

# Cholinergic system

## Cholinergic neurons :

I. Several neurons in CNS

II. Autonomic nervous system

- **preganglionic** efferent fibers

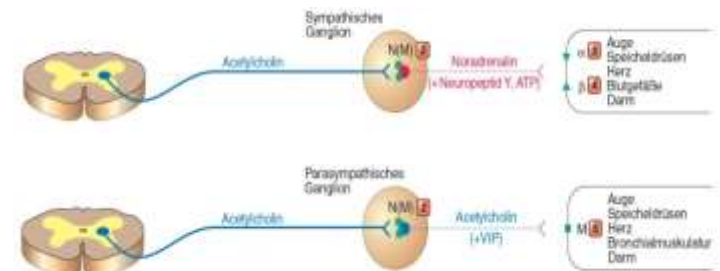
- **postganglionic parasympathetic** neurons

- postganglionic sympathetic neurons innervating the sweat glands and vascular beds in the skeletal muscle

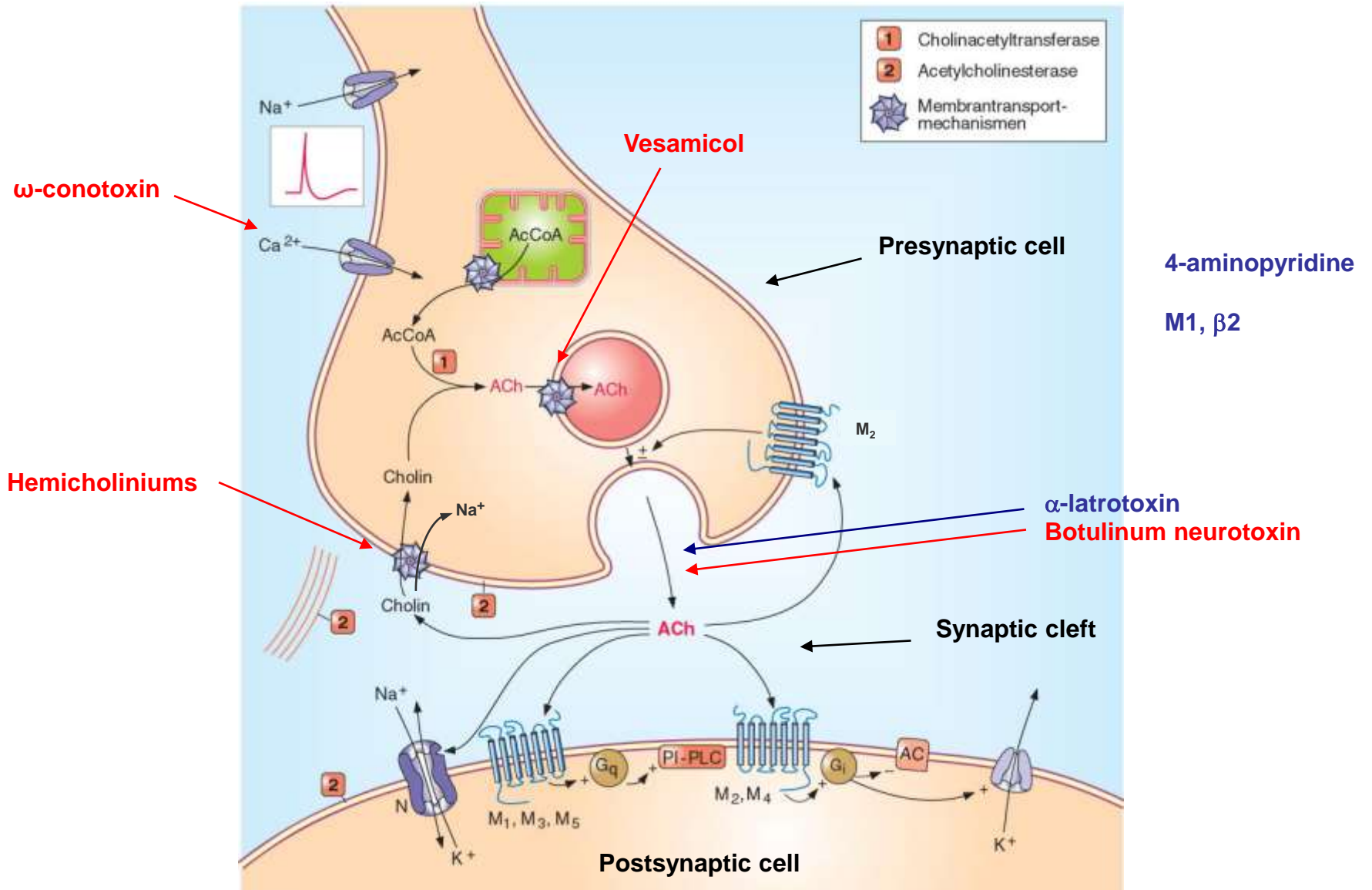
- many neurons in the enteric nervous system (ENS)

