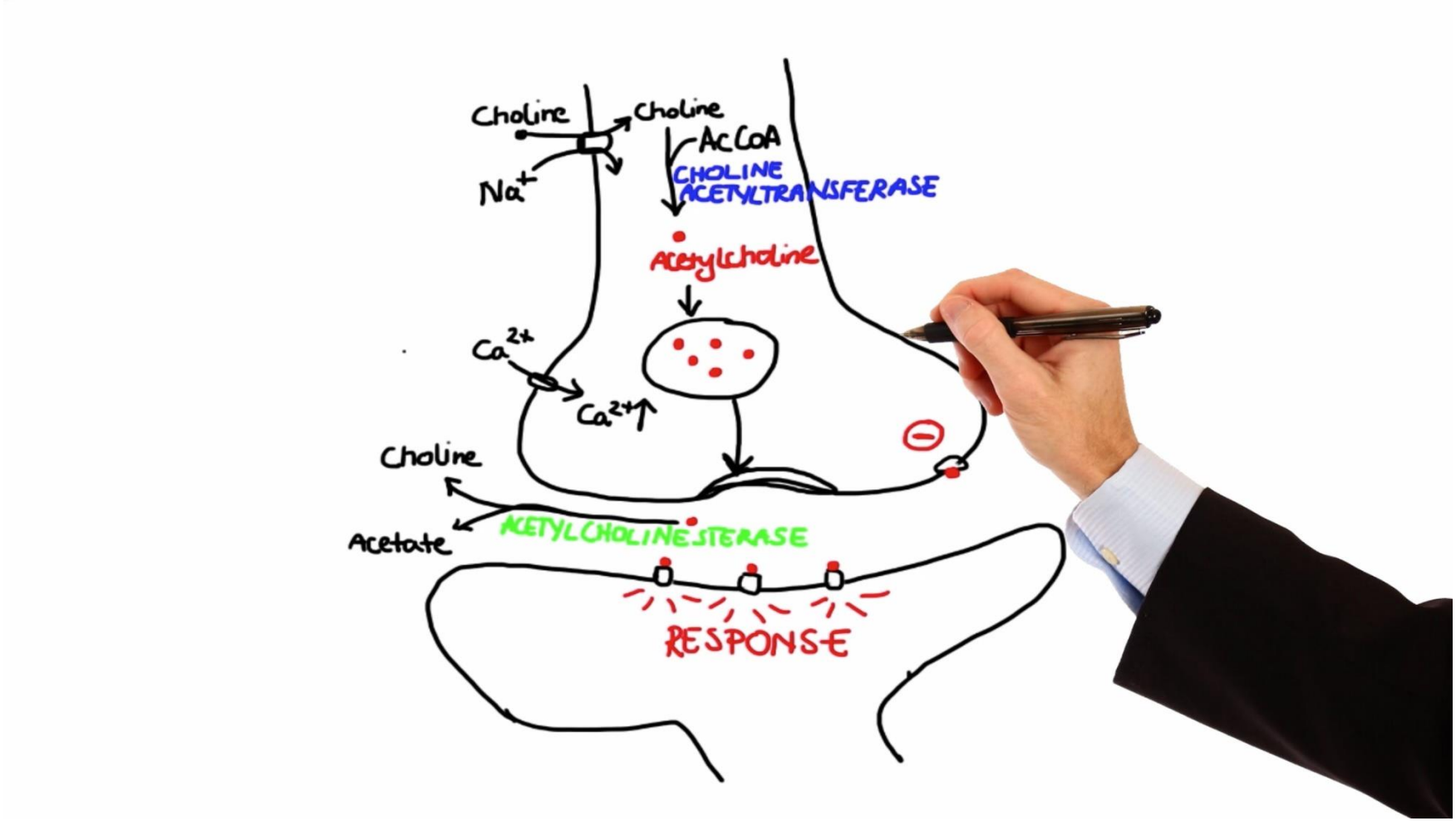
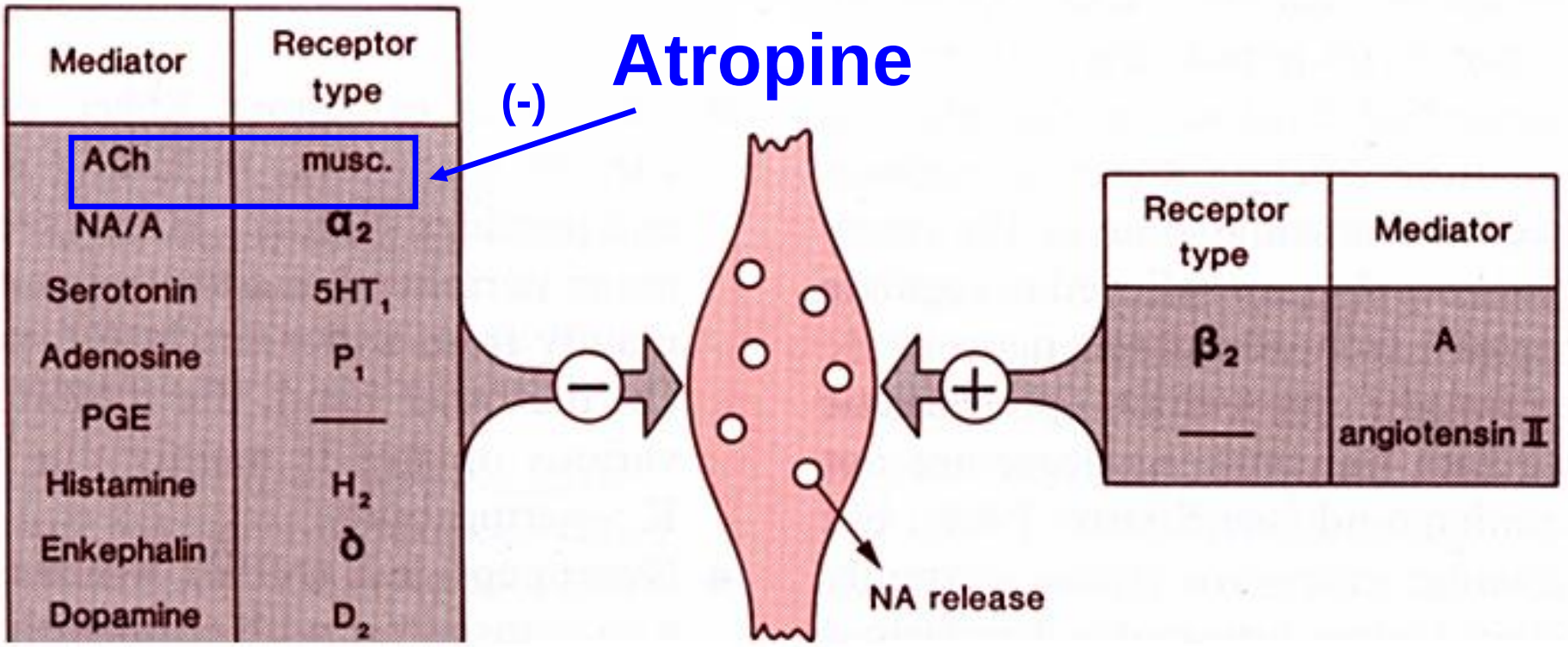
ANTICHOLINERGIC DRUGS

