus examination => contraction of sphincter of the iris.

glaucoma: group of eye disease characterized by an ↑ in intraocular pressure, causing pathological changes in the optic disk and typical visual field defects.
Glaucoma means increase aqueous humar amount (the increase in ocular pressure due to increase the aqueous)
Due to blockage in the canal of Schlemm ,
So increase ocular pressure => for this , we give the Patient cholinomemitics that cause contraction of Iris & ciliary muscle , causing the opening of the Canal so drainage will take place & pressure will Return back to normal .

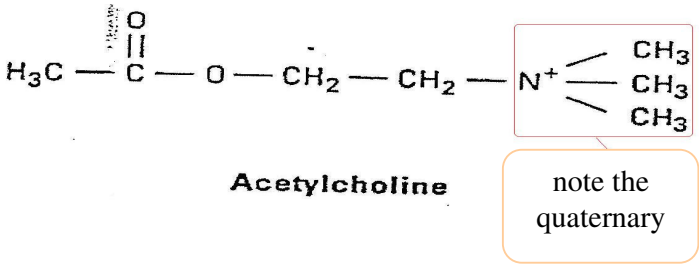
MCQ :
a patient with an acute attach of glaucoma is treated with pilocarpine. the primary reason for its effectiveness in this condition is its :
a. action to terminate acetylcholinesterase
b. selectivity for nicotinic receptors
c. ability to inhibit secretions. such as tears, saliva , and sweat.
d. ability to lower intraocular pressure
e. inability to enter the brain .
the answer is : d

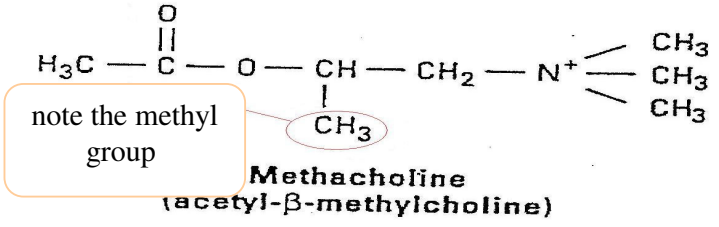
Acetylcholine:

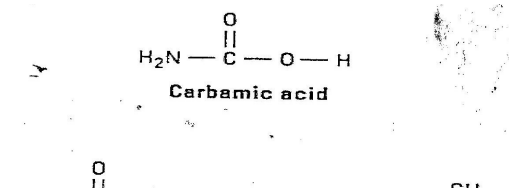
- direct cholinomimetic drug.

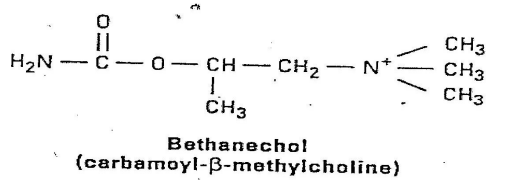
Examples:

- methacholine (Ach + methyl group).
- Bethanichol (choline + carbonic acid + CH_3).
- Carbachol (choline + carbonic acid).









Acetylcholine

- natural.
- Polar.
- Not absorbed orally.
- Poorly distributed in the CNS .
- Hydrolyzed in the GIT .
- Muscarinic and nicotinic agonist.
- Not used due to:
  - ✓ Non-selective.
  - ✓ Short duration of action. [cuz it will rapidly hydrolyzed by the true and pseudo cholinesterase (nonspecific cholinesterase)]

Synthetic choline esters (methacholine, Carbachol, Bethanechol):

Chemistry:

- Quaternary ammonium compound.

Kinetics:

- polar.
- Poor distribution.
- No cross BBB => no CNS actions.
- Metabolism by cholinesterases (true, pseudo..).

Dynamics:

- muscarinic agonists: methacholine, bethanichol (both have CNS action).
- Muscarinic and nicotinic agonists: acetylcholine, carbachol.