III. Somatic nervous system

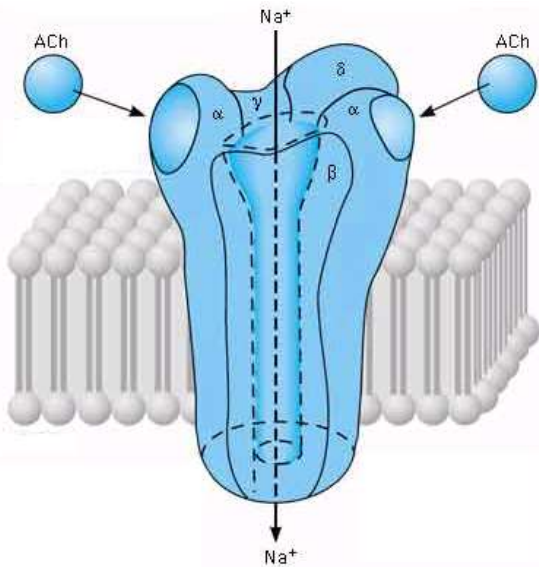
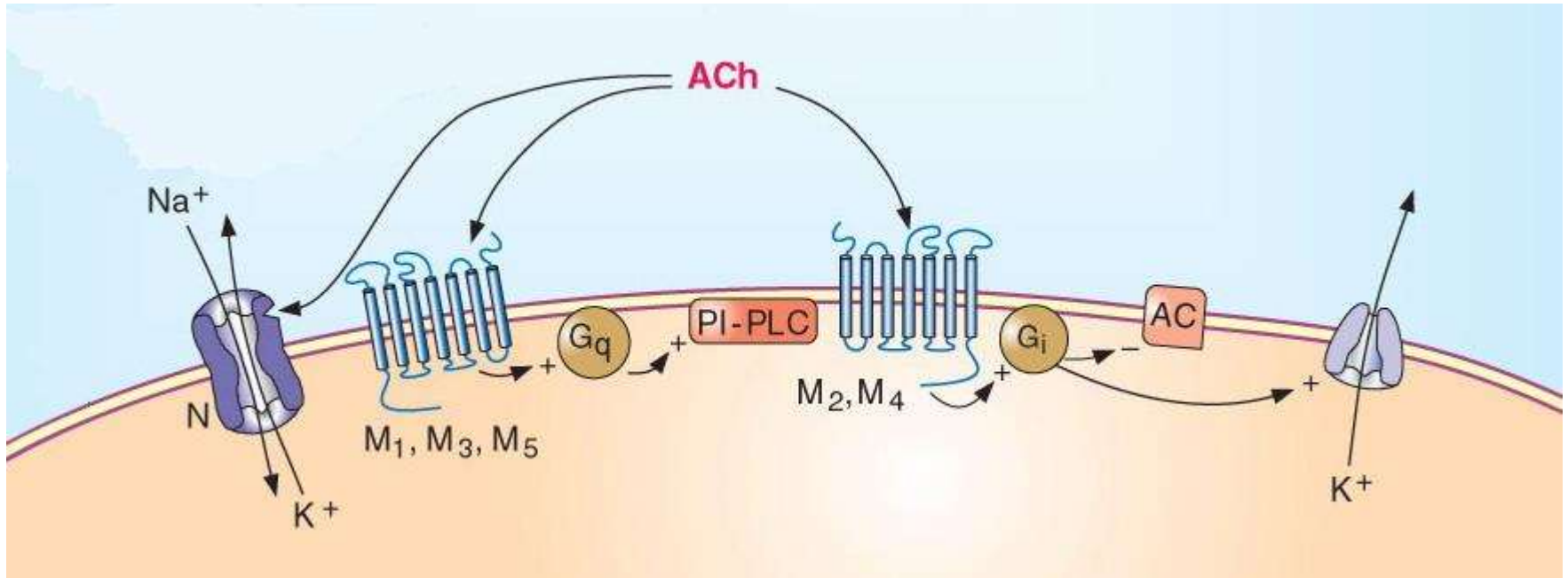
- somatic motor fibres to skeletal muscles



