

PARASYMPATHETIC NERVOUS SYSTEM

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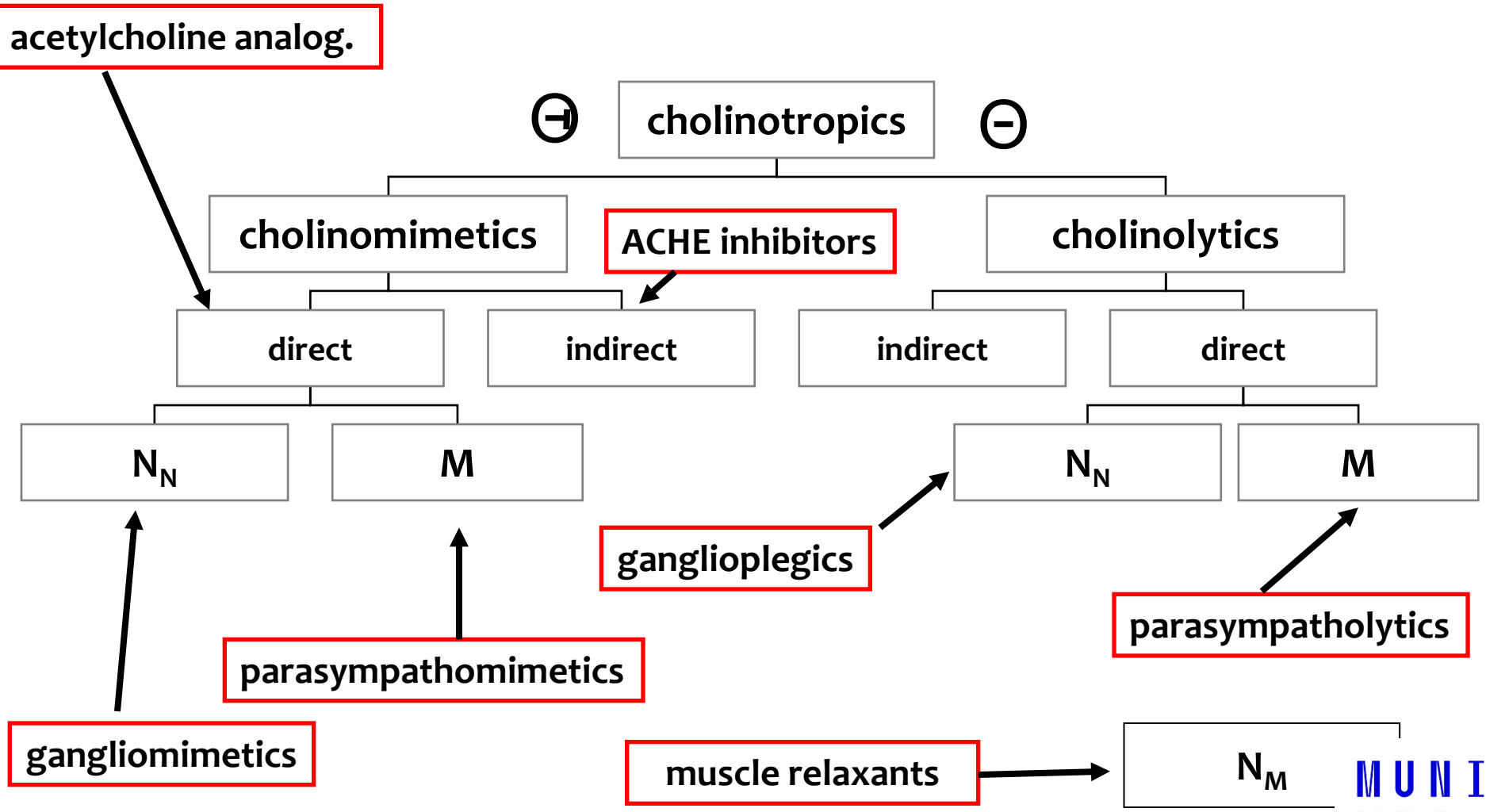
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Cholinergic nervous system

- pharmacological interventions



Terminology:

Cholinomimetics - ↑ activity at cholinergic synapses

- direct – ACh and its analogues
 - they imitate ACh effects on M and N receptors
- indirect - ACHE inhibitors
 - always non-selective
 - » short-term effect - edrophonium
 - » intermediate and long-term effect - carbamates („stigmins“)
 - » very long effect - organophosphates

Parasympathomimetics - they imitate ACh effect on M rc.