Comparison between Ach and synthetic choline esters: -MCQ-

- all are quaternary ammonium compound (=polar).
- More specific (the synthetic).
- Less metabolized => they have longer duration of action (the synthetic).
- Never given I.V. or I.M => given S.C. (the synthetic).

NOTE : ACH is not used systemically .

Methacholine:

- Polar => irregular absorption (can be taken: orally, S.C.).
- Metabolized by true cholinesterase only.
- Long duration of action.
- More specific (for CVS).
- Muscarinic action on CVS than GIT and urinary tract. (MCQ)
- No nicotinic actions.
- **Used for:**
  - ✓ Peripheral vascular disease.
  - ✓ Paroxysmal atrial tachycardia.

Carbachol: -MCQ-

- Quaternary: good absorption than Ach (orally, S.C).
- Not metabolized by cholinesterase.
- Longer duration of action than Ach.
- Selective muscarinic actions on eye, GIT, UT.
- Nicotinic action.
- **Used for:**
  - ✓ Glaucoma.
  - ✓ Urinary retention + paralytic ileus.

Lets take an example :
- after surgeries the intestine may not move (paralytic ileus) , so we give to the patient Carbachol that increase the intestine motility .

Bethanechol: -MCQ-

- Similar to carbachol but **no** nicotinic actions.
- More preferred than carbachol for paralytic ileus and urinary retention.

presence of the methyl group on the drug make it selective to muscarinic only

Uses : Glaucoma (pilocarpine).
Paralytic ileus (bethanichol).
Urinary retention (bethanichol).

Contraindications: Bronchial asthma (because it acts as bronchoconstrictor).
Peptic ulcer (because it increases the gastric acid secretion).
Angina pectoris (because it causes bradycardia).

MCQ :
Bethanechol produces all the following actions , EXCEPT
a. Relaxation of bronchial smooth muscle..
b. Relaxation of bladder sphincter.
c. Increases GI motility
d. Decreases heat rate and cardiac output.
the answer is : a

Indirect Cholinomimetics (Anti-Cholinesterase):

Inhibit acetylcholinesterase thus increase the Ach concentration at cholinergic receptors.

1- First step (initial binding):

Ach bind to enzyme's active site and is hydrolyzed => choline + acetylated enzyme.

2- Second step (hydration step):

acetylated enzyme bond is broken by hydration (+ H_2O) => enzyme + acetic acid.

Reversible Indirect Cholinomimetics :

1) Edrophonium (Quaternary alcohol)
2) Carbamates (Ester) :
   - -Physostigmine
   - -Pyridostigmine
   - -Neostigmine
   - -Ambenonium

Irreversible Indirect Cholinomimetics :

1) Organophosphorous esters:
   - -Ecthiophate
   - -Isoflurophate

Theses drugs are used in the treatment of Glucoma.
These drugs are irreversible because the organophosphorous esters combines with the Choline esterase with a covalent bond and if left for some time, it will become even stronger and last for more than 100 hours.
They are very well-absorbed from the skin, lungs, gut and conjunctiva except for Ecthiophate which is less stable in Aqueous solutions.

Edrophonium :

- Indirect cholinomimetic
- Simple alcohol
- Reversible anti cholinesterase (due to the weak, one-sited binding.)
- Not substrate for enzyme , attach mainly to anionic site

Does not contain and ester group so it can not bind to the Esteratic Site.

- Very short duration of action
- **Pharmacokinetics :**
  -Polar
  -Not absorbed orally (should given by injection)
  -Not hydrolyzed by cholinesterase
  -Excreted unchanged in the urine

short duration of action, as short as 15 minutes.

- **Uses :**
  Diagnosis of myasthenia gravis (weakness of the skeletal muscles)
  to differentiate between myasthenia gravis and toxicity

how to differentiate between myasthenia gravis and toxicity ?
muscle weakness could be due to two causes :
1) myasthenia gravis
2) taking two much anti-cholinergic drugs
we give the patient edrophonium , if cause muscle contraction improvement it means the patient has myasthenia gravis
if the muscle weakness increase ,we will say he has toxicity .