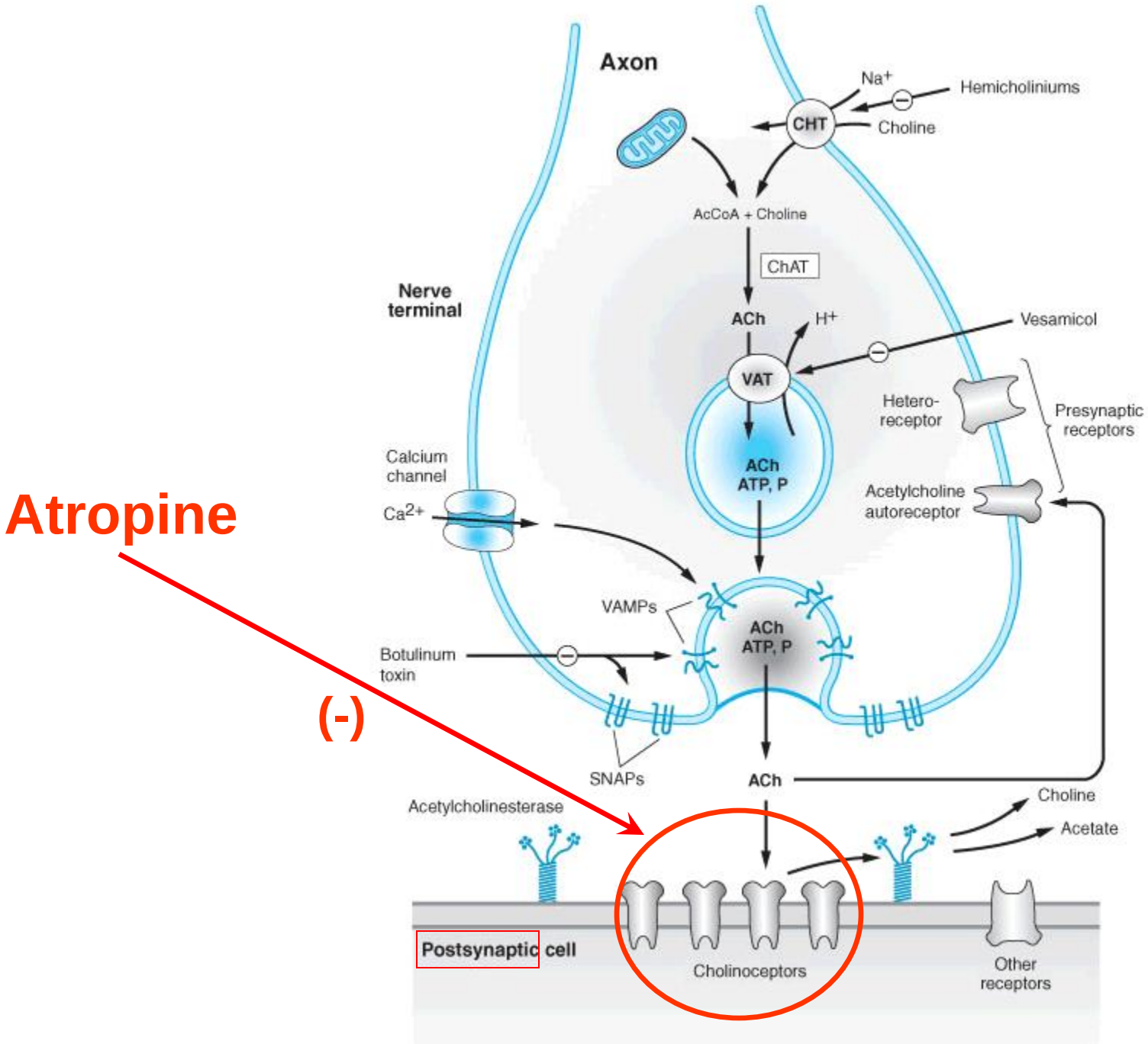


ANTICHOLINERGIC DRUGS
(Muscarinic Receptor Antagonist, Parasympatholytics, Cholinolytics Atropine-like Drugs)

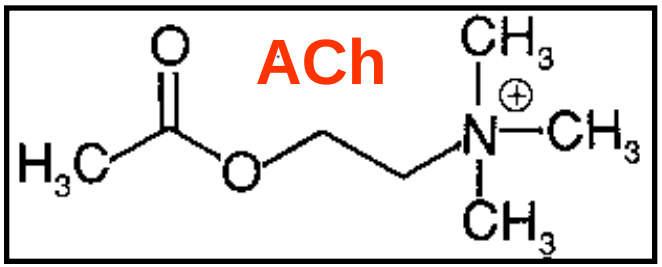
Atropine, the prototype drug of this class, is a highly **selective blocking agent for pre and postmuscarinic receptors**, but some of its synthetic derivatives have significant nicotinic blocking proparty as well.

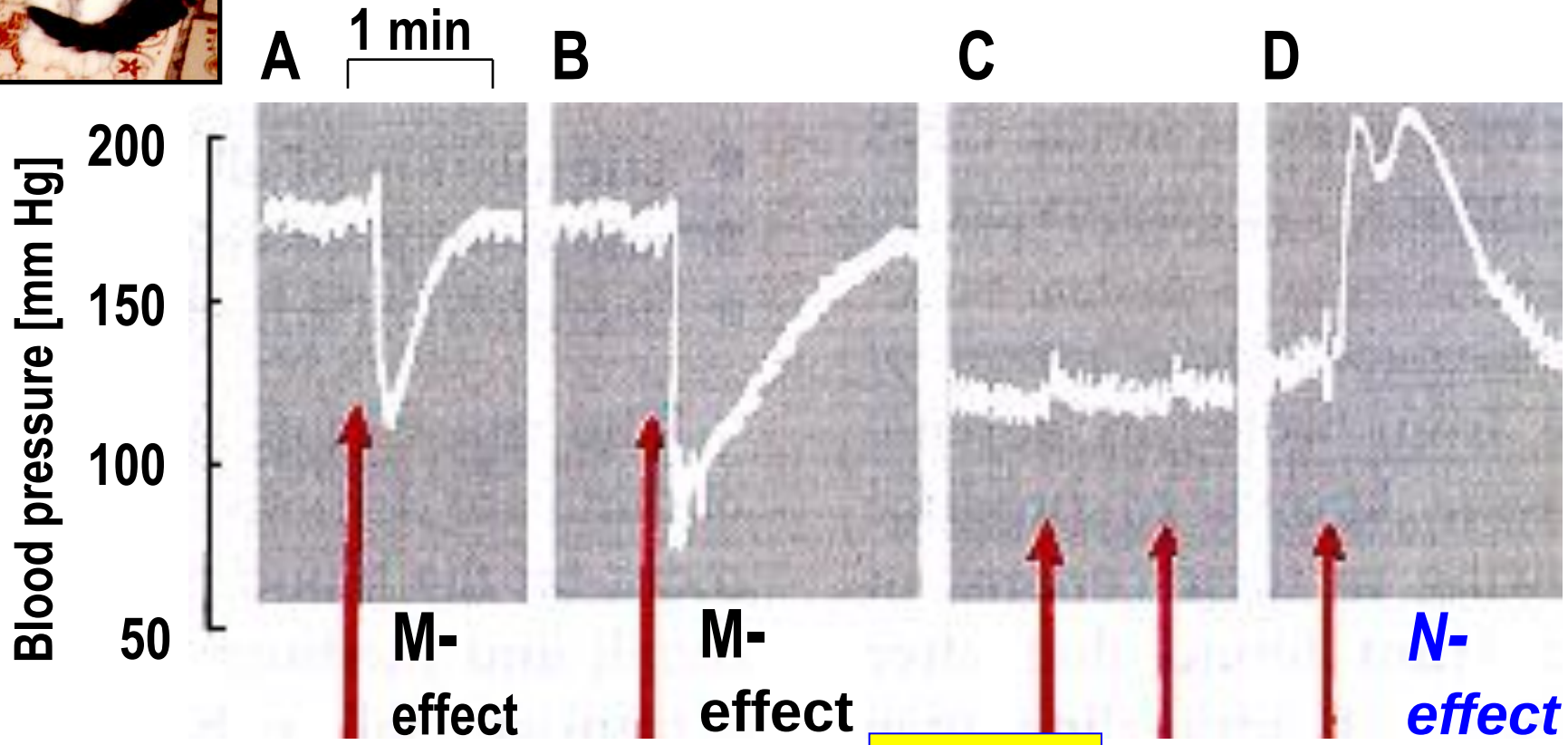


***Presynaptic* receptors in adrenergic synapse and their role in the regulative negative and positive feedback**

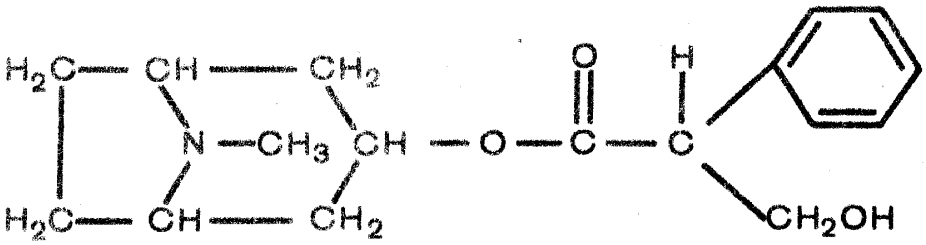

Atropine
(-)
Axon
Nerve terminal
Na+
Hemicholiniums
CHT
Choline
AcCoA + Choline
ChAT
ACh
H+
Vesamicol
VAT
Hetero-receptor
Presynaptic receptors
ACh ATP, P
Calcium channel
Ca2+
Acetylcholine autoreceptor
VAMPs
ACh ATP, P
Botulinum toxin
SNAPs
ACh
Acetylcholinesterase
Choline
Acetate
Postsynaptic cell
Cholinoceptors
Other receptors

Atropine blocks M-effects of ACh

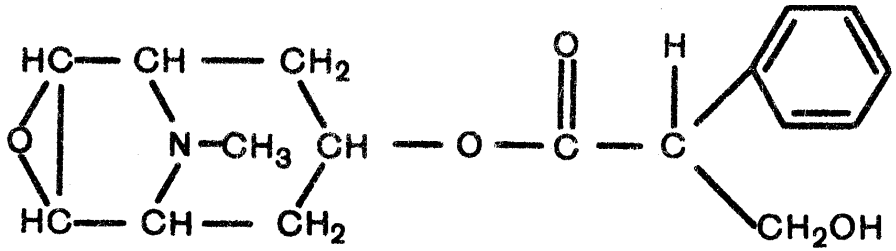




Tropane alkaloids



•Atropine



•Scopolamine (Hyoscine)