- direct (mostly non-selective effect)
- stimulatory agents selective to M receptors for ACh

Terminology:

Cholinolytics

- direct:

- agents blocking acetylcholine receptors

Parasympatholytics - M receptor blockers

- without any effect on nicotinic receptors

Ganglioplegics - N_N-receptor blockers

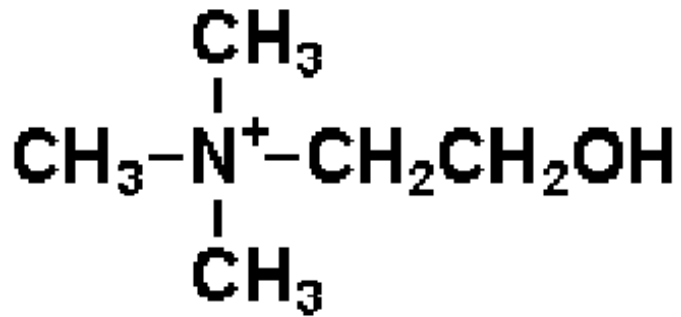
Peripheral muscle relaxants (non-depolarizing) –

- N_M-receptor blockers

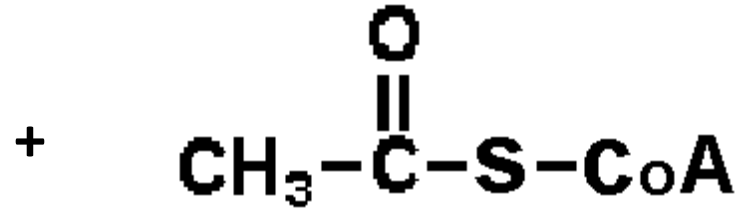
- indirect: e.g. presynaptic inhibition of ACh release

Acetylcholine synthesis

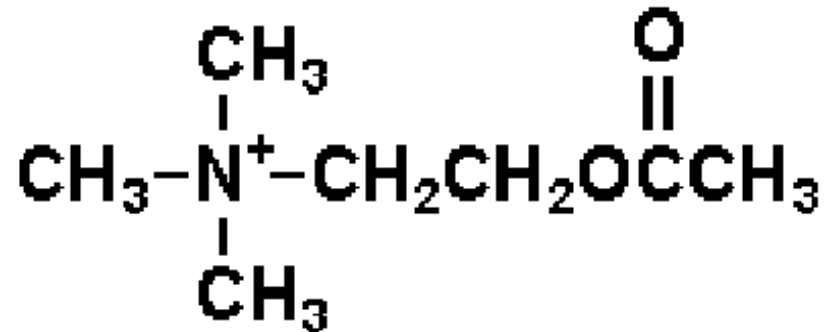
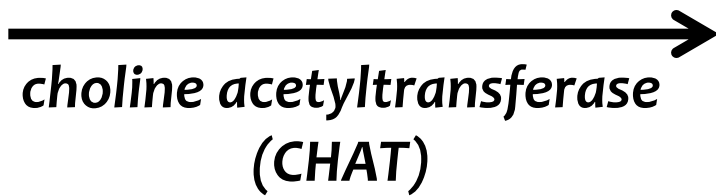
choline in a lecithin form is a dietary supplement
lecithin acts as a precursor to ACh



