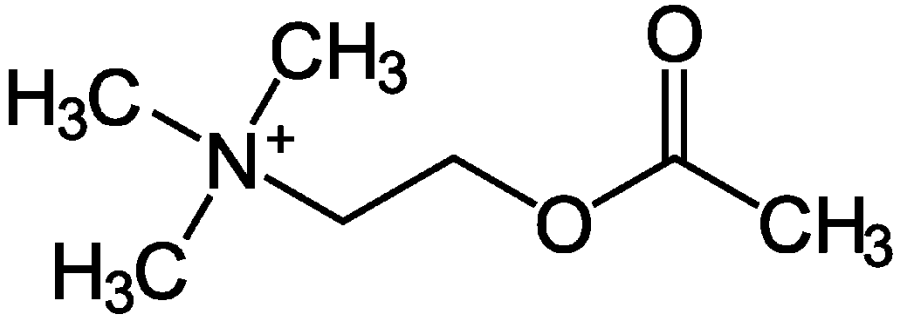
PARASYMPATHETIC NERVOUS SYSTEM

Cholinergic drugs elicit their effect:

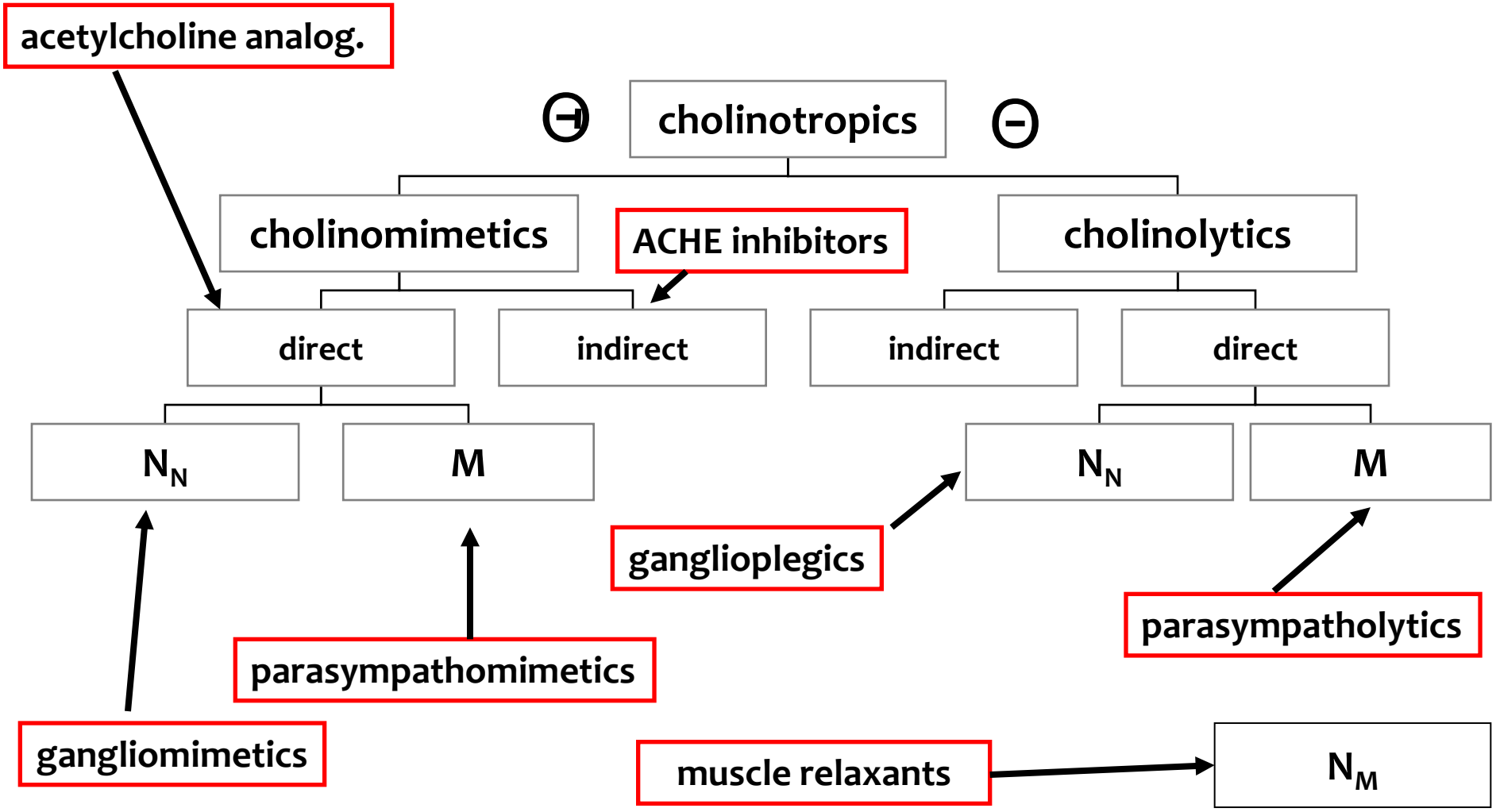
1) via the parasympathetic synapses of effector organs
2) via synapses of the autonomic nerve ganglia
3) via synapses of neuromuscular junctions
4) via synapses in CNS

