Skeletal Muscle Relaxants

2019

Skeletal muscle relaxants

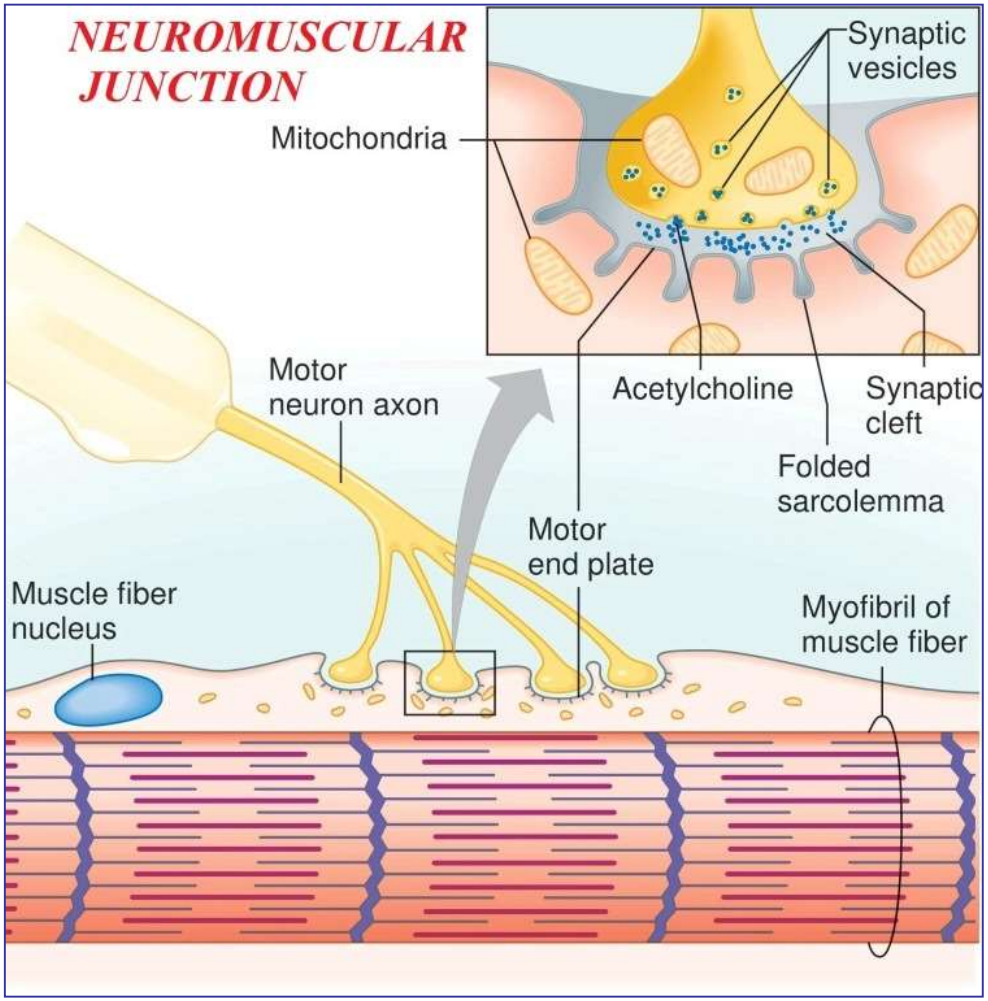
(neuromuscular blocking agents)

Cause decreased skeletal muscle tone and produce muscle paralysis

Primarily used in general anesthesia (to facilitate endotracheal intubation) and optimize surgical conditions

Only parenterally given

Neuromuscular junction (NMJ) - is the synapse or junction of the axon terminal and a motor neuron with the motor end plate



Neurotransmitter - acetylcholine

Main cholinergic transmission sites and receptors

1. Central nervous system — M and N_{CNS}
2. Autonomic ganglion (both sympathetic and parasympathetic) — N_G
3. Neuromuscular junction — N_M
4. Parasympathetic postganglionic nerve — M

