CHOLINERGIC TRANSMISSION

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Pharmacology and therapeutics

:Objectives

.To know the **Types of Receptors** -1

To know **the Distribution of cholinergic** -2

.Receptors with their functional action

To know the classification, MOA, -3 pharmacological effect, therapeutic uses and side effects, contraindications of the

.Cholinergic drugs agonists

- **Acetylcholine (ACh) synthesis and release :**
- ***ACh*** is synthesized within the nerve terminal of ***cholinergic neurons*** from ***choline***, which is taken up into the nerve terminal by a specific carrier (blocked selectively by **Hemicholinium**).
- Free choline within the nerve terminal is acetylated by a cytosolic enzyme, ***choline acetyltransferase*** **(*CAT*)**, which transfers the acetyl group from acetyl coenzyme A.
- The **rate-limiting process** in ACh synthesis appears to be **choline transport.**
- ACh synthesized, however, is packaged into synaptic vesicles, in which its concentration is very high, and from which release occurs by exocytosis triggered by Ca^{2+} entry into the nerve terminal.

- ***Cholinergic vesicles*** accumulate ACh actively, by means of a specific transporter, blocked selectively by the experimental drug **Vesamicol**.
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- ***ACh release*** can be **blocked** by **Botulinum toxins** and **stimulated** by **Spider venom**.
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- Following its release, the ACh diffuses across the synaptic cleft to combine with receptors on the postsynaptic cell.
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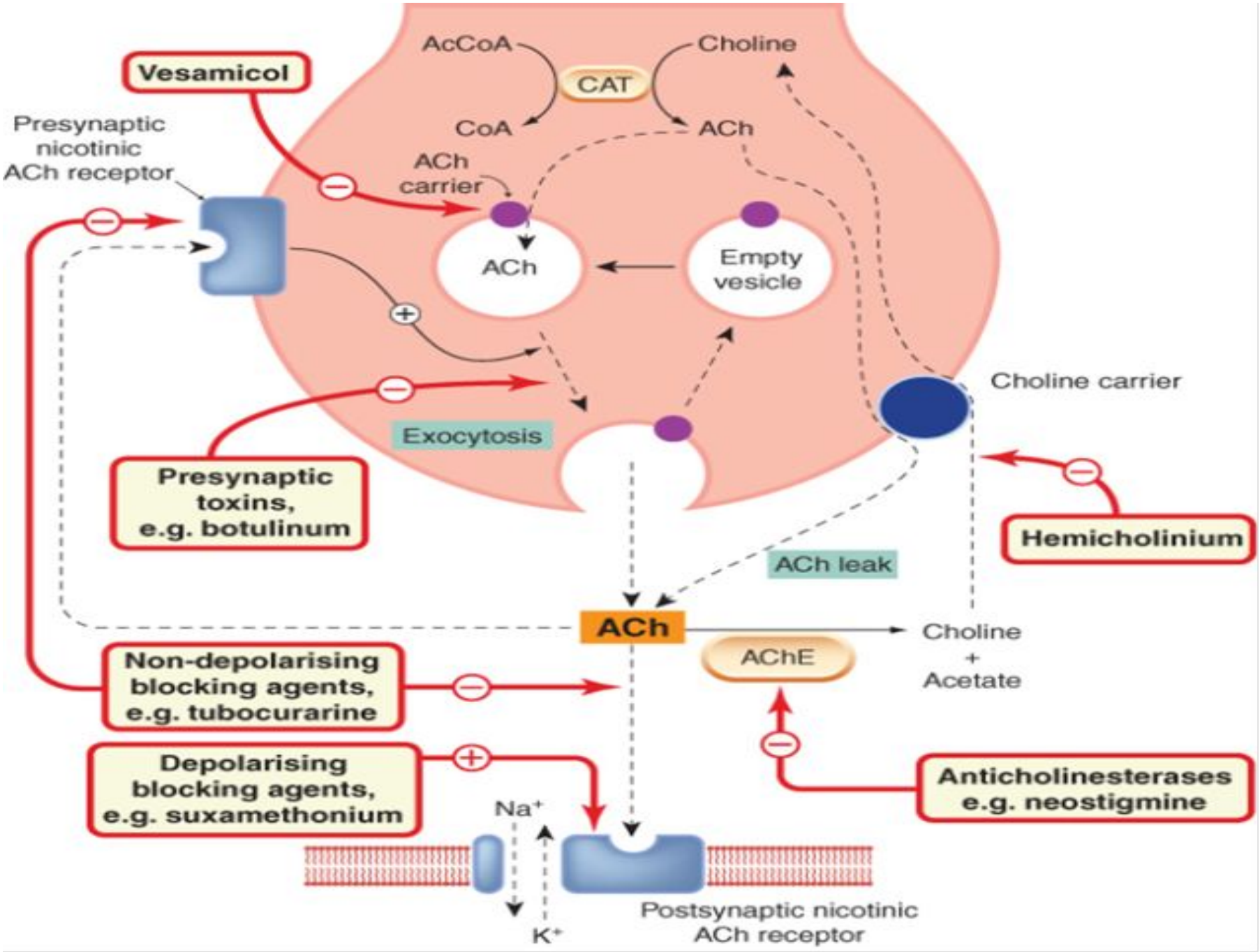
- Some of it subjected to hydrolysis by ***acetylcholinesterase (AChE)***, an enzyme that is bound to the basement membrane, which lies between the pre- and postsynaptic membranes, the released ACh is hydrolyzed very rapidly (within 1 ms) to ***choline*** and ***acetate***, so that it acts only very briefly.