- influence synapses, where acetylcholine (ACh) acts as their neurotransmitter



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

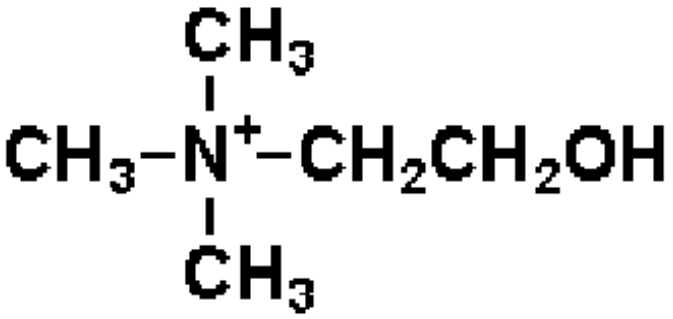
  Peripheral muscle relaxants (non-depolarizing) –

  - N_M-receptor blockers

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

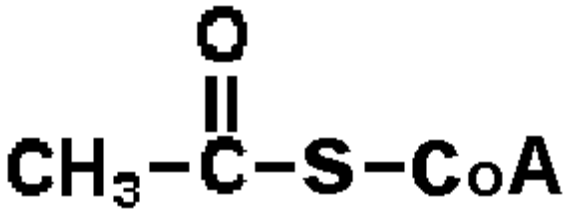
Acetylcholine synthesis

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



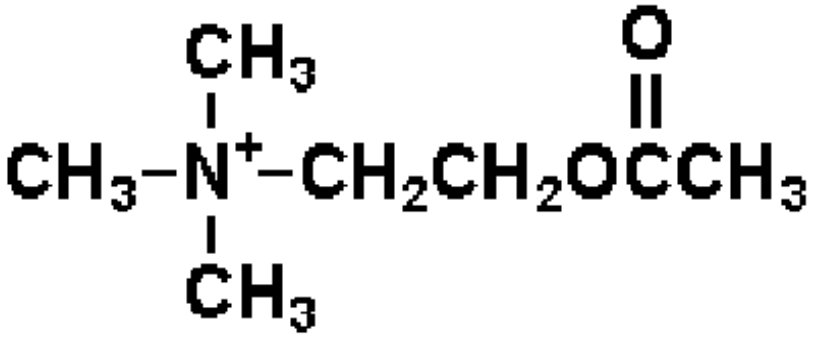
choline

+



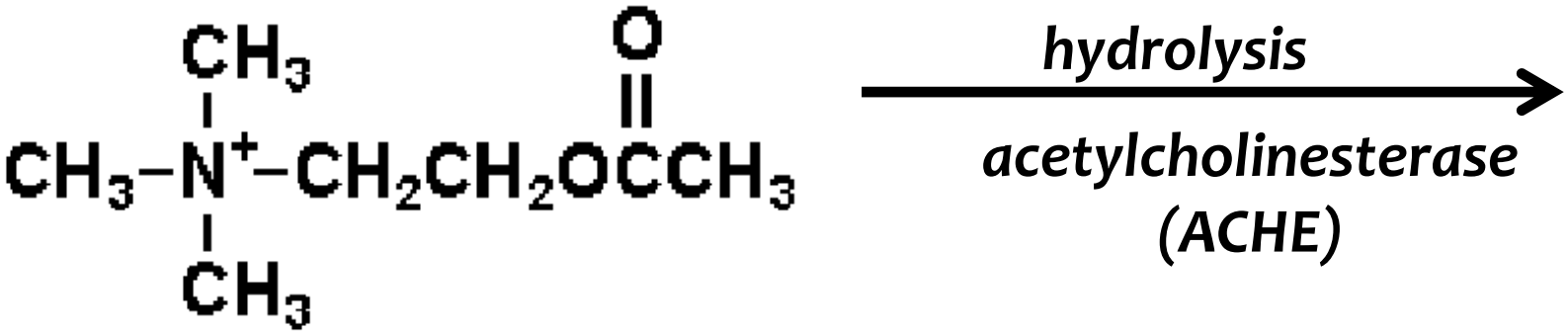
acetyl CoA

choline acetyltransferase (CHAT)