MCQ :
a patient being diagnosied myasthenia gravis would be expected to have improved neuromuscular function after being treated with :
a. donezepil
b. edrophonium
c. atropine
d. isoflurophate
e. neostigmine
the answer is : b

Carbamate Derivatives (ester): -MCQ-

- Physostigmine.
- Neostigmine.
- Pyrisostigmine.
- Ambenonium.

note :
»Neo- and Pyriostigmine are both quaternary-ammonia-containing drugs that can, themselves, activate the nicotinic receptors and can also inhibit the Choline Esterase Enzyme.
»Ambenonium.Has pretty long duration of action of about 4 to 8 hours.

- Attach at both sites of the cholinesterase enzyme.
- Substrate for cholinesterase.
- Hydrolyzed at slower rate than Ach.
- All are polar except: physostigmine
- longer half life 4-8 hrs
- They are staple in aqueous solutions but can be metabolized by choline esterases.

Physostigmine: -MCQ-

* Tertiary ammonium compound (methyl carbamate)

Pharmacokinetics:

- Non polar
- Good lipid solubility.
- Good oral absorption.
- Good BBB penetration.
- Hydrolyzed by cholinesterase (True & Psudo)

Pharmacodynamics:

- Attach at both site of the enzyme.
- Intermediate duration of action.
- Indirect action (Reversible anticholinesterase).
- Has muscarinic & nicotinic action.
- CNS (+) action.
- No direct action on NMJ.

Uses:

- Glaucoma. **where it is used topically on the eye**.
- To counteract the effect of mydriaties.
- Atropine intoxication.

Neostigmine: -MCQ-

* Reversible anticholinesterase.
* Quaternary ammonium compound (Dimethyl cabamate)

Pharmacokinetics:

- Polar compound.
- Poor lipid solubility.
- Irregular oral absorption.
- No BBB penetration.

Pharmacodynamics:

- Indirect action.
- Has muscarinic & nicotinic action.

(more prominent on GIT & urinary tract than CVS)

- Direct action on NMJ.

Uses:

- Treatment of myasthenia gravis (+ Atropine) → atropine is a muscarinic antagonist , neostigmine has nonspecific action it affects both muscarinic and nicotinic receptors. so if I want to work only on nicotinic I give the patient atropine with the neostigmine to block the action of muscarinic.
- Paralytic ileus & urinary retention.
- Curare intoxication.(skeletal muscle relaxant so we need to give the patient neostigmine to help the muscles contract to alleviate the symptoms and counteract them.)

Ambenonium & Pyridostigmin: -MCQ-

* Similar to neostigmine.
* Treatment of myasthenia gravis.

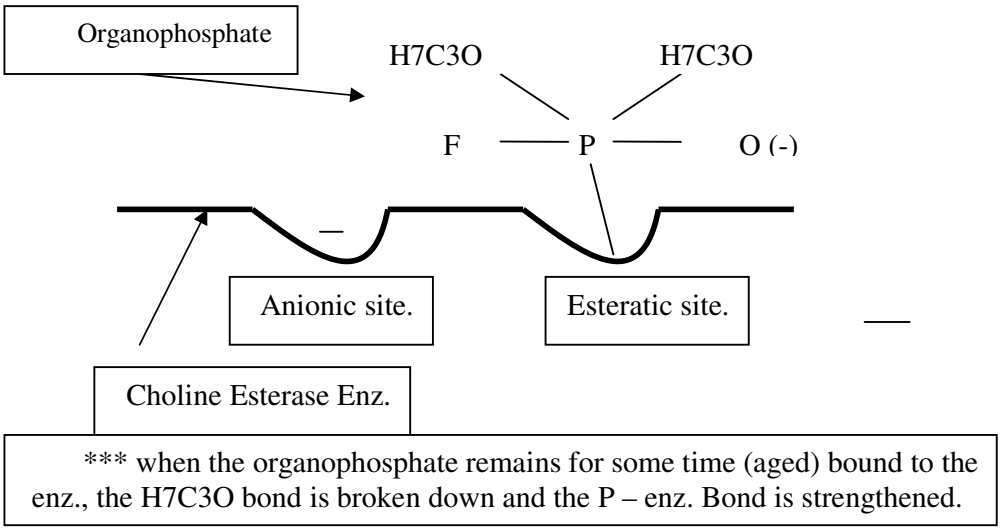
Indirect Cholinomimetics (Organophosphorous compounds):