M-muscarinic

N_{CNS} - nicotinic CNS type

N_G – nicotinic ganglion type

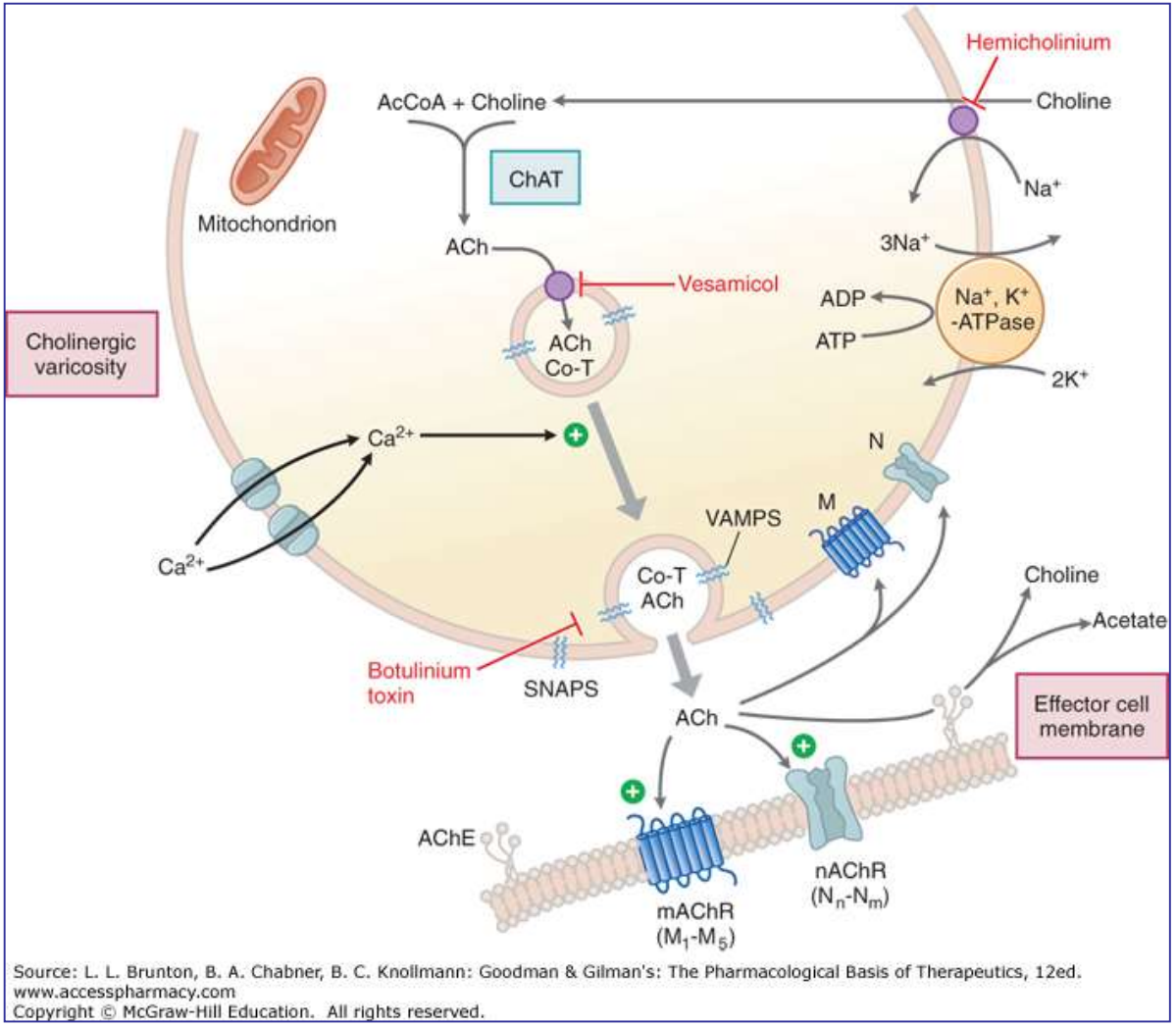
N_M – nicotinic muscle type

Praejunctional block

Ach synthesis inhibitor -
hemikolinium
(choline transport inhibitor)