•Solanine (*in potatoes*)

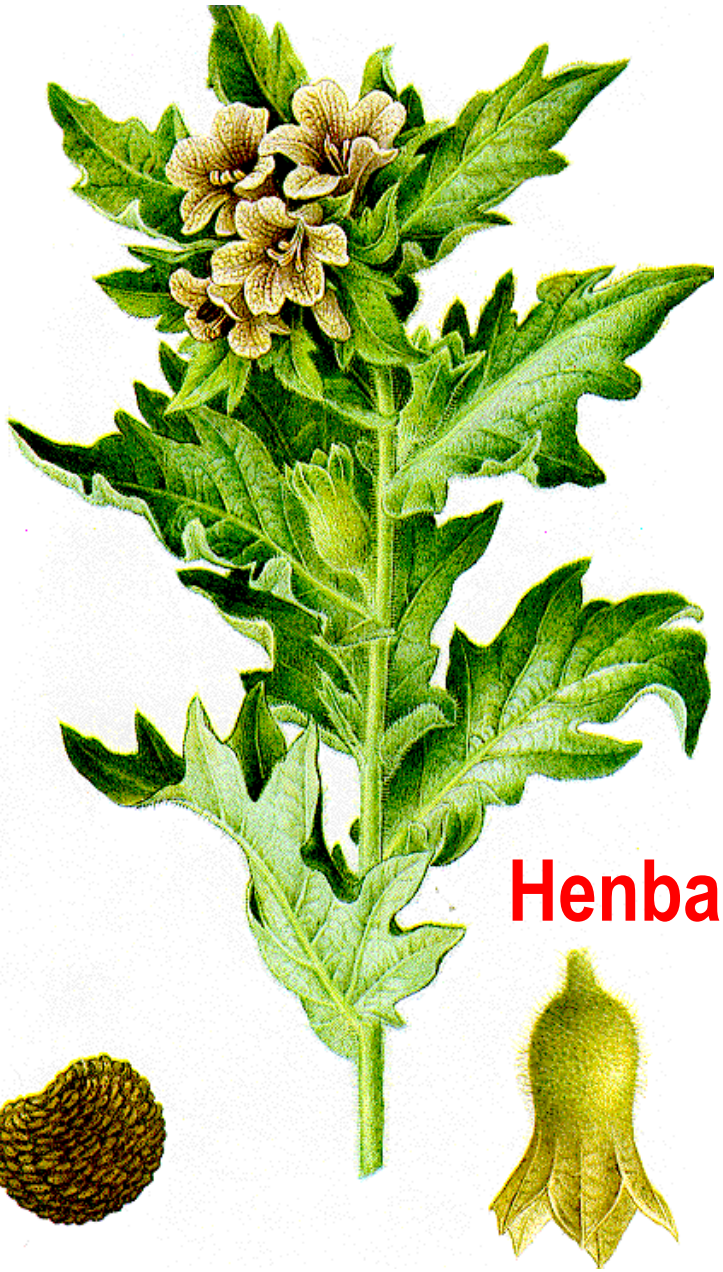
Atropa belladonna L.

(Deadly night shade)

Cura bulgara (Ivan Raev)

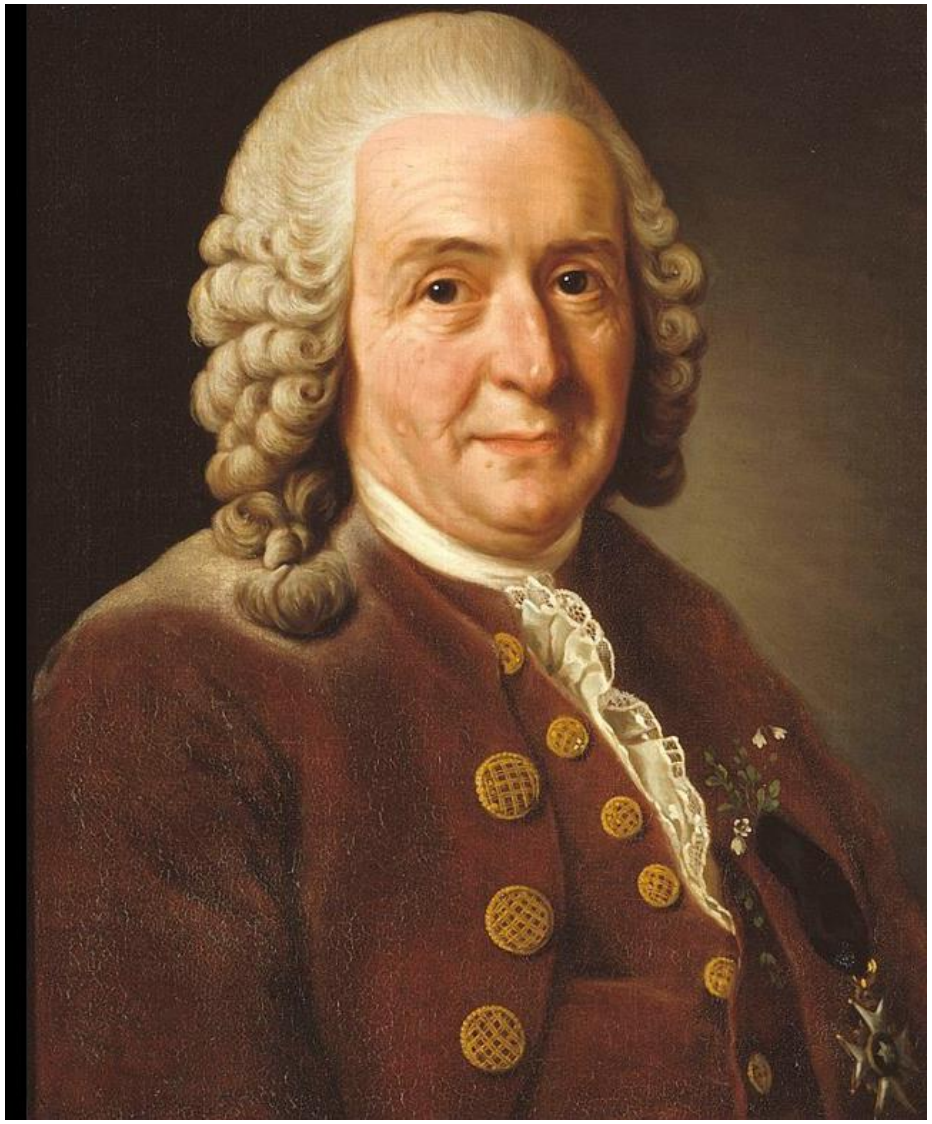
Jimson weed

Datura stramonium **L.**



Henbane

Hyoscyamus niger **L.**



Carl von Linné

(1707–1778)

– binominal system (genus and species).

Carl v. Linné

(Mr Flower Power)

7700 plants!!!

Action of atropine

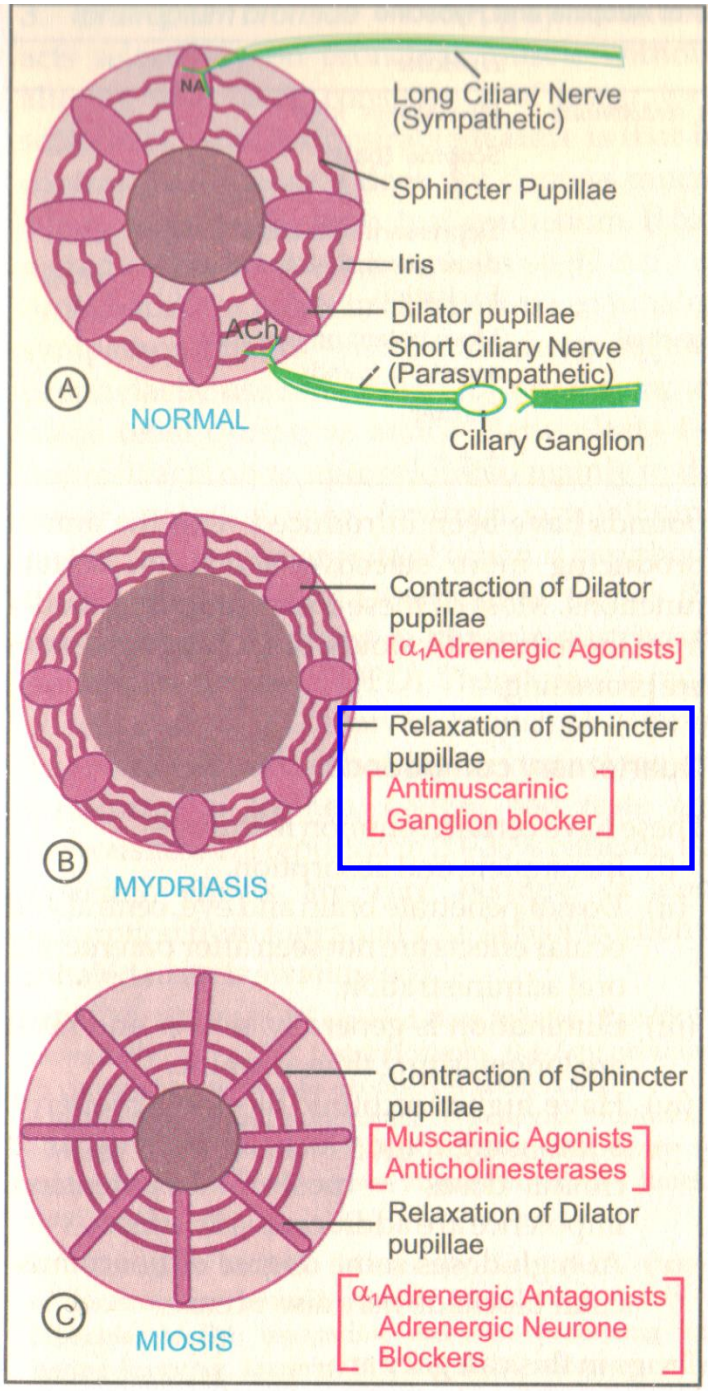
CNS. Atropine has an overall *stimulant action*. Its stimulant effects are not appreciable at low doses which produce peripheral effects because of restricted entry into the brain. *Hyoscine produces central depressant effects* even at low doses.