# Cholinergic transmission



# Cholinergic receptors (Cholinoceptors)



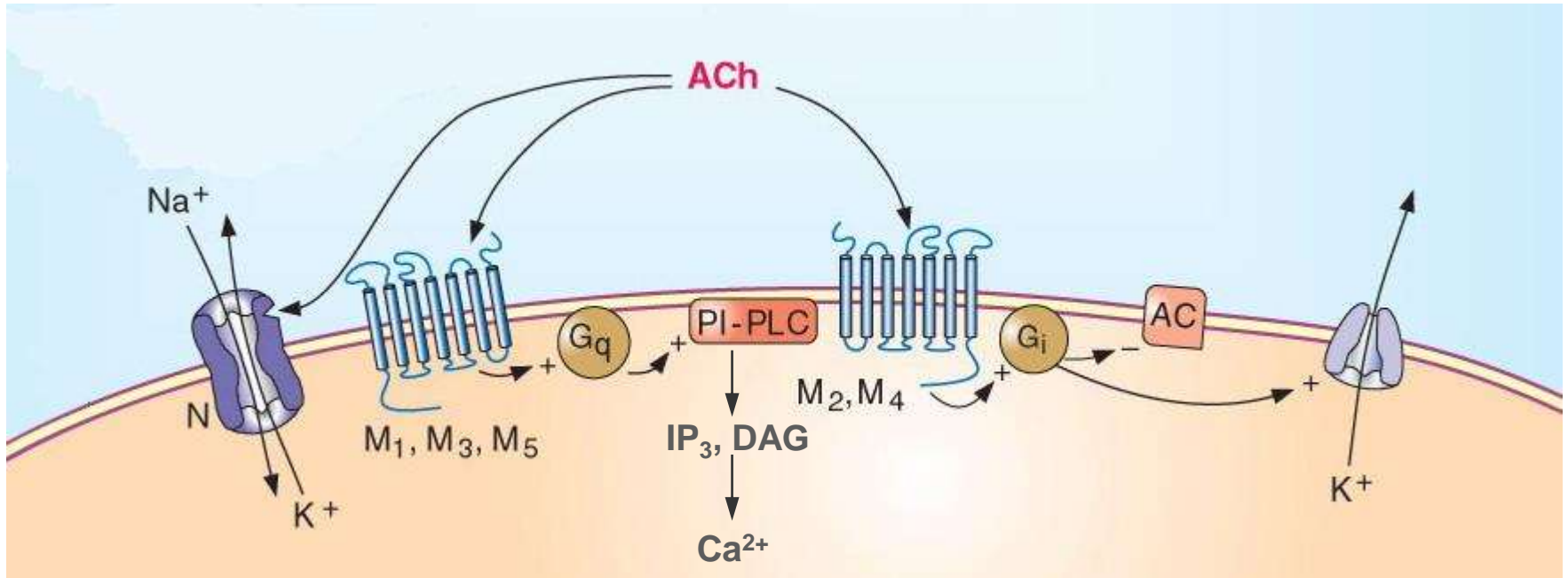
## I. Nicotinic receptors

Ligand-gated ion-channels

agonists: ACh, nicotine

- Muscle type ( $N_M$ )  $(\alpha_1)_2\beta_1\delta\epsilon$

- Neuronal type ( $N_N$ )  $(\alpha_4)_3(\beta_2)_2$ ;  $(\alpha_3)_3(\beta_2)_2$  ...



## II. Muscarinic receptors

G-protein-coupled (metabotropic) receptors (GPCRs)

- M<sub>1</sub> – neurons (CNS, ganglia)
- M<sub>2</sub> – heart, presynaptic
- M<sub>3</sub> – glands, smooth muscle, endothelium
- M<sub>4</sub> – CNS, uterus
- M<sub>5</sub> – CNS

# Organ system effects

## Effects

- Eye :                    **miosis** (M. sphincter pupillae)  
                              accommodation (M. ciliaris)
- Smooth muscle : **contraction**  
                              bronchoconstriction  
                              GI motility ↑  
                              gall bladder  
                              urinary bladder (detrusor)  
                              **relaxed sphincters**
- Glands :                **increased secretions**  
                              sweat-, salivary- and lacrimal  
                              GI and bronchial secretions
- Blood vessels :      direct – contraction  
                              indirect – **vasodilation** ( release of NO )

## Indication

- glaucoma



- disorders with atony  
(postoperative ileus,  
neurogenic bladder)

- xerostomia, Sjögren



## Effects

- Heart :
  - Heart Rate ↓(SA-node)
  - Contractile strength ↓ (Atria)
  - Conduction velocity ↓ (AV-node)
  - (ventricles: minimal effect)
  