choline

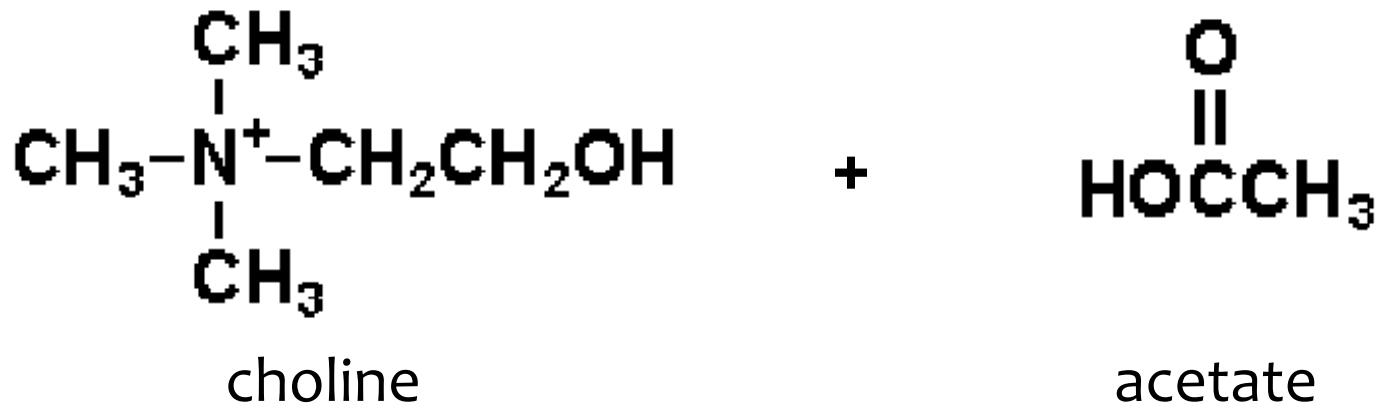
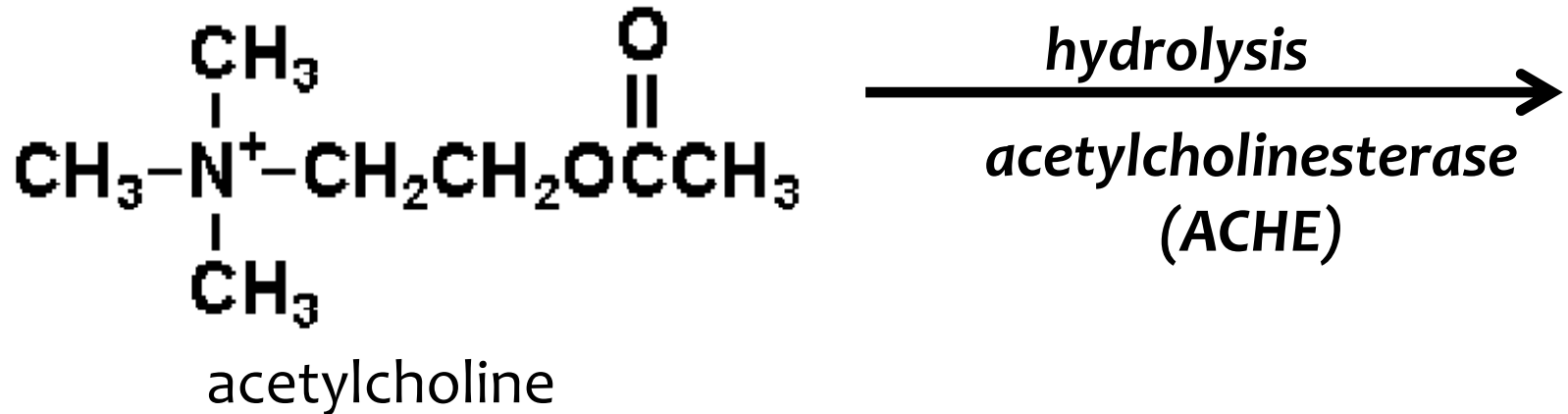


acetyl CoA



acetylcholine (ACh)

Acetylcholine degradation



Cholinotropic agents

- according to the chemical structure we distinguish:

- agents with quaternary ammonium cation
quaternary amines, e.g. muscarine
with low GIT absorption (they do not cross BBB)
- **tertiary amines**, e.g. natural alkaloids
(nicotine, physostigmine)

Cholinomimetics - cholinergic agonists

- pharmacological effects:

- **CVS** - negative chronotropic effect
 - heart depression
 - generalized vasodilation
- **GIT** - increased motility of smooth muscles
- **respiratory tract** - bronchoconstriction
 - ↑ **bronchial secretion**
- **eye** - miosis, ↓ intraocular pressure
 - ↑ **lacrimation**
- ↑ **sweating**, ↑ **salivation**
- **CNS** - tremor, increased locomotion

Acetylcholine and its analogues

acetylcholine

- rapid biodegradation by ACHE → not used in clinics
5-20 s effect after i.v. administration
- limited absorption after oral / s.c. administration
- does not penetrate BBB

- other choline esters:

carbachol

- poor absorption from GIT
- agonist of M and N R_c
- not hydrolyzed by cholinesterase → long duration of action

I: ophthalmology - miosis

cevimeline

- selective M agonist - parasympathomimetic

I: xerostomia (dry mouth)

