



Artery Academy

Done by Lama

sensitivity ↓, duration ↑

تأثير الدواء مع زيادة الجرعة هو ان لا يحد من التأثير

يستغلوا كل نوعين من receptor
↓
Muscarinic Nicotinic

Cholinomimetics

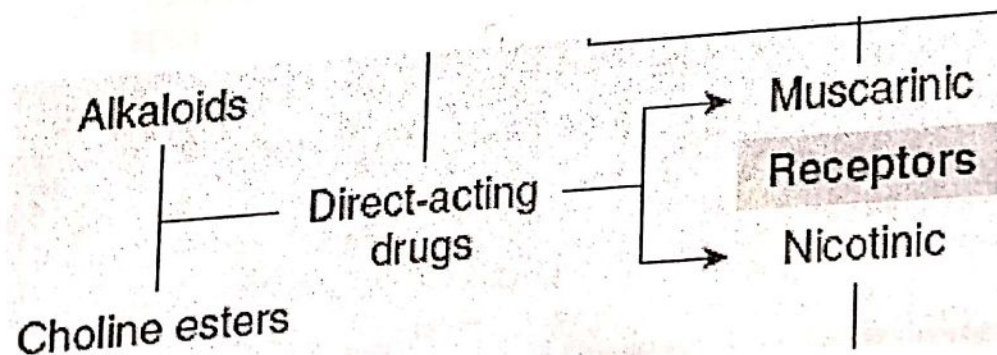
- ▶ Drugs with acetylcholine-like effects (**cholinomimetics**) consist of **2 major subgroups** on the basis of their mode of action:
 - **Act directly** at the **acetylcholine receptor** or
 - **Act indirectly** through **inhibition of cholinesterase**.
- Some **quaternary** cholinesterase inhibitors also have a modest direct action as well, eg, neostigmine, which **activates neuromuscular nicotinic cholinergic receptors** **directly** in addition to **blocking cholinesterase**.

activates neuromuscular nicotinic
addition to blocking cholinesterase.

1) Direct-acting cholinomimetic agents

- The direct-acting cholinomimetic drugs can be divided on the basis of chemical structure into:

- A. Esters of choline (choline esters)
- B. Alkaloids (such as muscarine and nicotine).

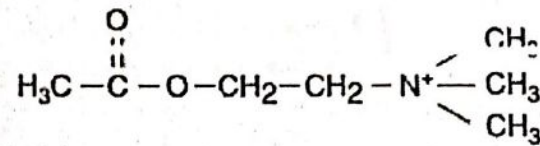


Handwritten notes at the top: *Handwritten notes: Sensitivity of acetylcholinesterase duration of action of choline is*

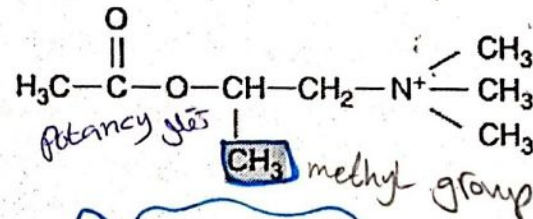
A) Choline esters

Structure and pharmacokinetics:

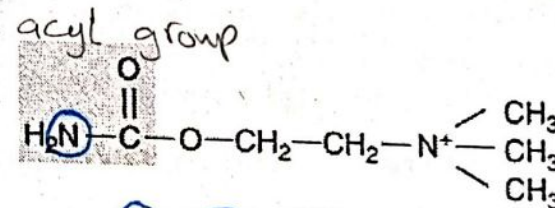
- Can be produced by substituting the acetyl group of acetylcholine with a carbamoyl group or by substituting a methyl group of the β -carbon.
- These substitution produce compounds that are **more resistant to acetylcholinesterase** and thus have longer duration of action (carbamic acid esters > Methacholine > Acetylcholine).