AcCoA
Choline
CAT
CoA
ACh
Vesamicol
Presynaptic nicotinic ACh receptor
ACh carrier
ACh
Empty vesicle
Choline carrier
Exocytosis
Presynaptic toxins, e.g. botulinum
Hemicholinium
ACh leak
ACh
Choline + Acetate
AChE
Non-depolarising blocking agents, e.g. tubocurarine
Depolarising blocking agents, e.g. suxamethonium
Anticholinesterases e.g. neostigmine
Na+
K+
Postsynaptic nicotinic ACh receptor

- **Presynaptic modulation :**
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- Acetylcholine release is regulated by mediators, including ACh itself, acting on presynaptic receptors.
- At postganglionic parasympathetic nerve endings, presynaptic inhibitory ***muscarinic*** M_2 receptors participate in ***autoinhibition*** of ACh release. (**Autoreceptors**)
- **Hetroreceptors** are also autoinhibitory receptors but activated by other transmitters e.g. α_2 presynaptic receptors on cholinergic neurons
- At the neuromuscular junction and autonomic ganglia , on the other hand, presynaptic ***nicotinic ACh*** receptors are believed to ***facilitate*** ACh release.

- **Distribution of cholinergic neurons :**
- All somatic motor neurons
- All preganglionic autonomic neurons (include those supply adrenal glands)
- All postganglionic parasympathetic neurons
- Postganglionic sympathetic neurons supply thermoregulatory sweat glands
- In the CNS
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- **Muscarinic and nicotinic actions of acetylcholine :**
- ***muscarinic actions*** :
- Similar to the effect produced by **muscarine**, (from the poisonous mushroom *Amanita muscaria*) which is abolished by **atropine**.
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- Muscarinic actions = parasympathetic stimulation with two other important effects :
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❖ ACh causes generalized vasodilatation, even though most blood vessels have no parasympathetic innervation. (**M_3 mediated NO pathway**) like Nebivolol

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❖ ACh evokes secretion from sweat glands (sympathetic)

- The ***nicotinic actions*** of ACh are closely similar to those of **nicotine**
  - (*tobacco* plant)
- Not abolished by **atropine** and include:

❖ Stimulation of all autonomic ganglia
❖ Stimulation of voluntary muscle (sk.m.)
❖ Secretion of adrenaline from the adrenal medulla.

- Nicotinic action is mediated through ***nicotinic receptors*** (time scale of action within milliseconds) which is much more faster than ***muscarinic receptors*** that mediate the muscarinic action (time scale of action within seconds).