- CNS : stimulation of cholinergic transmission
  
- Neuromuscular junction : N<sub>M</sub>-receptors

## Indications

- Alzheimer's disease
- Myasthenia gravis
  
- Atropine intoxication

# I. Cholinoceptor stimulants (Cholinomimetics)

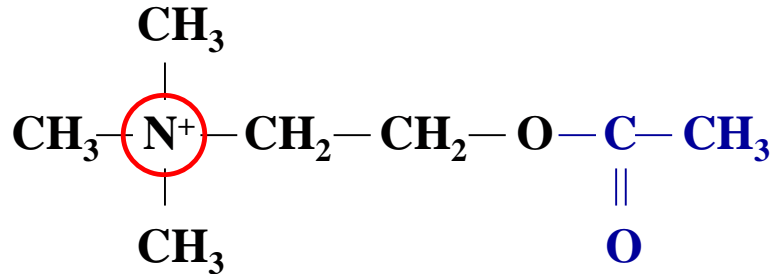
- Direct-acting cholinoceptor stimulants
  - Choline esters
  - Alkaloids
- Indirect-acting cholinoceptor stimulants (Cholinesterase-Inhibitors)
  - quaternary alcohols
  - esters
    - Carbamic acid esters
    - Phosphoric acid esters (Organophosphates, Alkylphosphates)



# Choline esters 1.

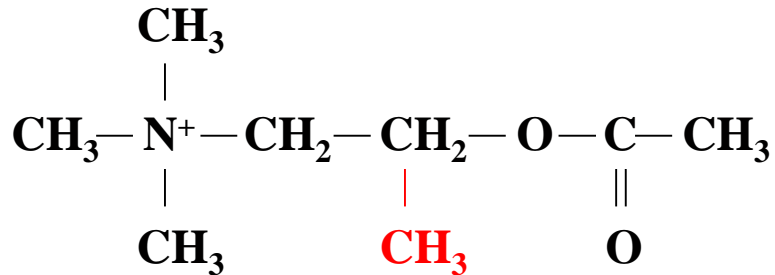
## Acetic acid esters

Acetylcholine



Susceptibility to cholinesterase	Muscarinic action	Nicotinic action
++++	+++	+++

Metacholine

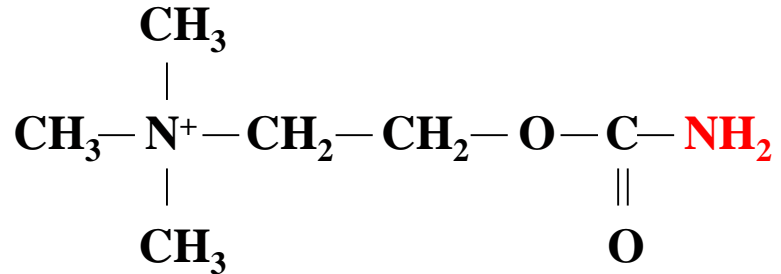


Susceptibility to cholinesterase	Muscarinic action	Nicotinic action
+	++++	∅

# Choline esters 2.

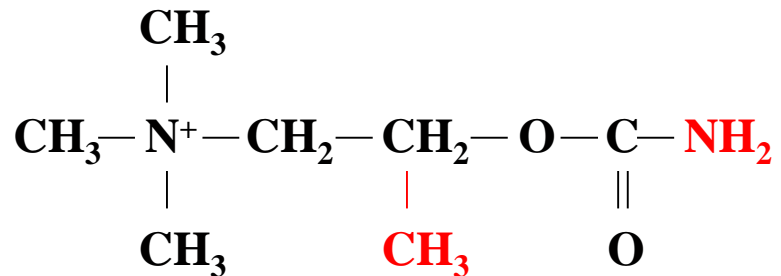
## Carbamic acid esters

### Carbachol



Susceptibility to cholinesterase	Muscarinic action	Nicotinic action
∅	++	+++

### Betanechol

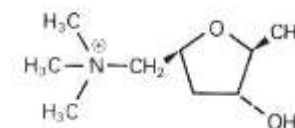


Susceptibility to cholinesterase	Muscarinic action	Nicotinic action
∅	++	∅

# Alkaloids

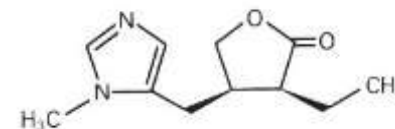
## Muscarine

- in certain mushrooms (*Amanita muscaria* – fly agaric)
- selective for muscarinic receptors
- Ø therapeutic relevance (toxic, experiments)