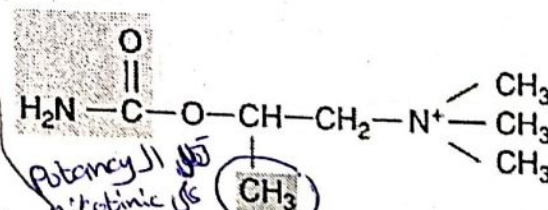
Acetylcholine



① **Methacholine**
(acetyl- β -methylcholine) *more resistance*



② **Carbachol**
(carbamoylcholine)



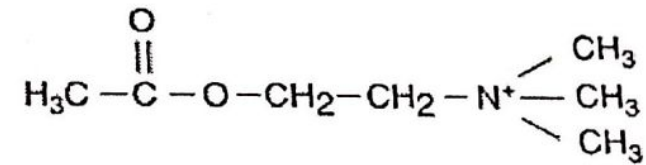
③ **Bethanechol** *both of groups*
(carbamoyl- β -methylcholine)

Handwritten notes: *hydrolyse in GIT $\Rightarrow$ less active in oral administration*

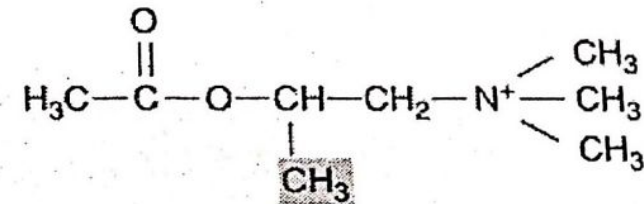
A) Choline este

selectivity jaw

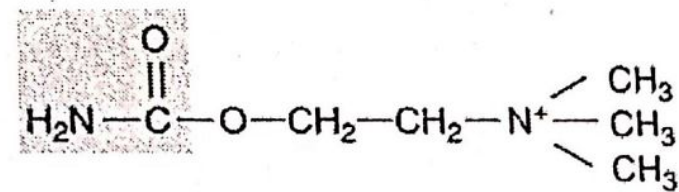
- The β -methyl group (methacholine, bethanechol) reduces the potency of these drugs at nicotinic receptors.
- Because they are hydrophilic (quaternary amines), these compounds are poorly absorbed and poorly distributed into the central nervous system.
- All are hydrolyzed in the gastrointestinal tract (and less active by the oral route).



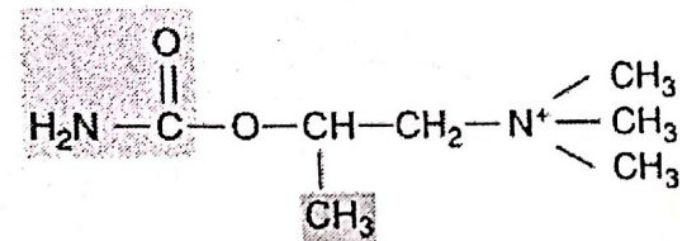
Acetylcholine



Methacholine
(acetyl- β -methylcholine)



Carbachol
(carbamoylcholine)



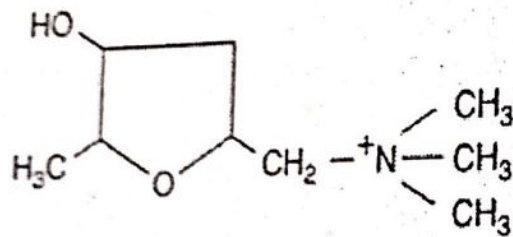
Bethanechol
(carbamoyl- β -methylcholine)