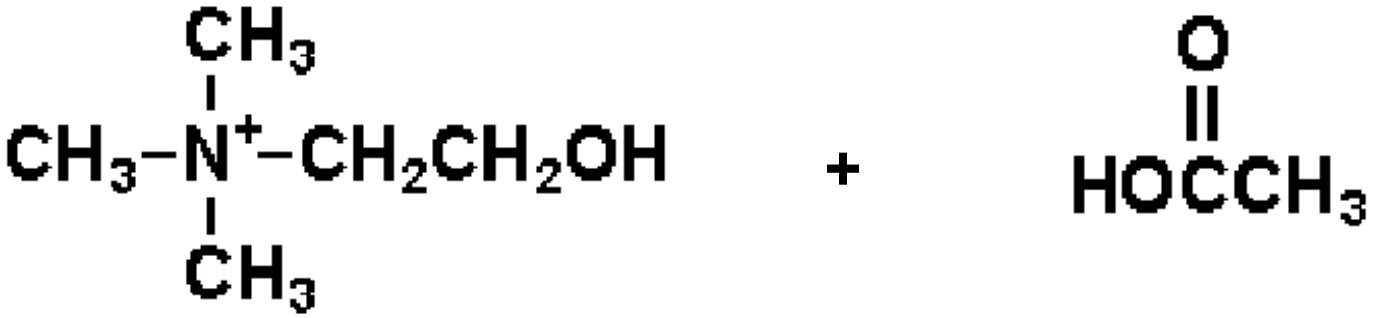


acetylcholine (ACh)

Acetylcholine degradation



acetylcholine



choline + acetate

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

<u>- other choline esters:</u>

carbachol

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

I: ophthalmology - miosis

cevimeline

- selective M agonist - parasympathomimetic

I: xerostomia (dry mouth), Sjögren's syndrome

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
  - nauzea, 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 pupilae* (eyedrops)

