PHARMACOLOGY

Number: 9

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Subject: Cholinergic Receptors

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بسم الله الرحمن الرحيم

In this lecture, we are going to talk about drugs that cause stimulation of cholinergic receptors:

We have two types of cholinoceptors stimuli:

1. Drugs that act directly on cholinoceptors (direct stimulation of receptors), like acetylcholine.

2. Drugs that don't directly act on the receptors, they inhibit the enzyme acetylcholine esterase, which leads to accumulation of acetylcholine in the receptor site, and gives a cholinergic response.

- **Drugs that directly act on cholinoceptors are of two types :**

1. Natural alkaloids, e.g. muscurine and nicotine (in tobacco leaves).

2. Synthetic drugs called choline esters.

- **Drugs that act by inhibiting the enzyme acetylcholine esterase are of two types :**

  1. Reversible inhibitors - inhibit the activity of the enzyme for a short period of time (2 minutes to few hours) then the enzyme then resumes its activity.

  2. Irreversible inhibitors – bind strongly (covalently) to the active site of the enzyme inhibiting it permanently.

- We already know that cholinergic receptors are either muscarinic or nicotinic (in the autonomic ganglia).

- Acetylcholine , as a choline esters' prototype , has a brief (short lived) effect because it is fast hydrolyzed into choline and acetate by the enzyme acetylcholine esterase .thus , certain changes are produced to produce new compounds :

  - The first change: replacement of acetate group with another carbonyl group, yielding a compound called Carbachol, which has a different action from acetylcholine.

  - Second change: the addition of methyl group at the beta carbon atom producing a compound called Methacholine (change in the effect).

- Now, by mixing the two changes, this yields a compound called Bethanechol.

- This will affect the enzyme acetylcholine esterase:

Looking at the figure below, you notice that:

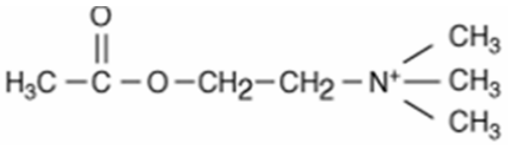
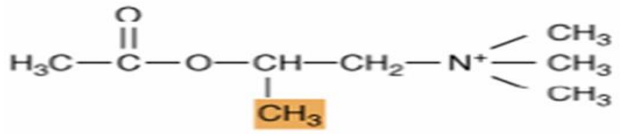
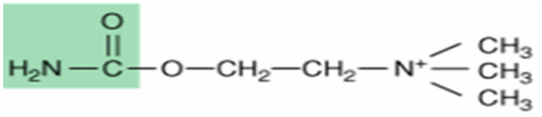
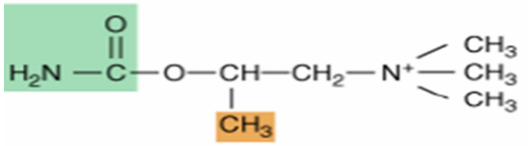
1. Acetylcholine is strongly affected by the enzyme AE.

2. Methacholine (which only has an additional methyl group) is slightly affected by the enzyme AE and thus prolonging its action and increasing its muscarinic effect. Methacholine shouldn't actually be used for systemic effect because it has a long effect which may cause the heart to stop, it's fatal .However, it has no effect on nicotinic receptors.

3. Carbachol is not affected by acetylcholine esterase, and has a lower effect on muscarinic receptors than that of acetylcholine and the same effect on nicotinic receptors.