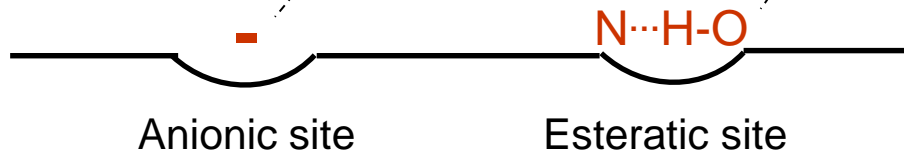
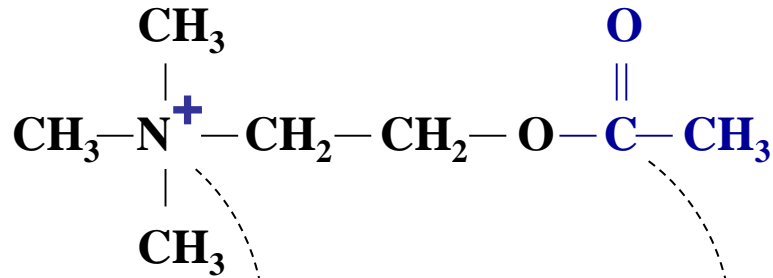
## Pilocarpine

- from tropical shrubs in South-America (*Pilocarpus*)
- strong muscarinic effect (slight nicotinic)
- secretions ↑ ↑
- Ind.: glaucoma (1-2 %), xerostomia, Sjögren



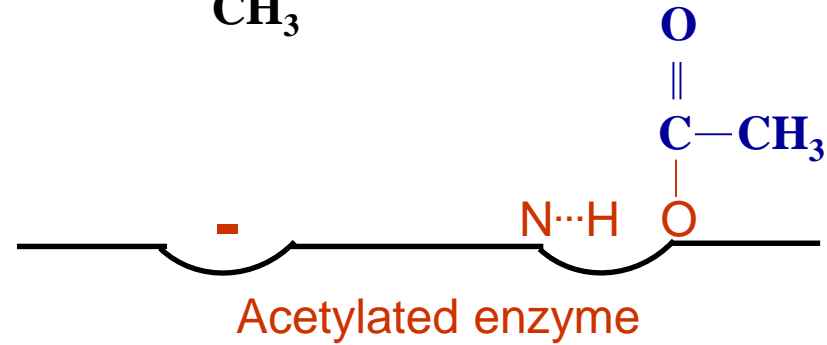
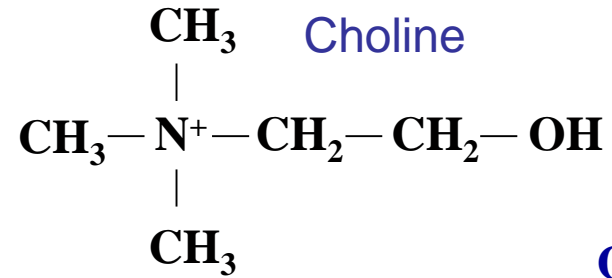
# Cholinesterase-Inhibitors

## 1. Acetylcholine

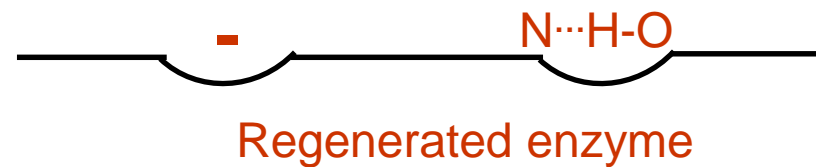
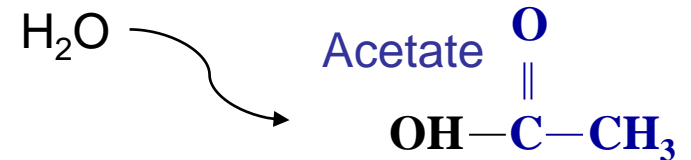