- **Acetylcholine receptors : (cholinergic receptors)**
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- **Nicotinic receptors:**
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- Previously Nicotinic ACh receptors (**nAChRs)** were subdivided into two types **Nm** (muscular) and **Nn** (neural) but now, they fall into three main subclasses:
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- ***Muscle*** (skeletal neuromuscular junction (***NMJ***))
- ***ganglionic*** **(**sympathetic and parasympathetic ganglia**)**
- ***CNS*** (widespread in the brain)
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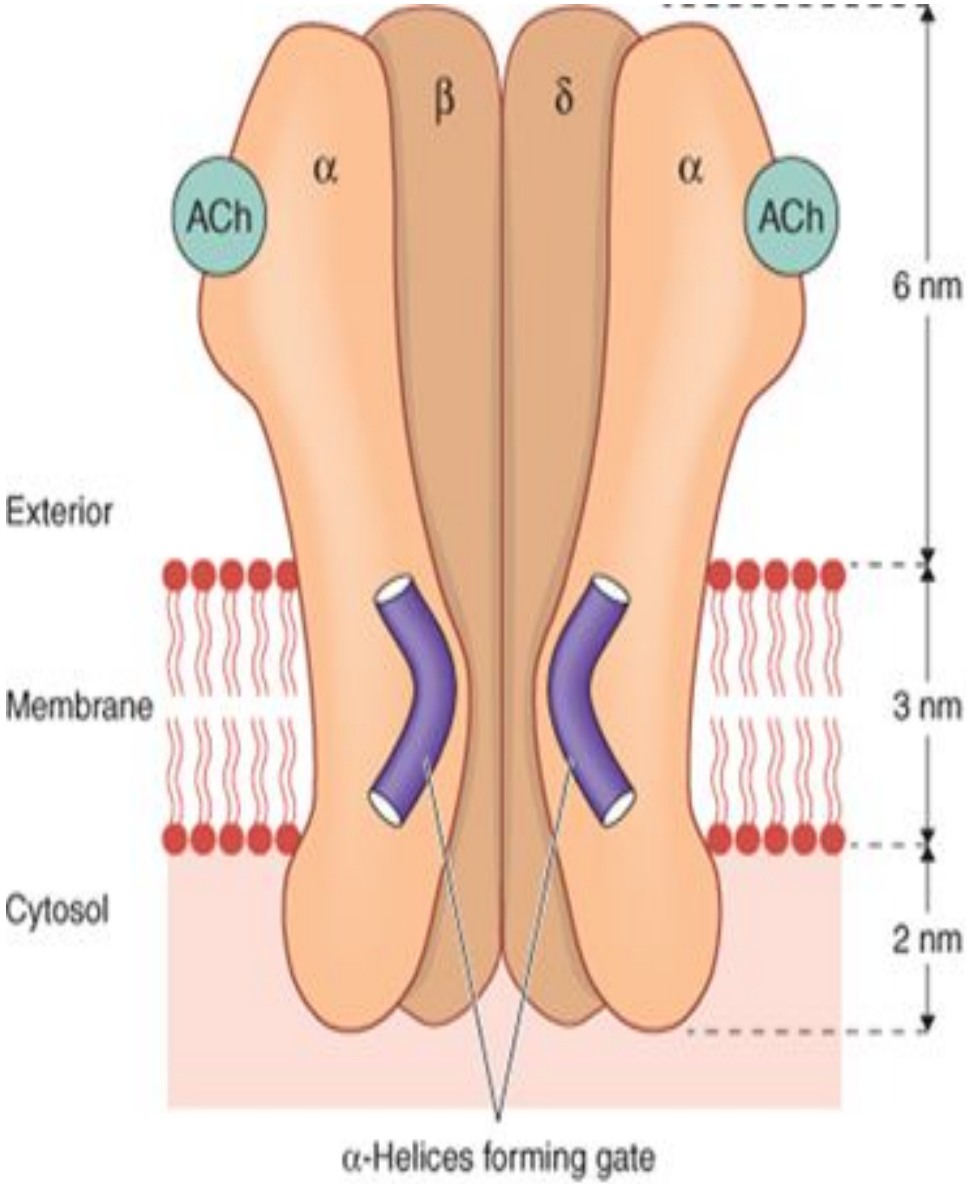
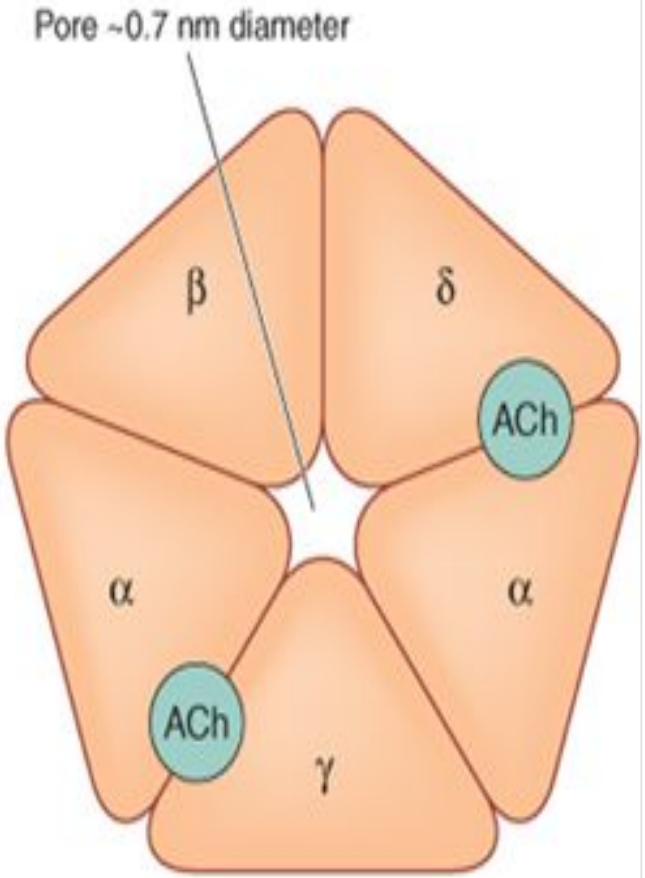
- All **nAChRs** are pentameric structures belong to the family of ionotropic (channel-linked) receptors that function as ***ligand-gated ion channels***. The five subunits form the receptor-channel complex. **nAChR** subtypes contain different subunits but generally all contain both **α** and **β** subunits.