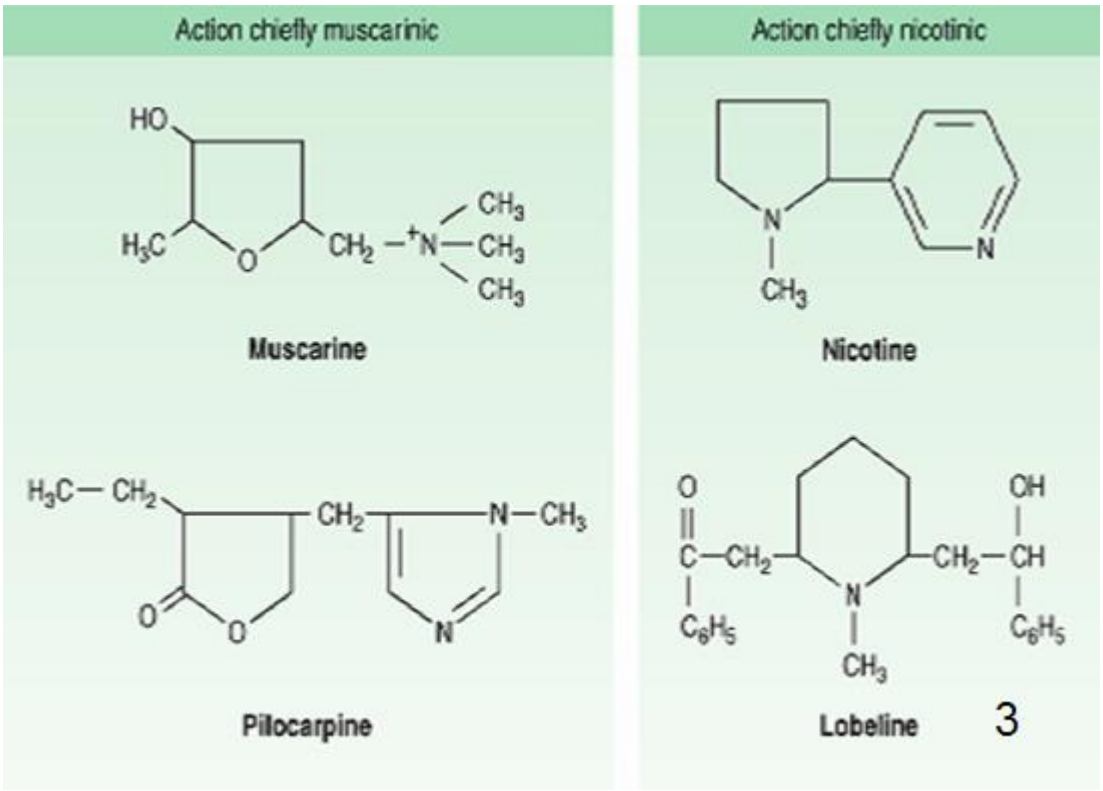
4. Bethanechol (which combines the two changes) is not affected by acetylcholine esterase so it has a longer duration of action, has a moderate muscarinic effect and no nicotinic effect.

So changing the structure will change the action of the drug.

Choline Ester	ACE	Muscarinic	Nicotinic	
Acetylcholine	++++	+++	+++	
Methacholine	+	++++	None	
Carbachol	Negligible	++	+++	
Bethanechol	Negligible	++	None	

- The drug that can be used for systemic effects is Bethanechol.

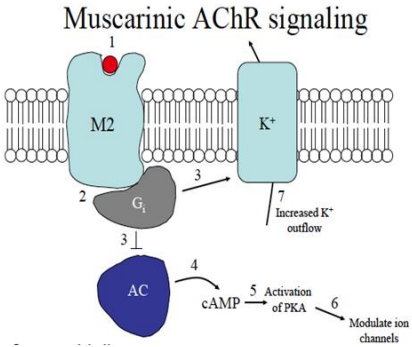
- The structures of cholinergic alkaloids :



- Liverolin and nicotine are present in plants.

    - Lobeline and nicotine are special alkaloids present in plants, nicotine is present in tobacco leaves & lobeline is present in lobelia. Both stimulate nicotinic receptors.

Mechanism of action of muscarinic receptors in the heart :



The heart has M2 receptors, which are bound to Gi proteins, Ach binds to an M2 receptor activating it and causing dissociation of the α-subunit, which then binds to and activates a potassium channel opening it. Once opened, the potassium inside goes out, the inside becomes more negative than it already is inducing **Hyperpolarization**, which means that a bigger stimulus is needed in order to elicit action potential.

- Hyperpolarization makes it harder for the pacemaker (which the heart follows) to generate

action potential, so it slows the heart rate.

- M2 receptors also reduce the phosphorylation of L-type calcium channels (calcium is needed for contraction) so they decrease the contraction.