- Atropine **stimulates many medullar centers** – vagal, respiratory, and vasomotor.
- By blocking the relative cholinergic overactivity in basal ganglia, it **suppresses tremor and rigidity** in parkinsonism.
- **High doses cause cortical excitation**, restlessness, disorientation, hallucinations, and delirium followed by respiratory depression and coma.

CVS. Atropine causes *tachycardia*, due to blockade of M_2-receptors on SA node through which vagal tone decreases HR. *The tachycardia is more marked in young adults than* in children and the elderly. Atropine *shortens the refractory period of AV conduction*, especially if it has been depressed by high vagal tone. Atropine does not influence BP. It blocks the vasodepressor action of cholinergic agonists.

Eye. Topical instillation of atropine (0.1%) causes *mydriasis, abolition of light reflex, and cycloplegia, lasting 7–10 days*. This results in photophobia and *blurring of near vision*. The *intraocular tension rises,* specially in narrow angle glaucoma, but conventional systemic doses produce minor ocular effects.

Autonomic control of pupil (A) and site of action of mydriatics (B) and miotics (C)



Smooth muscles. All visceral smooth muscles with parasympathetic inervation are relaxed (*M_3-blokade*). Tone and amplitude of GIT are reduced. *Spasm may be reduced, constipation may occur*. Peristalsis is only incompletely suppressed because it is primarily regulated by local reflexes and other neurotransmitters (serotonin, encephalin, etc.). Atropine causes *bronchodilation* and reduced airway resistance, especially in asthma patients. Inflammatory mediators (histamine, PGs, and kinins) increase vagal activity in addition to their direct action on bronchial muscle and glands. Atropine attenuates their action by antagonizing the reflex vagal component.It has a relaxant action on the ureter and urinary bladder. *Urinary retention* can occur in older men with prostatic hyperplasia.

Glands. Atropine decreases sweat, salivary, tracheo-bronchial, and lacrimal secretion (*M_3-blockade*). Skin and eyes become dry, talking, and swallowing my be very difficult.
Atropine decreases less the secretion of acid and pepsin and more of the mucus in the stomach.

Body temperature. Rise in body temperature occurs at higher doses, and is due to both inhibition of sweating as well as stimulation of the temperature regulating centre in the hypothalamus. Children are highly susceptible.

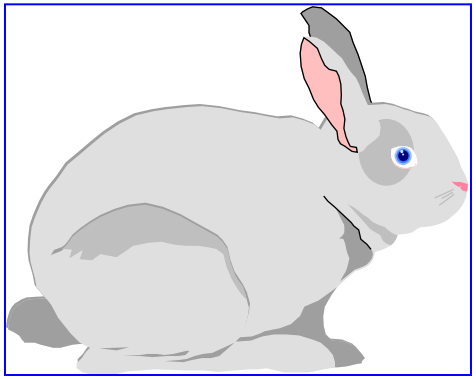
Local anaesthetic action. Atropine has a mild anaesthetic action on the cornea.

The sensitivity of different organs and tissues to atropine varies and can be graded as (*Tripathy, 2003*):

saliva, sweat, bronchial secretion > eye > bronchial muscles > heart > intestinal and bladder smooth muscles > gastric glands and gastric smooth muscles

Pharmacokinetics

Atropine and hyoscine are rapidly absorbed from GIT. Applied to the eyes they penetrate the cornea. Passage across BBB is somewhat restricted. 50% of atropine is metabolized in the liver and excreted unchanged in urine. It has $t_{1/2}$ 3–4 h. Hyoscine is more completely metabolized and has better BBB penetration. Some rabbits have a specific **atropine esterase** which degrades atropine very rapidly.



Unwanted effects:

Dry mouth, difficulty in swallowing and talking; dry, flushed, and hot skin (especially over the face and neck); fever; difficulty in micturition; a scarlet rash may appear; dilated pupils, photophobia, blurring of near vision; palpitation; excitement, psychotic behavior, ataxia, delirium, hallucinations; hypotension, weak and rapid pulse, cardiovascular collapse with respiratory depression; convulsion and coma (in very high doses).

Diagnosis: 1 mg neostigmine s.c. fails to induce typical M-effects.

Treatment: Gastric lavage with tannic acid ($KMnO_4$ is ineffective in oxidation of atropine). The patient must be kept in a dark quiet room. Galantamine or physostigmine (1-3 mg s.c./i.v.), diazepam against convulsion.

ANTICHOLINERGIC DRUGS

1. **Natural alkaloids:** Atropine (spasmolytic, mydriatic), Hyoscine (Scopolamine), Scopoderm® TTS (antiemetic)

2. Semisynthetic derivatives

- *Mydriatics*: Homatropine
- *GI spasmolytics*: Hyoscine butyl bromide (Buscolysin®)

3. Synthetic compounds

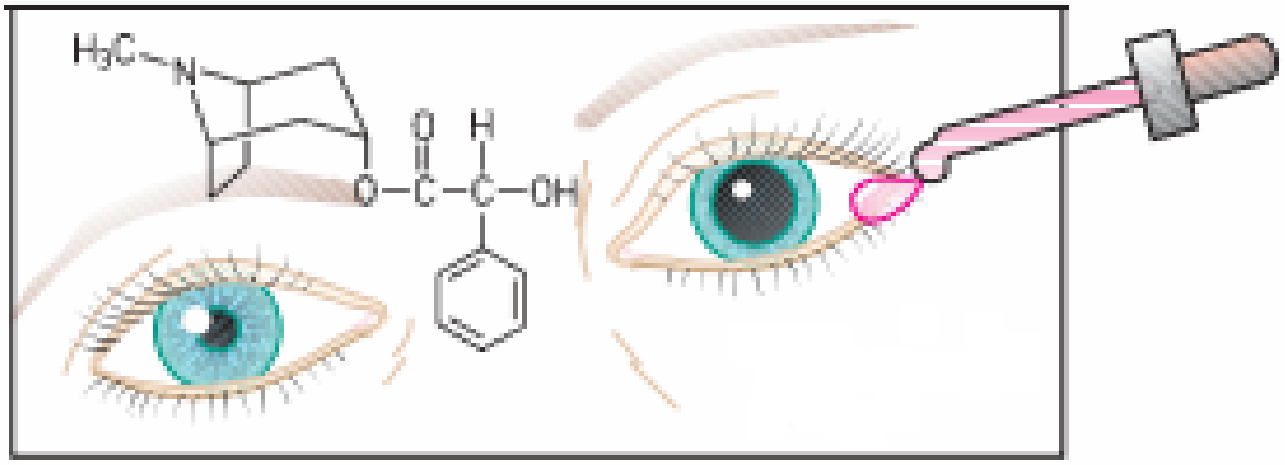
- *GI spasmolytics*: Oxyphenonium
- *Antiulcus drugs*: Pirenzepine (M_1-blockers)
- *Antiasthmatics*: Ipratropium and Tiotropium
- *Antidisurics*: Flavoxate, Oxybutynyne, Trospium
- *Mydriatics*: Tropicamide
- *Antiparkinsonian (central M-cholinolytics)*: Benztropine, Biperiden, Trihexyphenidyl

Central M-cholinolytics:
- **Biperiden**
- **Trihexyphenidyl**

Indications:
- **Drug induced (e.g. neuroleptics) parkinsonism**
- **Spastic paralysis**

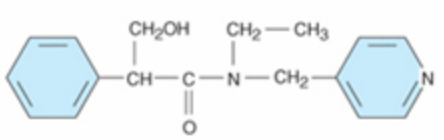
Atropa belladonna L.