Acetylcholine and its analogues

- **↑ postganglionic neuronal activity**
 - **↑ neuromuscular signal transduction**
 - **↑ activity of parasympathetic effectors**
 - **↑ sympathetic stimulation of sweat glands**
- pharmacological effects:
- ↓ BP, bradycardia, danger of heart arrest
 - nausea, cough, dyspnoe
 - vascular dilation: NO release
 - salivation, lacrimation, ↑ mucosal gland secretion
 - excessive sweating

Cholinomimetics - natural alkaloids

pilocarpine (*Pilocarpus*)

- non-selective M receptor agonist
- good absorption from GIT
- BBB crossing (→CNS excitation)
- stimulates gland secretion
- stimulates *m. sphincter pupillae* (eyedrops)

I: miotic agent used in ophthalmology 2-4%, Sjögren's syndrome

muscarine (*Inocybe, Clitocybe, Amanita muscaria/phalloides*)

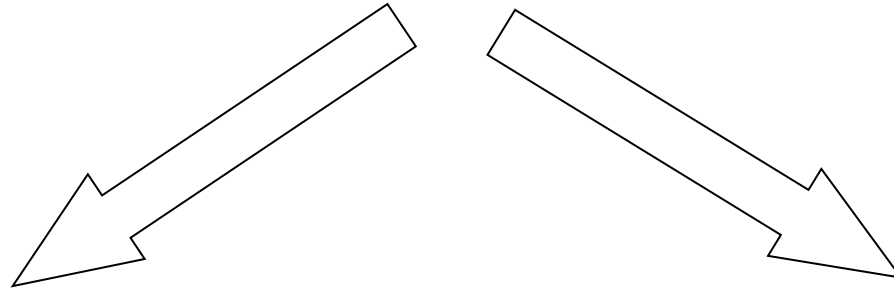
- M receptor agonist, quaternary amine

arecoline (*Areca catechu*)

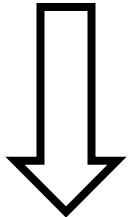
- CNS stimulant, tertiary amine
- M and N receptor agonist

Indirect cholinomimetics

ACHE inhibitors



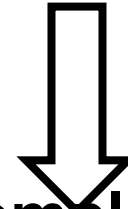
**short-term
(REVERSIBLE)**



**competitive
enzyme inhibition**

medicinal use

**long-term
(IRREVERSIBLE)**



**complex
inhibitor + enzyme**

COVALENT INHIBITION

toxicology

Indirect cholinomimetic agents

Reversible ACHE inhibitors

General indications:

- glaucoma
- GIT atony
- urinary retention
- antidotes of non-depolarizing muscle relaxants
- myasthenia gravis (use quaternary amines)
- Alzheimer's disease (use tertiary amines)
- intoxication with organophosphates
- poisoning associated with the central anticholinergic syndrome (atropine)

Indirect cholinomimetic agents

Reversible ACHE inhibitors

Side effects:

- miosis
- increased glandular secretion
- nausea, diarrhea
- heart depressants (negative chronotropic effect)
- CNS – stimulation followed by depression
- neuromuscular junction - fasciculation and twitching (overdose - depolarization blockade)
- overdosing = **cholinergic crisis** – depolarization blockade - muscle paralysis

Indirect cholinomimetics

Reversible ACHE inhibitors

neostigmine, (edrophonium)

- short-term effect
- I: diagnosis of myasthenia gravis
- „decurarization“, antidotes of competitive muscle relaxants

pyridostigmine, ambenonium

- longer effect than neostigmine, slower onset of action
 - weaker muscarinic effect - less GIT side effects
- I: myasthenia gravis

distigmine

- long-acting reversible ACHE inhibitor
- I: myasthenia gravis, atonic the urinary bladder, uterine atony, postoperative GIT atony, paralytic ileus

Indirect cholinomimetics

Reversible AChE inhibitors

- CNS effects of drugs, that can cross the blood-brain barrier

physostigmine

I: antidote in acute intoxications with central anticholinergic syndrome

galantamine, rivastigmine, donepezil

I: dementias of the Alzheimer s type

- galantamine has a positive allosteric effect on ACh binding on N rec.