α
β
δ
α
ACh
ACh
6 nm
Exterior
Membrane
3 nm
Cytosol
2 nm
α-Helices forming gate


Pore ~0.7 nm diameter
β
δ
ACh
α
α
ACh
γ

- There are two binding sites for ACh, both of which need to be occupied to cause the channel to open (two ACh molecules required to activate the receptor). When the channel opened , Na^+ will enter the cell and cause rapid **depolarization** and action potential (**EPSP** or excitatory postsynaptic potential). This EPSP will provoke the AP in postsynaptic cell **(neural transmission in ganglionic and CNS types or skeletal muscle contraction in muscle type)**.

- **Muscarinic receptors:**
- Muscarinic ACh receptors (**mAChRs**) are typical ***G-protein coupled receptors*** (metabotropic receptors) and there are five molecular subtypes **(M_1-M_5)** are known.
- (M_1, M_3, M_5) couple with G_q to activate the inositol phosphate pathway (IP_3 & DAG). When this type of receptors is activated the α-subunit of G-protein will activates phospholipase C (a membrane bound enzyme) that will act on **PIP_2** membrane phospholipid to produce **IP_3** (inositol trisphosphate) & **DAG** (diacyl glycerol) 2^{nd} messengers. **IP_3** will stimulate intracellular Ca^{++} release (important in contraction) while **DAG** will modulate the action of protein kinase C (an enzyme important in secretion)
- (M_2, M_4) act through G_i to inhibit adenylate cyclase and thus reduce intracellular ***cAMP*** .
- **Three of mAChRs (M_1, M_2, M_3) are well characterized:**