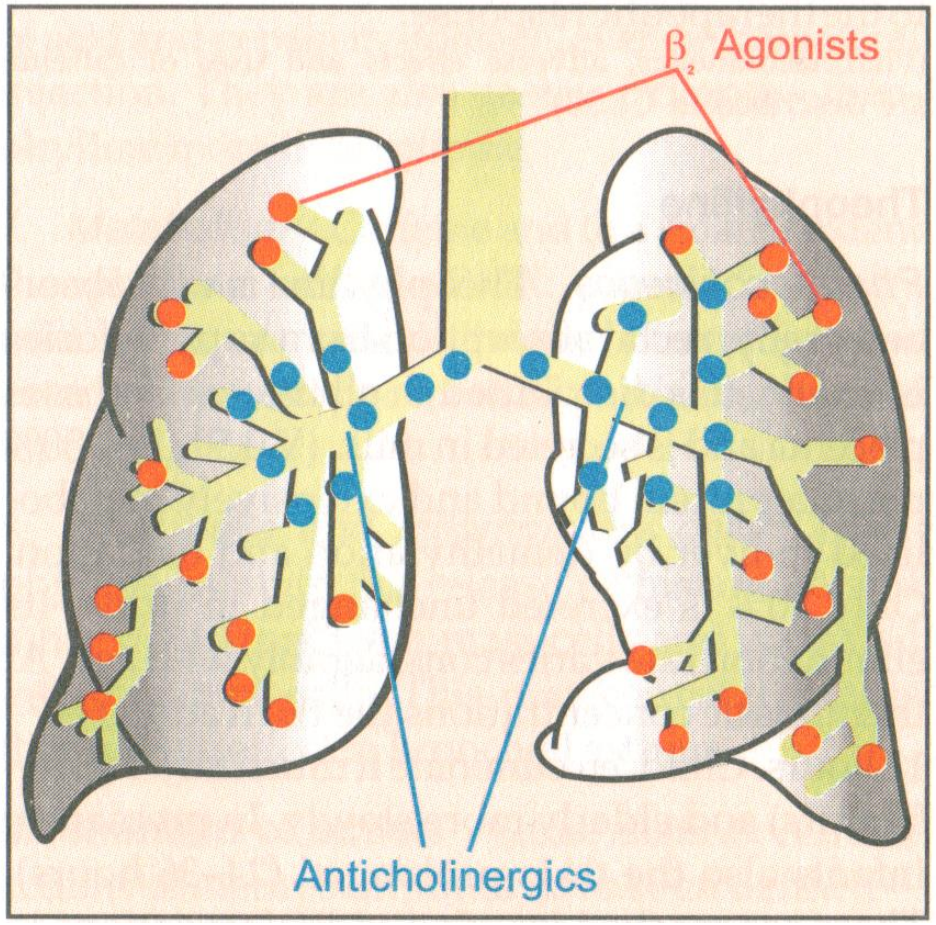
They remove tremor and hypersalivation. Atropine-like side effects!



Homatropine

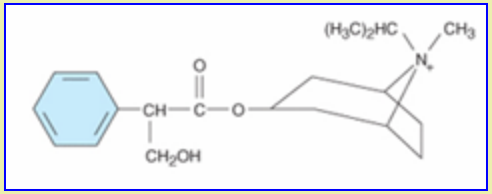
Tropicamide





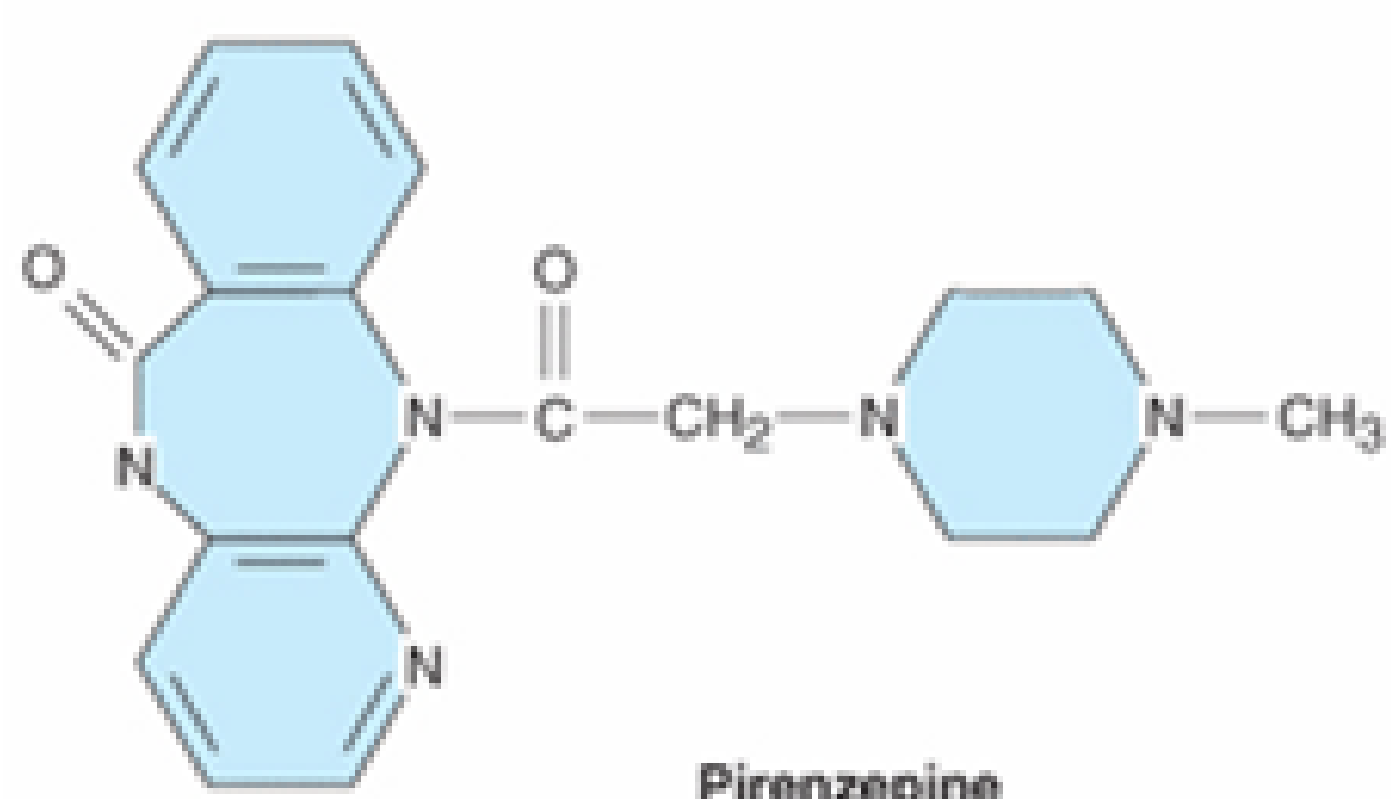
Anticholinergics in asthma

- Ipratropium



- Tiotropium

Primarily, the site of bronchodilation action of inhaled β_2-adrenergic agonists is mainly the bronchiolar smooth muscle. Atropinic drugs cause bronchodilation by blocking cholinergic constrictor tone, act primarily in large airways.



Pirenzepine
(peptic disease)

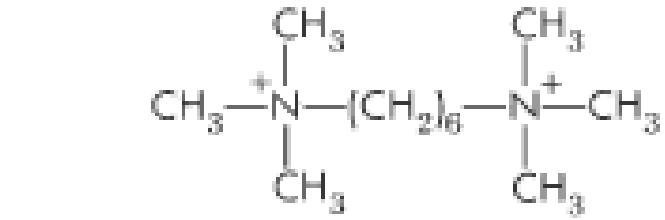
Main interactions of anticholinergic drugs

- Absorption of more drugs is slowed because atropine delays gastric emptying. As a result the dose of levodopa, needed to control parkinsonism may have to be increased. But the extent of digoxin, and tetracyclines absorption may be increased.
- Antacids interfere with the absorption of anticholinergics.
- Antihistaminics, tricyclic antidepressants, phenothiazines, pethidine, etc. have anticholinergic property: additive side effects with atropinic drugs are possible.
- MAO inhibitors interfere with the metabolism of central antiparkinsonian drugs (biperiden and others): delirium may occur.