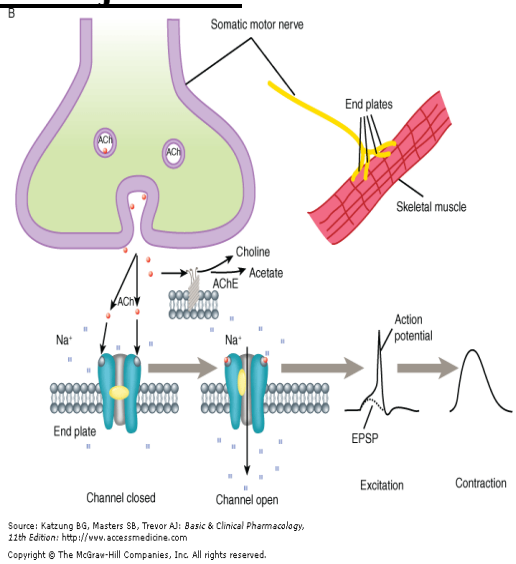
- M2 receptors also inhibit the enzyme adenylyl cyclase (through inhibitory alpha subunit) reducing the amount of cAMP, which is necessary for the synthesis of catecholamines (Epinephrin , NE, dopamine) which bind to B1 receptors, and this is reflected through the decrease in the contractility of the heart.

- So, decrease in the amount of calcium ions + decrease in the formation of cAMP + hyperpolarization → cause decrease in the heart rate and the force of contraction.

Nicotinic transmission at the skeletal neuromuscular junction

Acetylcholine binds to nicotinic receptors which guide sodium channels, causing the channel to open, and the sodium that is kept outside to get inside the cell through the channels, causing depolarization.

- Depolarization causes excitatory postsynaptic potential, which generates action potential and triggers contraction. Later, the enzyme Acetylcholine esterase causes hydrolysis of Ach into acetate and choline inducing muscle relaxation.



➢ Effects of direct - acting cholinoceptor stimulants (revision of what was discussed last lecture) :

In the eye:

1. Sphincter muscle of the iris → responds by contraction (miosis).
2. Ciliary muscle → contraction for nearer vision.

- These two effects in the eye (miosis and contraction of ciliary muscle) result in facilitation of the drainage of aqueous humor (the liquid inside the eye) through the canal of shlemm.

The filtration angle (an angle between the iris and cornea through which the aqueous humor readily permeates) can be narrow and there is a meshwork of pores through which the liquid is drained. However, in some people, these pores might be closed or the angle is so narrow that there is no adequate drainage of aqueous humor, this results in building up pressure in the eye, which causes something called **Glucoma**, which, if not fixed, can cause permanent damage to the retina and the optic nerve (causes blindness).

- Miosis means that the pupil is pulled to the inside; pulling out the muscles facilitating drainage (the angle becomes wider).
  Both contraction of ciliary muscles and miosis increase the drainage of aqueous humor.

- So, these drugs (which directly act) can be used to treat Glucoma. We'll come to that later on.

- In the heart (remember M2R):

1. SA node → decrease heart rate (negative chronotropic effect).

2. Atria → decrease in the strength of contractility (negative inotropic effect) .decrease in refractory period (the time through which no impulse is transmitted from the atria to ventricles and it's so important, because blood passes to the atria, then they contract completely emptying their content of blood to ventricles that are relaxed, if both atria and ventricles were contracted, there will be no chance for the blood to fill ventricles).

3. AV node (it's where the impulse goes down from the atria through the ventricles)→ decrease in the conductive velocity + increase in refractory period.

4. Ventricles → small decrease in contractile strength.

5. Blood vessels → not innervated by cholenirgic nerves, always sympathetic, but still have muscarinic receptors. Once activated, they produce **Nitric Oxide** that is a potent vasodilator.

6. Lungs:
   Bronchial muscle → contraction (bronchoconstriction).
   Bronchial glands → stimulation (secrete mucus).

- So if you give a drug of these, it may cause acute attack of bronchial asthma.

7. Gastrointestinal tract:
   Motility increase, sphincters relax, secretion is stimulated.

- So, these drugs may cause diarrhea. If someone suffers from diarrhea, he may take **atropine** which is a blocker of muscarinic receptors.

8. Urinary bladder:
Detrosur muscle contracted, trigone and sphincter are relaxed → voiding of urine (uniration).
Give these drugs to someone and they might urinate.

9. Glands: the secretion of all glands will be increased.

Organ system effect:

- **Cardiovascular system : (M2 receptors)**

- When we give acetylcholine, its effect lasts in a few seconds. Thus, we give it by infusion (continuously giving the drug), and thus a **small dose** of ach will cause vasodilatation due to the formation of nitric oxide leading to reduction in blood pressure → this triggers baroreceptors → increase in heart rate .