-e.g.
* Ecothiophate
* Isoflurophate (DFP), Di isoprobyl flurophosphate.

Mechanism: **-MCQ-**

- Bind only to esteriatic site by forming covalent bond with the phosphorous atom.
- Aging make bond extremely stable.
- Long duration of action.
- All are highly lipid soluble **EXCEPT** Ecothiophate (No CVS effect)
- used mainly for Glucoma. (eye drop)

note :
Because organophosphate compounds are lipid-soluble so they can cross the Blood Brain Barrier and they CAN not be easily hydrolysed by the choline esterases, their inhibition will be characteristically permanent which makes them toxic to the body (especially the brain). Therefore they are NOT used in the human body except for the Ecothiophate that is not very lipid-soluble, so it cant cross the BBB and can be, thus, used for treatment of glaucoma.



*** when the organophosphate remains for some time (aged) bound to the enz., the H7C3O bond is broken down and the P – enz. Bond is strengthened.

* **-Pralidoxime & obidoxime** (nucleophiles) are able to split the P-enzyme bond , if given **before aging**Used as cholinesterase **regenerator** for organic phosphate poisoning.

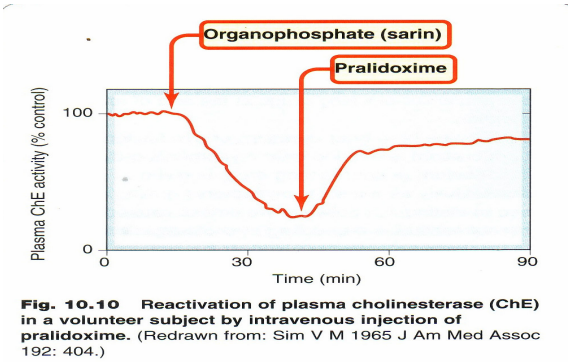


Fig. 10.10 Reactivation of plasma cholinesterase (ChE) in a volunteer subject by intravenous injection of pralidoxime. (Redrawn from: Sim V M 1965 J Am Med Assoc 192: 404.)

◙ **note :**
all the *irreversible cholinomimetics* are highly lipid soluble **except** *ecothiophate* so it has no CNS effect because it is non-lipid soluble .
all the *reversible cholinomimetics* are polar (non-lipid soluble) **except** *physostigmine*

Indirect Antcholinesterase:

Pharmacological effect of Organophosphorous:

1- Muscarinic action. (see table of Ach)
2- Nicotinic action.
- Ganglia
- Neuromuscular junction

Therapeutic dose → increase acton of Ach, contraction.
Toxic dose → muscle twitching & fibrillation.

* Explanation:
Neuromuscular junction:- low concentration intensify the effect of endogenous Ach →↑ force of contraction,
High concentration →**fibrillation** of muscle fibers, membrane depolarization becomes sustained →**depolarization block.**

3- CNS, excitation , convulsion , respiratory failure , coma .
a)in low concentration the high lipid-soluble inhibitors cause diffuse activation of **EEG**→alerting response.
b)↑con→generalized convulsions followed by **coma** & respiratory arrest.