Properties of choline esters

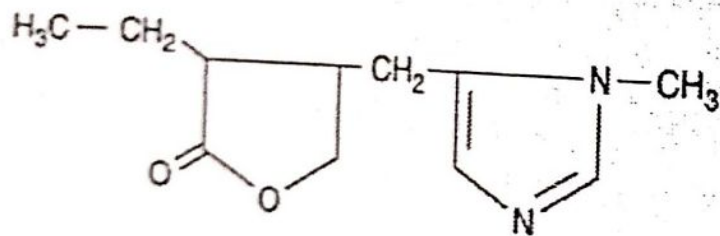
Choline Ester	Susceptibility to Cholinesterase	Muscarinic Action	Nicotinic Action
Acetylcholine chloride	+++++	+++	+++
Methacholine chloride	+	+++++ <i>افضل واحد</i>	None
Carbachol chloride	Negligible	++	+++
Bethanechol chloride	Negligible <i>يحدث تأثير لكن بشكل غير ملحوظ</i>	++	None

B) Alkaloids

Action chiefly muscarinic

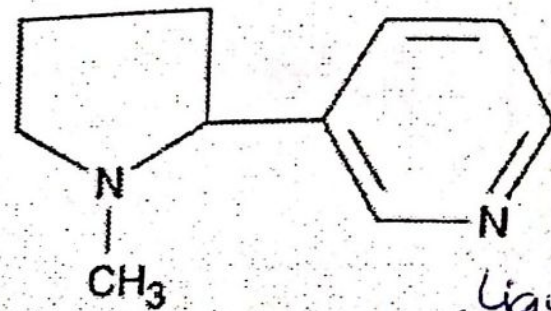


Muscarine



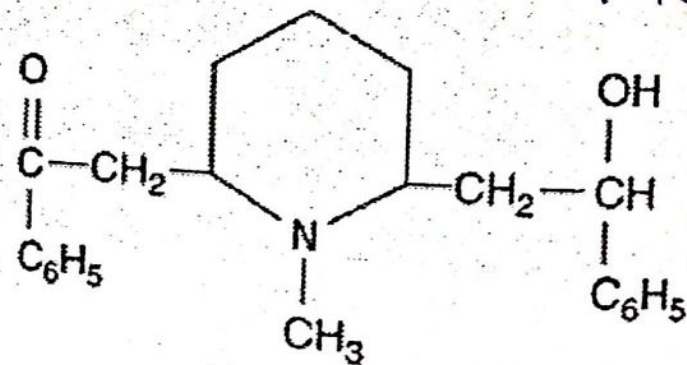
Pilocarpine

Action chiefly nicotinic



Nicotine

Liquid compound
Lipid soluble



Lobeline

Source: Katzung BG, Masters SB, Trevor AJ: Basic & Clinical Pharmacology, 12th edition:
www.accessmedicine.com

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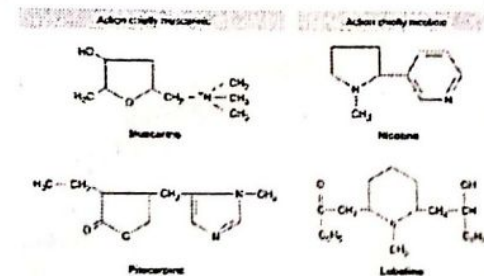
B) Alkaloids

Poorly absorb
Less toxicity

Structure and pharmacokinetics:

- ▶ The tertiary natural cholinomimetic alkaloids (pilocarpine, nicotine, lobeline) are well absorbed from most sites of administration. Nicotine, a liquid, is sufficiently lipid-soluble to be absorbed across the skin.
- ▶ Muscarine, a quaternary amine, is less completely absorbed from the gastrointestinal tract than the tertiary amines but is nevertheless toxic when ingested—eg, in certain mushrooms—and it even enters the brain.
- ▶ Lobeline is a plant derivative similar to nicotine.
- ▶ These amines are excreted chiefly by the kidneys. Acidification of the urine accelerates clearance of the tertiary amines.