- If we increase the dose , this may lead to
  - Bradycardia.
  - Decrease in the AV conductive velocity which may cause hypotension.
  - Decrease in the contractility of atria and ventricles.

- The direct slowing of sinoatrial rate and ventricular conduction is often opposed by the reflex sympathetic discharge elicited by the decrease in blood pressure. Any decrease in the cardiac output will stimulate the sympathetic nervous system.

- We already mentioned that IV injections of muscarinic agonists produce Vasodilatation as these agonists produce nitric oxides from the endothelial cells, NO works by activating guanylyl cyclase producing cGMP, resulting in relaxation.

- Pilocarpine (Natural alkaloid) produces a brief initial hypotensive response, followed by Hypertensive (longer-lasting hypertension) response, due to the **Sympathetic ganglionic activation** caused by the activation of M1 receptors in the ganglia which elicit slow excitatory (depolarizing) post synaptic potentials. [The ganglia has nicotinic receptors, these produce fast excitatory post synaptic potential]

  - These effects, like hypotensive and hypertensive effects, can be blocked by atropine (an antimuscarinic drug).

- **Respiratory system :**
  - Bronchoconstriction due to contraction of smooth muscles of bronchial tree.
  - Increased bronchial secretion.

- **Gastrointestinal tract :**
  - Secretions are increased (some secretions are more stimulated than others)→
    1. Salivary and gastric glands are strongly stimulated.
    2. Panceriatic and small intestinal glands are less stimulated.
  - Increased motor activity of the gut.
  - Peristaltic activity is increased and most sphincters are relaxed.

- The M3 receptor is required for **direct** activation of smooth muscle contraction, whereas the M2 receptor reduces cAMP formation and prevents relaxation caused by sympathomimetic drugs.

- **Genitourinary tract :**

  - Muscarinic agonists stimulate the **detrusor** muscle and relax the **trigone** and **sphincter** muscles of the bladder, thus promoting voiding.
  - M3 → direct activation of detrusor muscle and relaxation of trigone and sphincter muscles.
  - M2 → indirect through the reduction of cAMP. (Same as in GIT).

- **Miscellaneous Secretory Glands**

  Muscarinic agonists stimulate secretion of sweat, lacrimal, and nasopharyngeal glands.

- **Central Nervous System:**

  The CNS contains both muscarinic and nicotinic receptors, the brain is richer in muscarinic sites and the spinal cord contains more nicotinic sites.

  - Mental disorders, like Alzheimer's disease, are often caused due to degeneration of muscarinic receptors in the brain.

  - Pilocarpine, when injected to animals, caused **Chronic epilepsy** especially in rats.

  - Pilocarpine is used to examine different treatments (M1 effect).

  - Oxotremorine (a muscarinic agent that can pass through the bbb), when injected, produces symptoms similar to those of Parkinson's disease. It produces tremor (ارتجاف), muscular rigidity, hypothermia and antinociception (increased pain tolerance). (M2 effect).
    It's also used to study the effect of new drugs antagonism.
  - Presynaptic nicotinic receptors regulate the release of many neurotransmitters in the brain.

- High concentrations of nicotine induce tremor, nausea and vomiting.
- If you are non-smoker and tried a cigarette, you might vomit and feel nauseous, suffer from emesis and maybe tremor. Even higher doses of nicotine produce convulsions and fatal coma. Nicotine is very poisonous; one drop of pure nicotine is fatal.

- In the CVS, the effects of nicotine are chiefly sympathomimetic, that's why nicotine causes hypertension, tachycardia which may alternate with a bradycardia mediated by vagal discharge.

- **GIT and urinary tracts:**

  • The effects are parasympathomimetic: nausea, vomiting, diarrhea, and voiding of urine are commonly observed. Prolonged exposure may result in depolarizing blockade of the ganglia.

  Nictonine in small amount: activates the autonomic ganglia.

  Nicotine in prolonged exposure: blocks autonomic ganglia, as repolarization doesn't occur, the membrane remains in the depolarized state, making it unresponsive to stimulation.

- **Neuromuscular Junction:**

  Nicotinic applied directly to the muscles can produce something called fasciculation (unorganized muscle contraction) and a higher dose causes full muscle contraction.

  Nicotine also causes rapid development of depolarization blockade; transmission blockade persists even when the membrane has repolarized. This latter phase of block is manifested as flaccid paralysis of skeletal muscle (Relaxation of the whole muscle).

Sorry for mistakes.