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

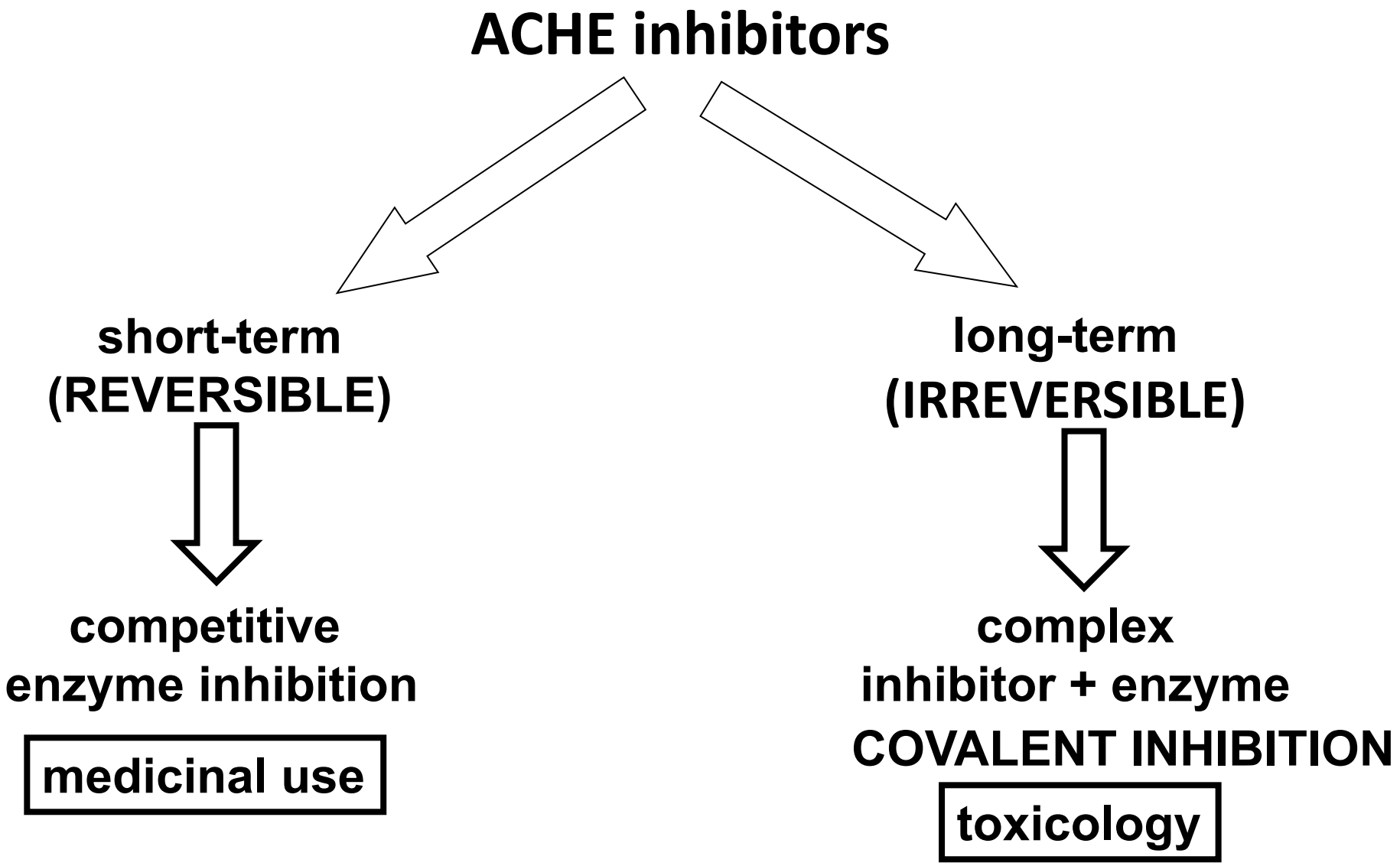
muscarine *(Inocybe, Clitocybe, Amanita muscaria/phalloides)*

- M receptor agonist, quaternary amine

arecoline *(Areca catechu)*

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

Indirect cholinomimetics



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

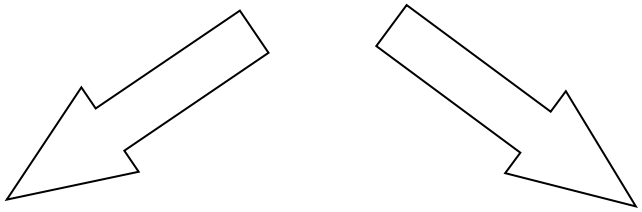
- effects: nausea, vomitus, sweating, CVS collapse, breath depression, fasciculation and twitching
  → muscle paralysis, CNS convulsions
- agents: organophosphates
  - insecticides (**malathion**, **parathion**)
  - chemical weapons such as nerve gas **sarin** or VX, soman, tabun
- their antidotes: **obidoxime**,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

Indirect cholinomimetics
Irreversible ACHE inhibitors

Therapy of organophosphate itoxication:

1. reduce further neurotoxine 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, cyklopentolate
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 pupilae)
- 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

- M_3 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. Centraly 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

<u>indirect</u> muscle relaxants: dantrolene, botulinum toxin