Indirect cholinomimetics

Irreversible ACHE inhibitors

- effects: nausea, vomitus, sweating, CVS collapse, breath depression, fasciculation and twitching
→ muscle paralysis, CNS convulsions
- agents: organophosphates
 - insecticides (**malathion, parathion**)
 - chemical weapons such as nerve gas **sarin** or VX, soman, tabun
- their antidotes: **obidoxime**, trimedoxime, pralidoxime

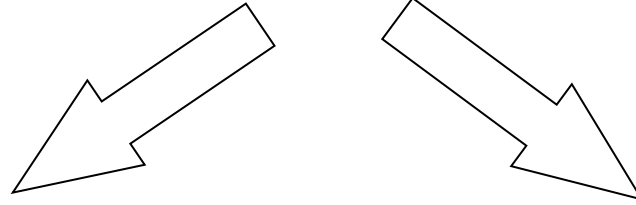
Indirect cholinomimetics

Irreversible AChE inhibitors

Therapy of organophosphate intoxication:

1. reduce further neurotoxic absorption
2. mechanical ventilation
3. **atropine** i.v. in high doses 2 mg every 5 min until a slight overdose (in mass-casualty settings s.c.)
4. **AChE reactivators : obidoxime, (pralidoxime)**
5. therapy of muscle convulsions i.v. **benzodiazepines**
6. high doses of reversible AChE inhibitors
7. bioscavengers

Parasympatholytics



tertiary amines

blockade of M receptors

atropine

scopolamine

tropicamide, cyclopentolate

oxybutynine

tolterodine, fesoterodine

solifenacin, darifenacin

procyklidine, biperiden

(pirenzepine, telenzepine)

(homatropine)

quaternary amines

blockade of **M** > N receptors

butylscopolamine

phenpiverine, propiverine

otilonium, glycopyrrolate

ipratropium, tiotropium

aclidinium, umeclidinium

trospium

(oxyfenonium), (poldin)

Parasympatholytics

direct antimuscarinic agents

General indications:

- spasmolytics
- bronchodilating agents
- antiarrhythmics
- mydriatics
- premedication prior to GA
- antiemetics
- antiparkinson agents
- antidotes of pilocarpine, ACHEI poisoning (physostigmine)

Parasympatholytics

direct antimuscarinic agents

Side effects:

- dry mouth (xerostomia)
- dry eyes (xerophthalmia)
- loss of accommodation (cycloplegia)
- heart palpitations
- constipation
- urinary retention
- CNS: seizures, severe dyskinesias, hallucinations, agitated delirium, respiratory depression, coma

PL with tertiary N

atropine, tropicamide, cyclopentolate, homatropine

- mydriasis (stimulation of m. sphincter pupillae)
- cycloplegia (paralysis of the ciliary muscle of the eye)

I: for diagnostic and therapeutic mydriasis

scopolamine (hyoscine) TTS, supp.

I: therapy of kinetosis, CNS depression

oxybutinine

- orally, TTS
- pharmacokinetics: high 1st pass effect

I: antispasmodic agent used for overactive urine bladder

PL with tertiary N

Selective parasympatholytics:

darinefacin, solifenacin

- M₃ uroselective antagonists

I: symptomatic therapy of overactive urinary bladder

(pirenzepine)

- gastric M1 receptor selective antagonist
- former indication: gastroduodenal ulcers

PL with quaternary N

- do not cross BBB (blood-brain barrier)
- **spasmolytics** for functional bowel disorders: **otilonium**
N-butylscopolamine
phenpiverine
(oxyphenonium),(poldin)
- **urinary antispasmodic** for hyperactive urinary bladder:
trospium
- **bronchodilator agents:**
ipratropium (SAMA)
(LAMA) { **tiotropium, aclidinium**
glycopyrrolate, umeclidinium

* *long acting muscarinic antagonists (LAMA)*
short acting muscarinic antagonists (SAMA)

Drugs affecting autonomic ganglia

- direct:

Gangliomimetics
(ganglia stimulating agents)
 N_N receptor agonists

- nicotine at lower doses
- varenicline (partial agonist)
- experimental pharmacology:
- lobeline
- dimethylphenylpiperazinium

Ganglioplegic agents
 N_N receptor antagonists

- nicotine at high doses
→ prolonged depolarization
- experimental pharmacology:
- hexamethonium
- trimetaphan

- indirect:

presynaptic mechanism
blockade of ACh release

- botulinum toxin

Skeletal muscle relaxants

1. Centrally acting

2. Peripheral effect on neuromuscular junctions

nondepolarizing

- N_M antagonists
- antag. by ACHEI
- tubocurarine
- mivacurium
- atracurium, cisatracurium
- rocuronium, pipecuronium
- (pancuronium, vecuronium)

depolarizing

- N_M agonists
- suxamethonium

indirect muscle relaxants: dantrolene, botulinum toxin