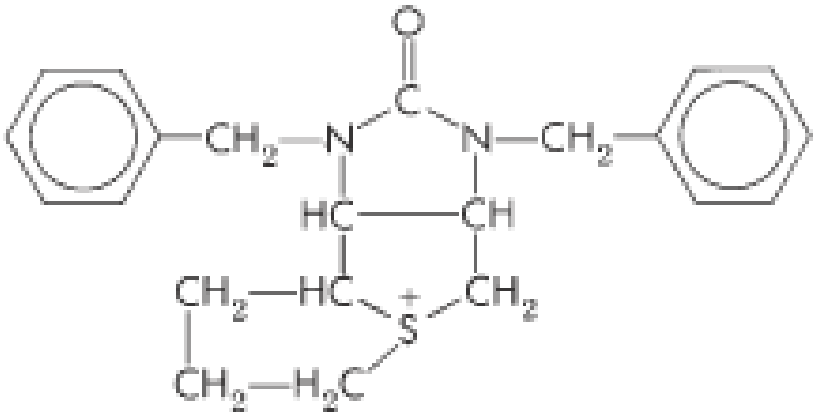
Ganglion blocking agents

- many side effecs

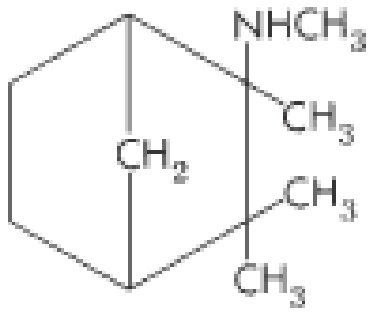
- out of date



HEXAMETHONIUM (C6)



TRIMETHAPHAN

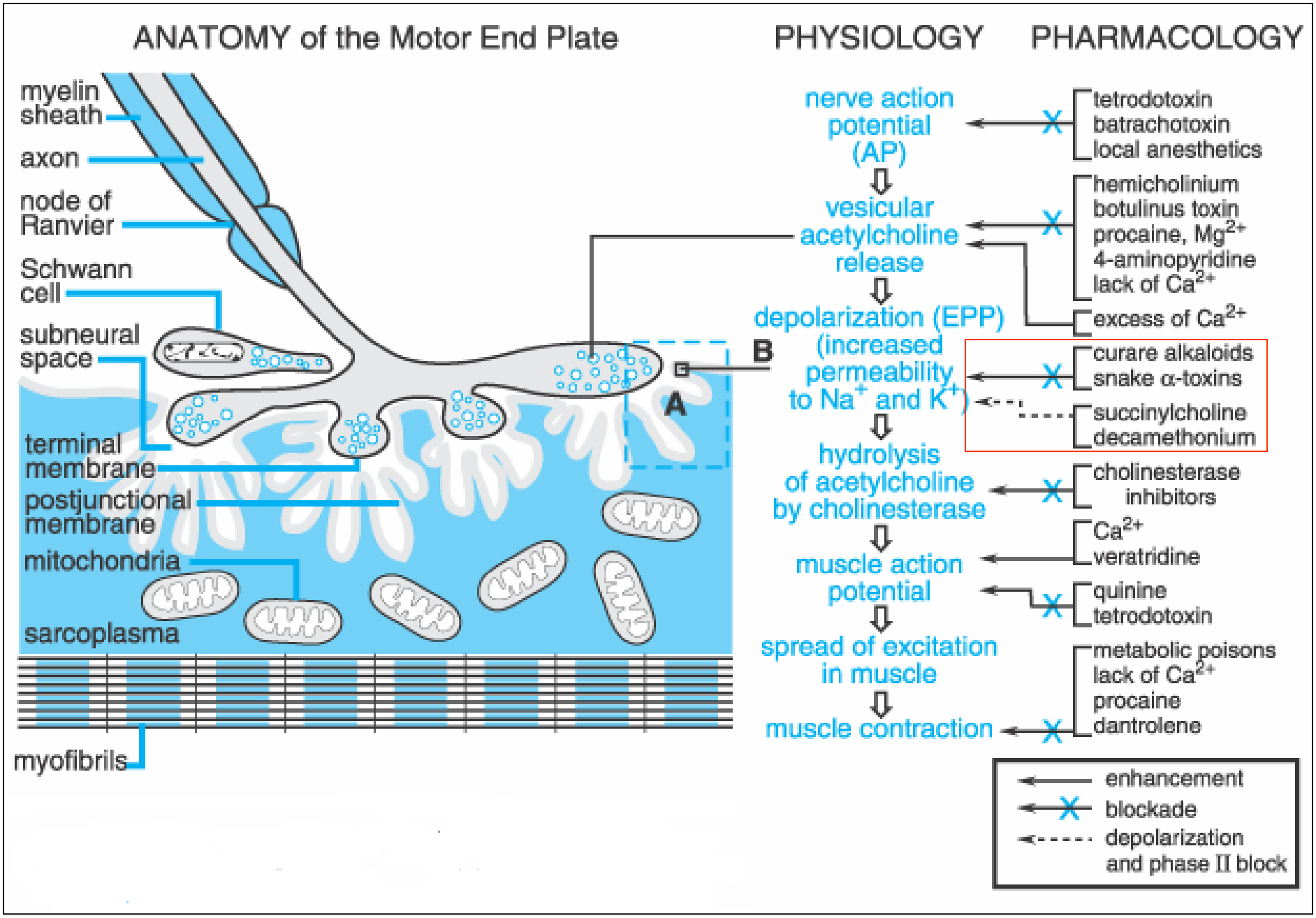


MECAMYLAMINE

NEUROMUSCULAR BLOCKING AGENTS

Skeletal muscle relaxants act peripherally at neuromuscular junction. According to their action they are divided into the following groups.

- Nondepolarizing (competitive) agents or curare-like drugs
- Depolarizing (hyperdepolarazing) agents


ANATOMY of the Motor End Plate
PHYSIOLOGY
PHARMACOLOGY
myelin sheath
axon
node of Ranvier
Schwann cell
subneural space
terminal membrane
postjunctional membrane
mitochondria
sarcoplasma
myofibrils
A
B
nerve action potential (AP)
vesicular acetylcholine release
depolarization (EPP) (increased permeability to Na+ and K+)
hydrolysis of acetylcholine by cholinesterase
muscle action potential
spread of excitation in muscle
muscle contraction
tetrodotoxin
batrachotoxin
local anesthetics
hemicholinium
botulinus toxin
procaine, Mg2+
4-aminopyridine
lack of Ca2+
excess of Ca2+
curare alkaloids
snake α-toxins
succinylcholine
decamethonium
cholinesterase inhibitors
Ca2+
veratridine
quinine
tetrodotoxin
metabolic poisons
lack of Ca2+
procaine
dantrolene
enhancement
blockade
depolarization and phase II block

NEUROMUSCULAR BLOCKING AGENTS

(1) Nondepolarizing (competitive) agents

Long acting: d-Tubocurarine, Pancuronium, Doxacurium, Pipecuronium

Intermediate acting: Atracurium, Vecuronium

Short acting: Mivacurium

(2) Depolarizing agents

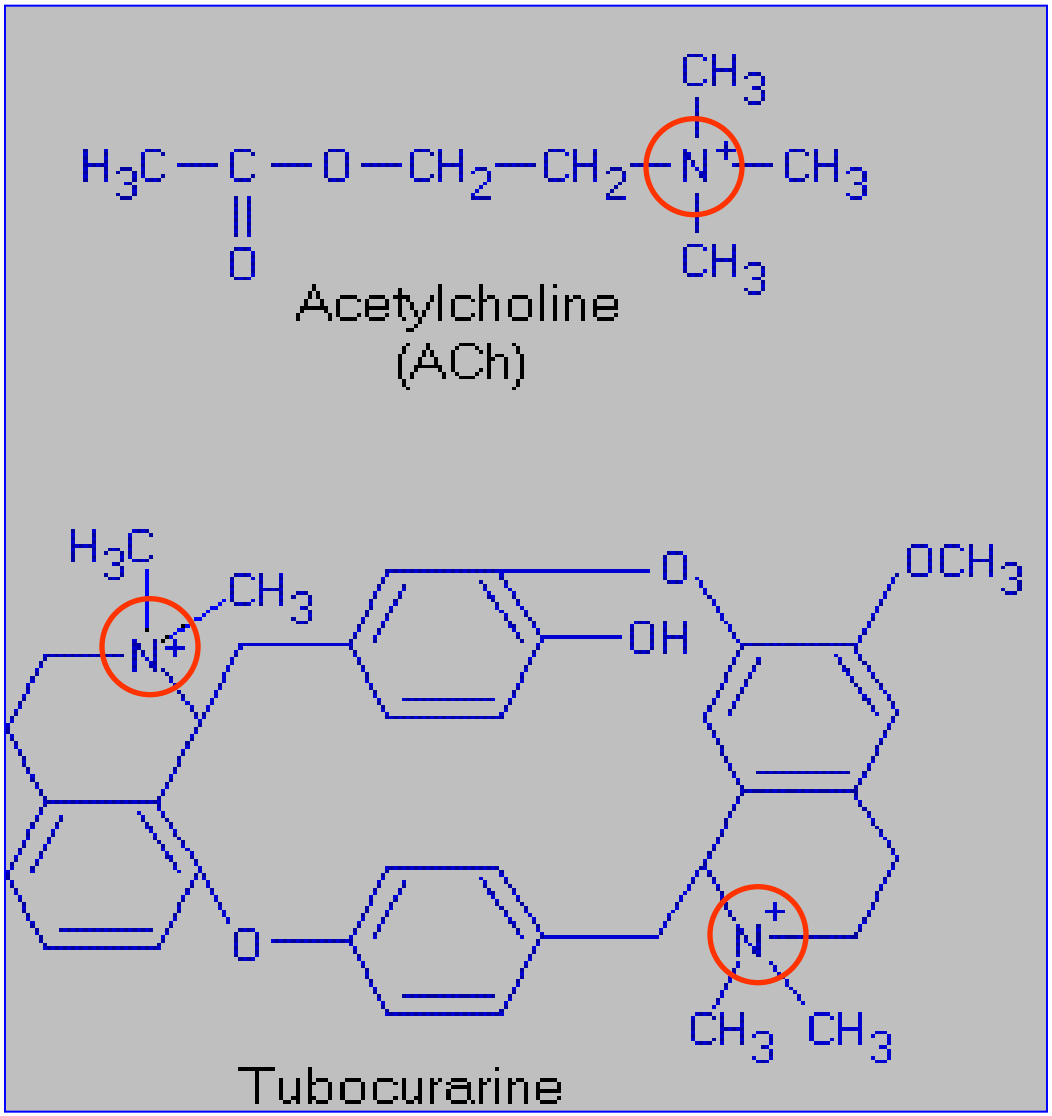
Suxamethonium (Succinylcholine)
Decamethonium (C-10)