Acetylcholinesterase

## 2.



## 3.



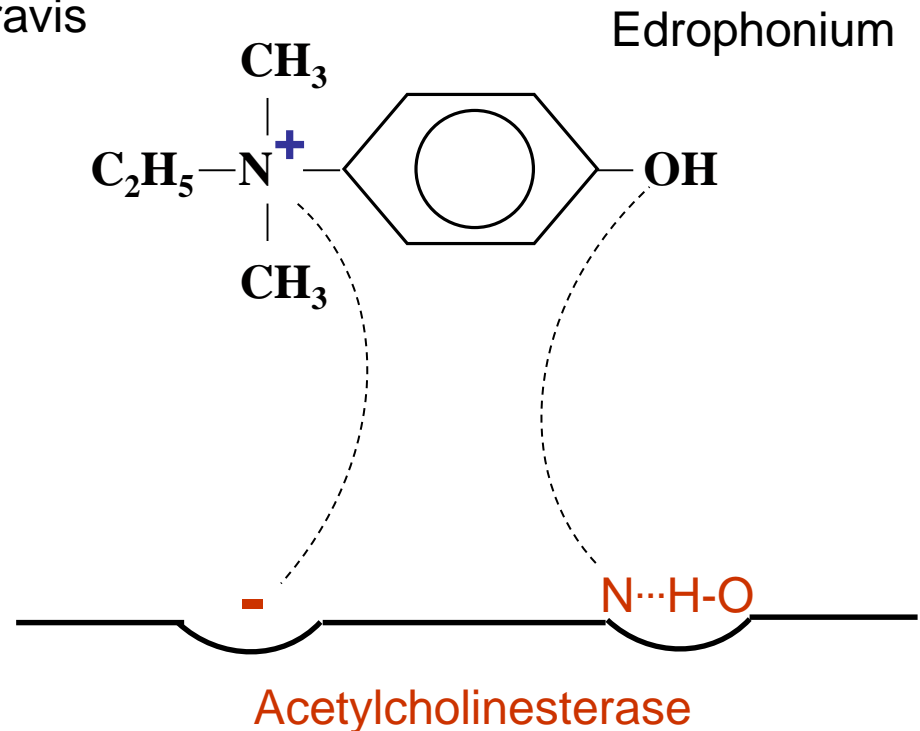
# Alcohols

## Edrophonium

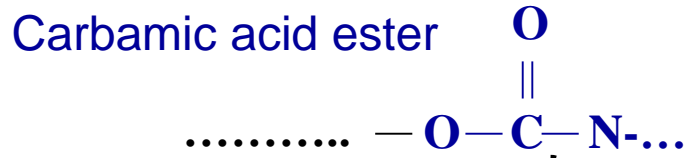
- quaternary ammonium group
- short effect (5-15 min)  
fast dissociation
- Ind.: diagnosis of Myasthenia gravis

## Donepezil

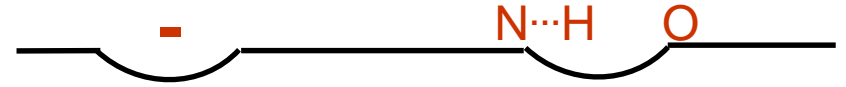
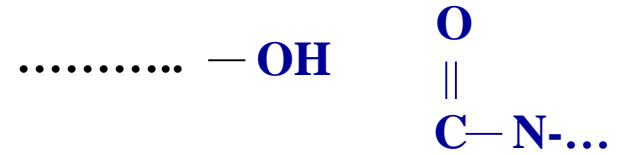
- tertiary compound
- Ind.: Alzheimer's disease



# Carbamic acid esters



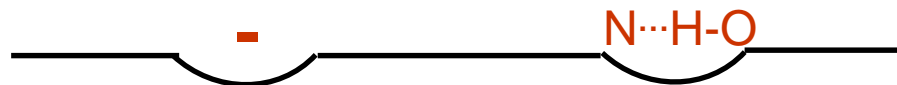
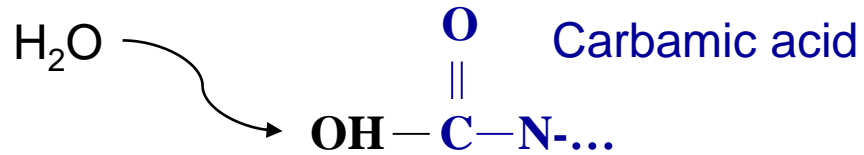
Acetylcholinesterase



Carbamoylated enzyme



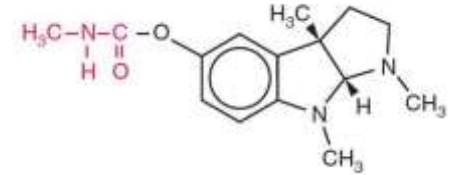
slow (min - hours)



Regenerated enzyme

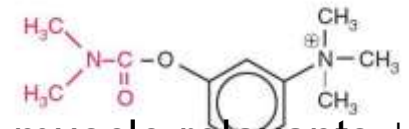
## Physostigmine (eserine)

- Alkaloid of Calabar bean (*Physostigma venenosum*)
- tertiary ammonium group
- duration of action: 0,5 – 2 h
- Ind.: glaucoma (eye drops, 0,25 – 0,5 %), Atropine intoxication