- **M_1 receptors *(neural)* :** (excitatory effects)
- CNS and peripheral neurons and on gastric acid secreting cells (ECL cells).
- Deficiency of this kind of ACh-mediated effect in the brain is possibly associated with dementia. M_1 receptors are also involved in the increase of gastric acid secretion following vagal stimulation.
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- **M_2 receptors *(cardiac)* :** (inhibitory effects)
- Heart, and also on the presynaptic terminals.
- (M_2 receptor activation is responsible for cholinergic inhibition of the heart, as well as presynaptic inhibition in the CNS and periphery).
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- **M_3 receptors *(glandular/smooth muscle)* :** (excitatory effects)
- stimulation of glandular secretions (salivary, bronchial, sweat, etc.) and contraction of visceral smooth muscle. M_3 receptors also mediate relaxation of vascular smooth muscle, which results from the release of nitric oxide from neighboring endothelial cells
- **M_4** and **M_5** receptors are largely confined to the CNS, and their functional role is not well understood.

mAChRs	M_1	M_2	M_3	M_4	M_5
Main locations	Autonomic ganglia. Gastric enterochromaffin-like cells. Cerebral cortex.	*Heart:* atria CNS Presynaptic	*Exocrine glands:* salivary, lacrimal, sweat, gastric etc. *Smooth muscle:* gastrointestinal tract, eye (circular & ciliary), airways, bladder *Blood vessels:* endothelium *CNS*	CNS	CNS
Functional response	CNS excitation Gastric acid secretion	*Cardiac inhibition:* -ve chronotropic effect -ve inotropic effect -ve dromotropic effect (↓Conduction velocity) Neural inhibition Autoinhibition of ACh release	Salivation, lacrimation, sweating, bronchial and GI secretion GI , Bronchial & urinary s.m. contraction : (defecation, vomiting, urination, bronchoconstriction) Ocular (miosis, near vision accommodation) Vasodilatation	Enhanced locomotion	Not known

Drugs produce effects similar to that of ACh called ***(Cholinomimetic Drugs)*** or ***(Parasympathomimetic)*** or ***(Cholinergic Agonist)***

Drugs produce effects apposite to that of ACh called ***(Anticholinergic Drugs)*** or ***(Parasympatholytic)*** or ***(Cholinergic Antagonist)***

Cholinergic drugs agonists(cholinomimetics)

.**Direct acting** cholinomimetic-1

.A- choline esters

.B- alkaloids

Indirect acting cholinomimetic(C E-2 .inhibiters)

A-reversible anticholinesterases

.B- irreversible anticholinesterases

- **Choline Esters :**
- Include: ***Acetylcholine*** and it's analogues ***Methacholine***, ***Carbachol***, and ***Bethanechol***
- ***Acetylcholine*** can't be used as systemic drug (*but used as topical drug* ***to induce miosis during eye surgery***) because:
- It has very short $t_{1/2}$ (rapidly hydrolyzed)
- It has very wide effects if used systemically

Choline Ester	Susceptibility to Cholinesterase	Muscarinic Action	Nicotinic Action
Acetylcholine	++++	+++	+++
Methacholine	+	++++	None
Carbachol	Negligible	++	+++
Bethanechol	Negligible	++	None

- ***Bethanechol:*** selective (**muscarinic**) and **not hydrolyzed** by cholinesterases. It acts **mainly on M_3** receptors and has little effect on the heart.
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- **Clinical uses of bethanechol :**
- Postoperative stimulation of GIT and bladder (postoperative abdominal distention, and urinary retention)
- Bladder and GIT hypotonia
- **Side Effects:**
- **Sweating, salivation, lacrimation, bronchial secretion, flashing**
- **Contraindications:** Asthma, sever cardiac disease
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- ***Methacholine:*** is **muscarinic selective** but **hydrolyzed** by cholinesterases, so has short duration of action.
- **Clinical uses**
- Slow the heart rate in some types of arrhythmia like **paroxysmal atrial tachycardia.**
- Diagnosis of asthma (**methacholine challenge chest**)
- ***Carbachol:*** is **poorly hydrolyzed** by cholinesterases but it is **non-selective** and can cause release of adrenaline from adrenal medulla
- Carbachol is used topically as miotic agent to decrease IOP but pilocarpine is preferred.
  - ***All choline esters are quaternary amines, have +ve charge and can't cross the BBB to enter the CNS***

THANK YOU!