Competitive (curare-like) blocking agents

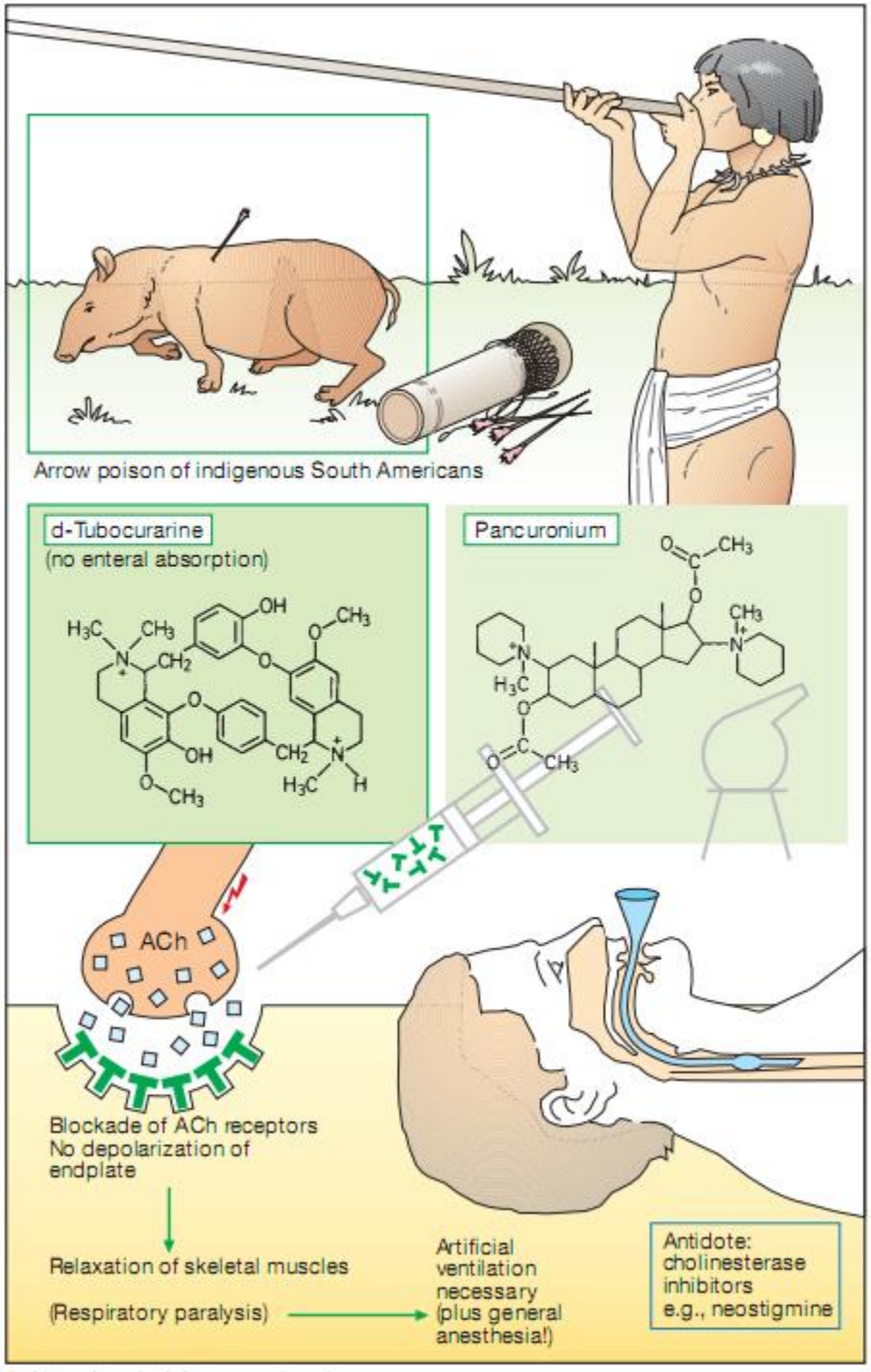
N^+ (14 Å) N^+

~~**GI resorption**~~

BBB



Curare is plant extract from *Chondrodendron tomentosum, Strychnos toxifera etc.* It is used by South America tribals as arrow poison for game hunting. The animals got paralyzed even if not killed by the arrow. Muscle paralyzing active principles of curare are **alkaloids tubocurarine, toxiferine** etc.



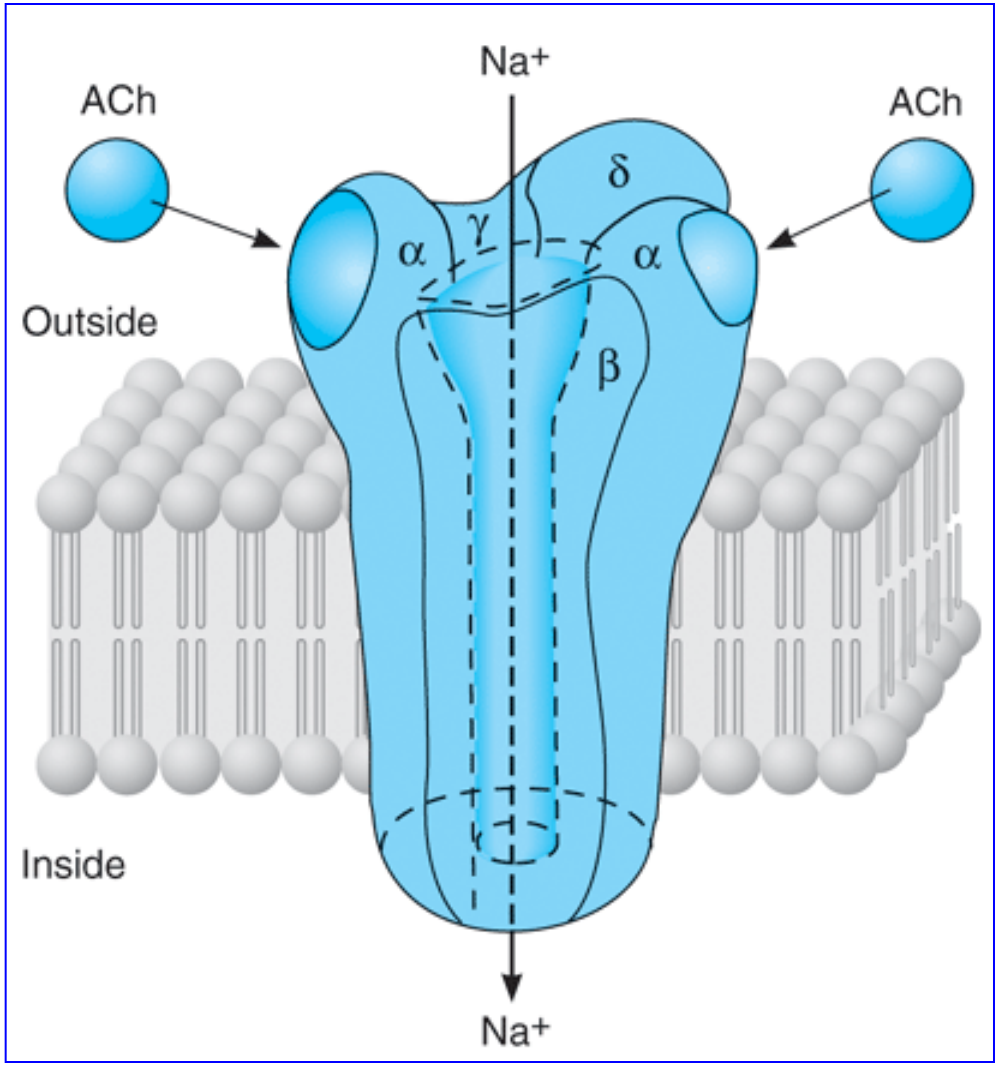
The South Americam lianas

Chondrodendron tomentosum

Strychnos toxifera

The competitive blockers have affinity for the nicotinic (N_M) cholinoceptors at the muscle end-plate, but no intrinsic activity.