## Neostigmine

- synthetic derivative, quaternary ammonium group
- duration of action: 0,5 – 2 h
- Ind.: glaucoma, Myasthenia, GI / urinary bladder atony, muscle relaxants ↓



## Pyridostigmine

- duration of action: 3 – 6 h
- Ind.: Myasthenia gravis, GI atony

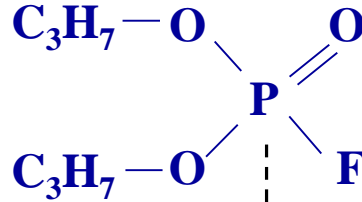
## Rivastigmine

- Ind.: Alzheimer's disease



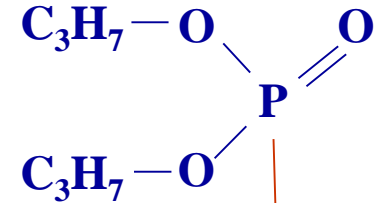
# Phosphoric acid esters (Organophosphates, Alkylphosphates)

Fluostigmine



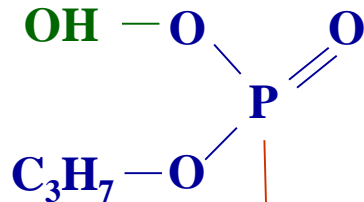
Acetylcholinesterase

HF



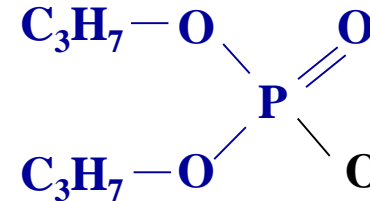
Phosphorylated enzyme

„Aging”  
(min – 1 h)



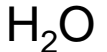
Irreversibly phosphorylated („aged”) enzyme

Days!



Regenerated enzyme

Pralidoxime  
Obidoxime



high **Toxicity**



Strong parasympathetic symptoms

CNS-effects

Fasciculation → depolarizing neuromuscular blockade, paralysis

Therapy:      Atropine (repeatedly, high doses i.v. (2-4 mg))  
                  Acetylcholinesterase-regenerators (Pralidoxime, Obidoxime)  
                  symptomatic therapy

## Insecticides

- e.g. Parathion

## Nerve gases

- e.g. Sarin

## **II. Parasympatholytics (Cholinoceptor-Blocking Drugs)**

# Organ system effects

## Effects

- Eye : **Mydriasis** (M. sphincter pupillae ↓)  
Cycloplegia (M. ciliaris ↓)
- Smooth m.: **Relaxation**  
Bronchodilation  
GI Motility ↓  
relaxation of gall bladder,  
urinary bladder and ureters
- Glands : **Secretions ↓**  
sweat-, salivary- and lacrimal  
GI and bronchial secretions
- Blood vessels : ∅ effect, but :  
parasympathetic vasodilation ↓  
toxic effect – cutaneous vasodilation

## Indications

- Ophthalmoscopic examination of the retina
- Uveitis, Iritis
- Asthma / COPD
- GI Spasm, Hypermotility
- Biliary colic
- Renal colic, Incontinence
- Premedication
- Parkinson, Tuberculosis
- Peptic ulcer disease

## Effects

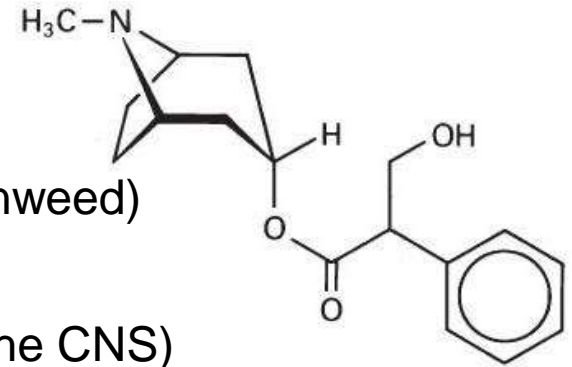
- Heart : **Tachycardia** (SA-node)  
Conduction velocity ↑ (AV-node)
  
- CNS : inhibition of cholinergic transmission in
  - Vestibular nuclei, Area postrema
  - Striatum