4-CVS:- activation in both symp., parasymp. Ganglia & neuroeffector junction.
In the heart effects of **parasympathetic** limb predominate, ↓HR, ↓conduction velocity through AV node, ↓atrial contractility, ↓CO. Modest change in Bp.

Organophosphate Cholinesterase Inhibition Toxicity:

- Serve bradycardia, hypotension.
- Difficulty in breathing (bronchospasm)
- Increase GIT motility → cramps & diarrhea.
- CNS effect → convulsion, coma and respiratory failure.
- Twitching & fibrillation of skeletal muscle → depolarize block → muscle weakness.

"twitching" is the state at which each muscles fiber contracts alone with no coordination with the other fibers. In other words, it means loss of homogenous contractility.

Treatment of Organophosphate Toxicity : -MCQ-

1- Prevent further absorption.
2- Support respiration.
3- Cholinesterase reactivation which must taken BEFORE aging occurs.
4- Atropine (to block muscarinic (peripheral) & central action)

Cholinesterase Reactivation (Oximes).

e.g. **Pralidoxime** (PAM): **-MCQ-**

- Accelerate the hydrolytic regeneration of cholinesterase enzyme .
- The reactivate recently inhibited enzyme before aging.

Uses: - I.V→over 15–30 min. for Organophosphate cholinesterase inhibition toxicity.
- Not recommended for use in carbamate toxicity.

New Drug:

* Cevimeline:

- Direct acting cholinomimetics.
- Given orally.
- Cholinergic enhancer.
- Increase salivation.
- Use for treatment of dry mouth symptom associated with sjorgren's syndrome.

- **Sjogren's Syndrome is an autoimmune disease** resulting in inflammation of lacrimal and salivary glands→ eye and mouth dryness.
, with particular effect on M3 receptors.muscarinic agonistCevimeline is salivary , **By activating the M3 receptors** cevimeline stimulates secretion by the ,salivary glands thereby alleviating dry mouth.
Rapidly absorbed after oral administration and excreted unchanged in urine

Anticholinestrase Drug:

Donepezil : -MCQ-

- Given orally.
- Treatment of dementia of Alzheimer's disease.

General Pharmacodynamics about the Indirect Anti-Cholinesterases.

ON CNS:-

In low conc., the high lipid soluble inhibitors cause diffuse activation of the ElectroEncephaloGram leading to mental alertness.
But in high conc, convulsions may result followed by coma and respiratory arrest.

ON CVS:-

It causes increase in the activity of Nicotinic receptors in both Sympathetic and Parasympathetic ganglia and muscurinic receptors in the neuroeffector junction.
In case of the Neuroeffector junction, low conc. Will intensify the effects if endogenous Ach. which will lead to increase in the force of contraction.
But in high conc., fibrillation occurs of the muscle fibers and the membrane depolarization becomes sustained (also called depolarization block).

In the heart, the effect of parasympathetic nervous system predominates so it leads to decrease in the heart rate.
In the AV node, the atrial contractility and the Cardiac Output decrease with modest (slight) change in the Blood Pressure.

difference between pilocarpine and bethanechol :

pilocarpine	bethanechol
Goes to the brain → tertiary ammonium → uncharged → pass through blood brain barrier BBB	Doesn't go to the brain → quaternary amine → charged → doesn't pass through BBB
More effective in secretion than muscle contraction	More effective on muscle contraction than secretion
Used in treatment of secretary problem	Used in the treatment of urinary problem

MCQ
in the comparison of pilocarpine and bethanechol , which one of the following is correct :
a. both hydrolyzed by Achesterase
b. both inhibit nicotinic receptors
c. both may decrease sweating
c. both may increase GI motility
e. neither causes tachycardia
the answer is : e

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

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

Long duration of action (2 to 4 hrs)

Short duration of action (10 to 20 min)

Long duration of action (1 week)

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
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
Edrophonium	For diagnosis of myasthenia gravis As antidote for tubocurarine
Isoflurophate	Treatment of open-angle glaucoma