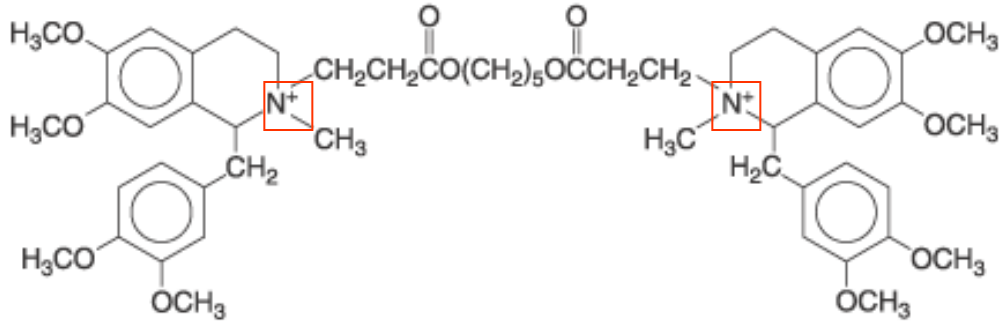
The N_M-receptor is a macroprotein with 5 subunits, which are arranged like a rosette surrounding the Na^+ channel. The two alpha subunits carry two ACh binding sites with negatively charged groups which combine with the cationic group of ACh and open Na^+ channel.



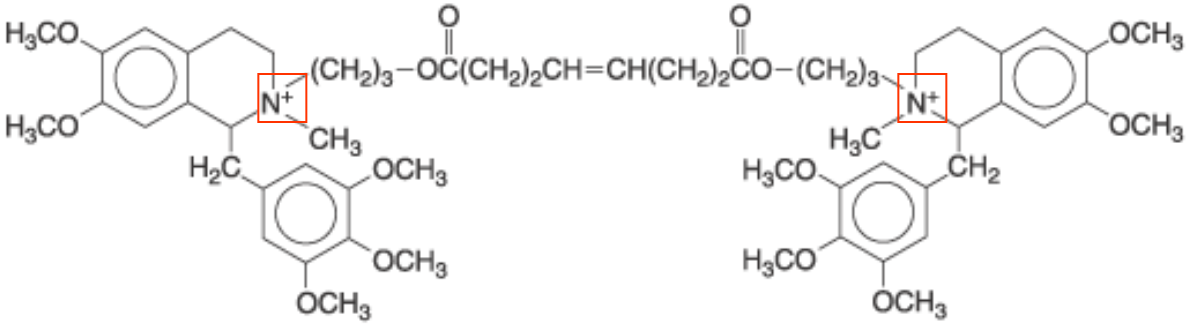
Competitive (nondepolarizing) block

Most of the competitive blockers have two or more quarternary N^+ atoms which provide the necessary attraction to the same site, but the bulk of the antagonist molecule does not allow conformational changes in the subunits needed for opening the channel. Competitive blockers generally have thick bulky molecules and were termed ***Pachycurare*** by Bovet (1951). ACh esterase released from motor nerve endings is not able to combine with its N_M-receptors to generate end-plate potential (EPP).

Competitive Agents

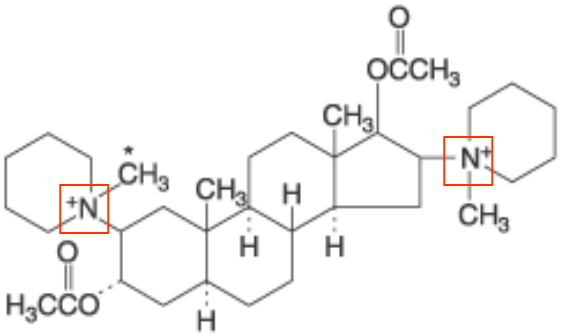


ATRACURIUM

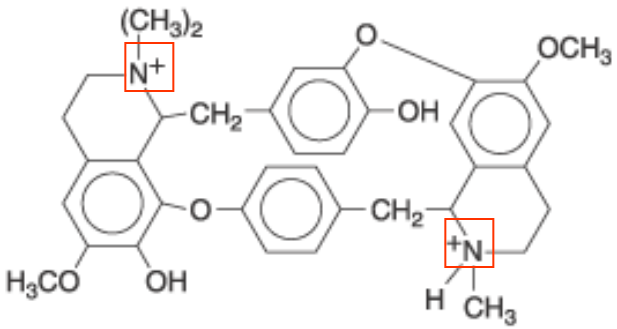


MIVACURIUM

N^+: quarter-nary N-atom



PANCURONIUM



TUBOCURARINE

Depolarizing block

Succinylcholine (SCh) and decamethonium have affinity as well as **submaximal intrinsic activity at the N_M-cholinoceptors**. They depolarize muscle end-plates by opening Na^+ channels (just as ACh does) and initially produce twitching and fascilations. These drugs do not dissociate rapidly from the receptor, induce prolonged partial depolarization of the region around muscle end-plate, and inactivation of Na^+ channels.

Depolarizing agents also have two quaternary N^+ atoms but their molecule is long, slender, and flexible. They are termed ***Leptocurare*** by Bovet (1951).

Depolarizing agents produce dual mechanism neuro-muscular blockade which can be divided in two phases:
Phase I block. It is rapid in onset, results from persistent depolarization of muscular end-plate and has features of depolarization blockade.
Phase II block. It is slow in onset and results from desensitation of the N_M-receptor to ACh. It superficially resembles block produced by tubocurarine.

Effects of neuromuscular blocking drugs

Skeletal muscles. Intravenous injection of competitive blockers rapidly produces muscle weakness, followed by flaccid paralysis. Small fast response muscles *(fingers, extraocular)* are affected first. Paralysis spreads to *hands, feet, arm, leg, neck, face, trunk,*

intercostal muscles, diaphragm, and respiration stops.
Recovery occurs in the reverse sequence: diaphragmatic contractions resume first.
Depolarizing agents produce fasciculations , lasting few seconds before inducing flaccid paralysis, but fasciculations are not prominent in well anaesthetized patients. The action of SCh develops very rapidly. Apnoea occurs within 45–90 sec, but lasts only 2–5 min and recovery is rapid.
Autonomic ganglia. Competitive blockers can produce some degree of ganglionic blockade. SCh as an agonist of N-receptors may cause ganglionic stimulation.
Histamine release with hypotension and bronchospasm can cause tubocurarine from the mast cells. This does not involve the immune system.

CVS. Tubocurarine produces significant fall in BP and sometimes – tachycardia (due to vagal ganglionic blockade). SCh initially produces bradycardia due to activation of vagal ganglia, followed by tachycardia and rise in BP, due to stimulation of sympathetic ganglia.

GIT. The ganglion blocking action of competitive agents may enhance postoperative paralytic ileus after abdominal operations.

Pharmacokinetics

All neuromuscular blockers are quaternary compounds. They are not absorbed in GIT, do not cross placental, and BBB. The unchanged drug is excreted in urine, and bile.

SCh is rapidly hydrolyzed by plasma pseudocholin-esterase to succinylmonocholine and then to succinic acid and choline (the action lasts 3–5 min). Some patients (1:3000) have genetically determined abnormality (low affinity for SCh) or deficiency of pseudocholin-esterase. In these patients SCh causes dominant phase II blockade, resulting in muscle paralysis and apnoea, lasting hours. In this case the intubation of the patient must be continuous until full recovery.

Indications

- The most important use of neuromuscular blockers is as *adjuvant drugs to general anaesthesia*. Surgical procedures are performed more safely and rapidly.

- *The competitive neuromuscular blockers* are particularly helpful in abdominal and thoracic surgery, intubation and endoscopies, orthopedic procedures.

- *SCh* is employed for brief procedures, e.g. endotracheal intubation, laryngoscopy, bronchoscopy, esophagoscopy, reduction of fractures, and dislocations.

- *SCh* is mostly used to avoid convulsions and trauma from electroconvulsive therapy.

- In severe cases of tetanus and status epilepticus, which are not controlled by diazepam or other anticonvulsive drugs, *competitive neuromuscular blockers are used*.

Main drug interactions

- There is *in vitro* incompatibility between SCh and thiopental (thiopentone).
- General anaestetics, aminoglysides (gentamicin, etc.) and hypokalemic diuretics potentiate competitive blockers.
- ***Anti-ChEs (galantamine, neostigmine) and amino-pyridine (Pymadine®) reverse the action of competitive neuromuscular blockers.***
- ***SCh potentiates malignant hyperthermia, produced by halothane. SCh has not any antagonists.***
- Calcium channel blockers potentiate both depolarizing and nondepolarizing neuromuscular blockers.
- Sympathomimetics (adrenaine, etc.) reduce the competitive block by increasing ACh release.

Depolarizing agents

SUCCINYLCHOLINE

DECAMETHONIUM

Action of succinylcholine (suxamethonium)

Toxicity

- Cardiac arrhythmias
- Prolonged apnoea
- Malignant hyperthermia (which needs treatment with directly acting muscle relaxant ***Dantrolene i.v.***)