## Indications

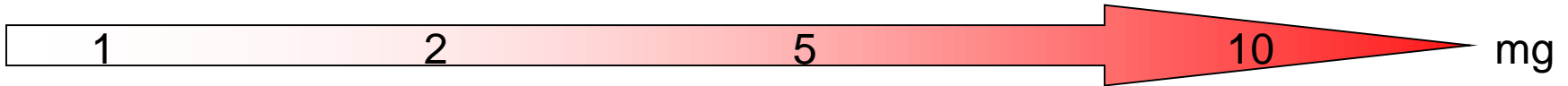
- Sinusbradycardia
- AV-block
  
- Motion sickness  
(seasickness)
  
- Parkinson's disease
  
- Cholinergic poisoning

## Atropine

- Alkaloid of deadly nightshade (*Atropa Belladonna*) and other plants of *Solanaceae* (e.g. mandrake, jimsonweed)
- Tertiary amine
  - good absorption
  - wide distribution (also in the CNS)
- Duration of action : ~ 3 h (but mydriasis : 7-10 days!)
- D.: 0,3 – 0,5 mg
- Indications :
  - Mydriatic (Eye drops: 0,5 – 1 %)
  - Sinusbradycardia, AV-block
  - GI Spasm, renal colic, biliary colic
  - Cholinergic poisoning



# Atropin intoxication



**Dry mouth**  
**Tachycardia**  
**Dry skin**

**Mydriasis**  
**Palpitation**  
**Visual disturbances**

**Dysphagia**  
**Excitement**  
**Headache**

**Hot, dry skin**  
**Hyperthermia**  
**Delirium**  
**Hallucinations**

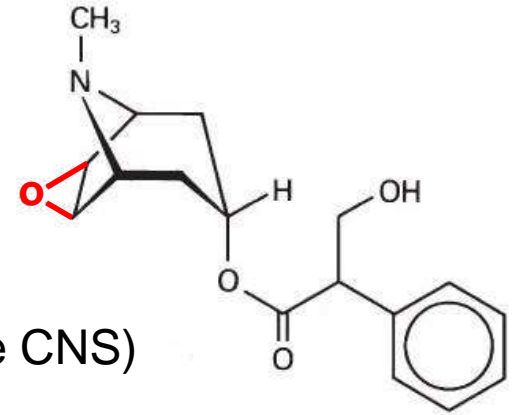
Lethal dose : ~ 100 mg (Coma, Respiratory arrest)  
Infants: 2 mg !

Therapy: symptomatic treatment (e.g. cooling, diazepam)  
physostigmine (small doses, slowly i.v.)



## Scopolamine

- Alkaloid (jimsonweed, henbane)
  - Tertiary amine
    - good absorption
    - wide distribution (also in the CNS)
  - Duration of action : ~ 3 h (mydriasis : 3-7 days)
  - Sedative effect in the CNS! (drowsiness, amnesia)
- Ind.: motion sickness



***Further tertiary amines:***

Mydriatics : e.g. Cyclopentolate (0,5-2 %)

Antiparkinson – drugs: e.g. Benztropine

Incontinence : e.g. Oxybutynin

Antiulcer drugs : e.g. Pirenzepine (M<sub>1</sub>-receptor antagonist)

***Quaternary amine antimuscarinic agents:***

Spasmolytics : e.g. Butylscopolamine

Antiasthmatics : e.g. Ipratropiumm, Tiotropium

# III. Pharmacology of the ganglia

## Ganglion-activating drugs :

- Mainly alkaloids : e.g. **Nicotine** (Tobacco)

### Effects :

small doses - activation :

- Tachycardia, Blood pressure  $\uparrow$  (sympathetic ggl  $\uparrow$ )
- GI motility  $\uparrow$ , Secretions  $\uparrow$ , Myosis (parasympathetic ggl  $\uparrow$ )
- Concentration and memory  $\uparrow$ , Tremor, Tachypnoe (CNS  $\uparrow$ )
- Muscle twitches, fasciculations ( $N_M$ -receptors  $\uparrow$ )

high doses - inhibition due to depolarization blockade :

- Blood pressure  $\downarrow$ , GI motility  $\downarrow$ , Secretions  $\downarrow$ , Mydriasis and Cycloplegia
- Paralysis, Respiratory paralysis (central + peripheral effect)

/- **Varenicline** (partial agonist at  $\alpha_4\beta_2$ -receptors, Ind.: smoking cessation treatment)/

**Ganglion-blocking drugs (non-depolarizing competitive antagonists):**

- e.g. Hexamethonium

- Effects :

- sympathetic ggl ↓ - hypotension

- parasympathetic ggl ↓

smooth muscle relaxation (constipation, urinary retention,  
cycloplegia)

secretions ↓ (dry mouth, reduced sweating)

Strongly limited clinical use (originally antihypertensive drugs)