بالعقل



Organ system effects

Inotropic : $\uparrow$ Contractility القلب

Contractility $\uparrow$: positive inotropic agent

Contractility $\downarrow$: negative inotropic agent

Chronotropic :

heart rate $\uparrow$: positive chronotropic agent

heart rate $\downarrow$: negative chronotropic agent

heart rate $\downarrow$: negative chronotropic agent

Dromotropy : velocity of signal transduction

Organ	Response
Eye	
Sphincter muscle of iris	Contraction (miosis) <i>dilation</i>
Ciliary muscle	Contraction for near vision
Heart	
Sinoatrial node	Decrease in rate (negative chronotropy)
Atria	Decrease in contractile strength (negative inotropy). Decrease in refractory period
Atrioventricular node	Decrease in conduction velocity (negative dromotropy). Increase in refractory period
Ventricles	Small decrease in contractile strength
Blood vessels	
Arteries, veins	Dilation (via EDRF). Constriction (high-dose direct effect)
Lung	
Bronchial muscle	Contraction (bronchoconstriction)
Bronchial glands	Stimulation $\rightarrow$ excretion $\uparrow$
Gastrointestinal tract	
Motility	Increase
Sphincters	Relaxation
Secretion	Stimulation
Urinary bladder	
Detrusor	Contraction
Trigone and sphincter	Relaxation
Glands	
Sweat, salivary, lacrimal, nasopharyngeal	Secretion

EDRF, endothelium-derived relaxing factor.

blood vessel
exceptions

nitric oxide → relaxin factor → endothelial cell
dilation ← (EDRF)

Some notes...

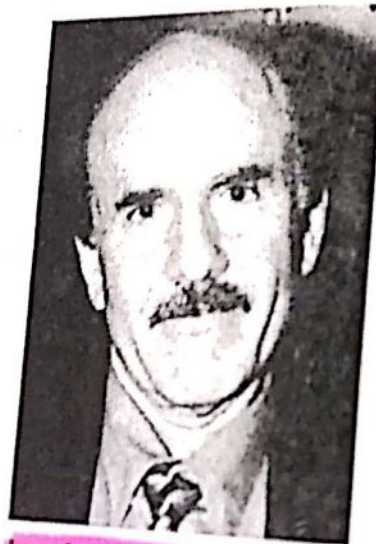
- 1) Vasodilation (and decreased blood pressure) is not a parasympathomimetic response (ie, it is not evoked by parasympathetic nerve discharge, even though directly acting cholinomimetics cause vasodilation).

This vasodilation results from the release of endothelium-derived relaxing factor (EDRF; nitric oxide and possibly other substances) in the vessels, mediated by uninnervated muscarinic receptors on the endothelial cells.

The Nobel Prize in Physiology or Medicine 1998



Robert F. Furchgott
Prize share: 1/3



Louis J. Ignarro
Prize share: 1/3



Ferid Murad
Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1998 was awarded jointly to Robert F. Furchgott, Louis J. Ignarro and Ferid Murad "for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system".

Photos: Copyright © The Nobel Foundation

Some notes...

2) Note also that decreased blood pressure evokes the baroreceptor reflex, resulting in strong compensatory sympathetic discharge to the heart. As a result, injections of small to moderate amounts of direct-acting muscarinic cholinomimetics often cause *tachycardia*, whereas parasympathetic (vagal) nerve discharge to the heart causes *bradycardia*.

↳ low heart rate

3) Another effect seen with cholinomimetic drugs but not with parasympathetic nerve stimulation is thermoregulatory sweating; this is a *sympathetic cholinergic* effect.

- The tissue and organ level effects of nicotinic ganglionic stimulation depend on the autonomic innervation of the organ involved:
 - The blood vessels are dominated by sympathetic innervation; therefore, nicotinic receptor activation results in vasoconstriction mediated by sympathetic postganglionic nerve discharge.
 - The gut is dominated by parasympathetic control; nicotinic drugs increase motility and secretion because of increased parasympathetic postganglionic neuron discharge.
 - Nicotinic neuromuscular end plate activation by direct-acting drugs results in fasciculations and spasm of the muscles involved. Prolonged activation results in paralysis, which is an important hazard of exposure to nicotine-containing and organophosphate insecticides.

rest and digest