Ach storage inhibitor
vesamicol

Ach release inhibitor -
aminoglycosides
BOTULINUM TOXIN



Effect of Botulinum toxin

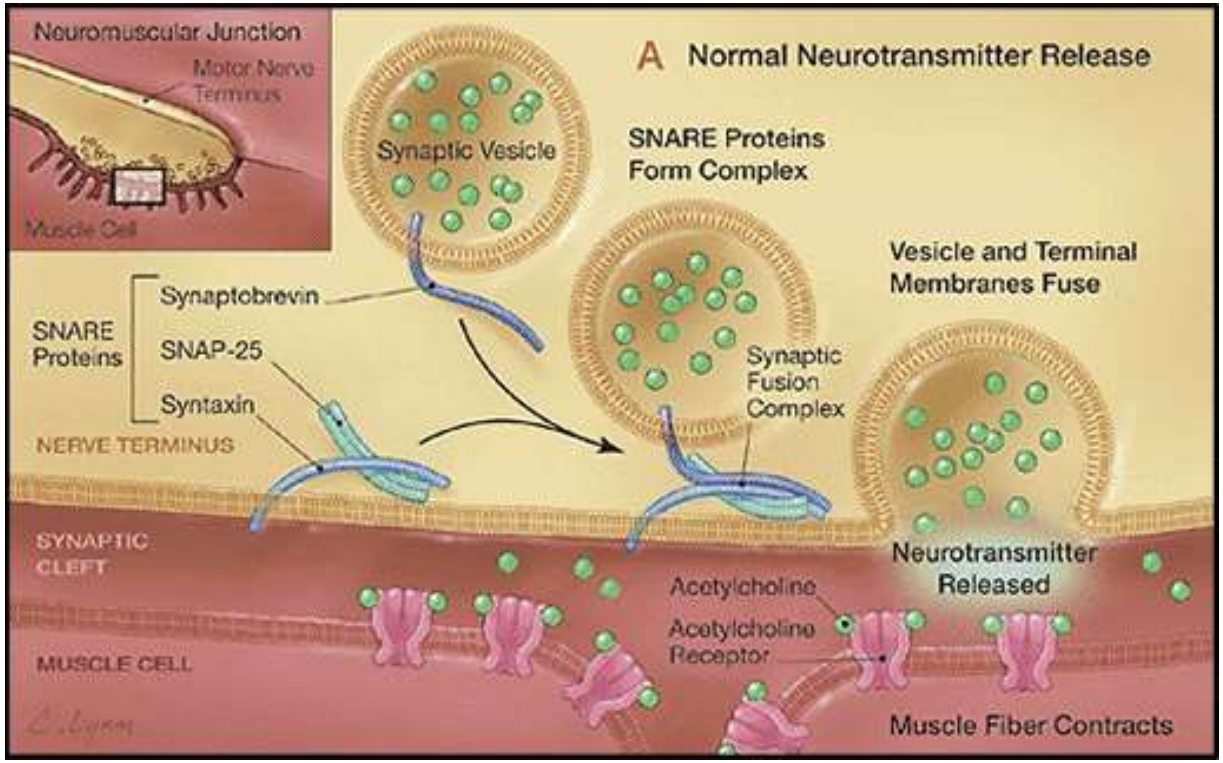
-three peptides needed to Ach release: SNARE proteins

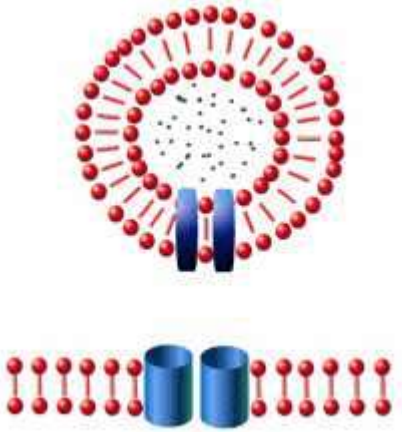
synaptic membrane-associated proteins

SNAP-25, syntaxin

vesicle–associated protein: synaptobrevin

-the toxin metabolizes SNAP-25 peptide





Botulinum toxin

Mechanism of action:

inhibit the ACh release

Therapeutic use:

in different spasms:

- hemifacial spasm
- after stroke (hand spasm)
- cervical dystonia

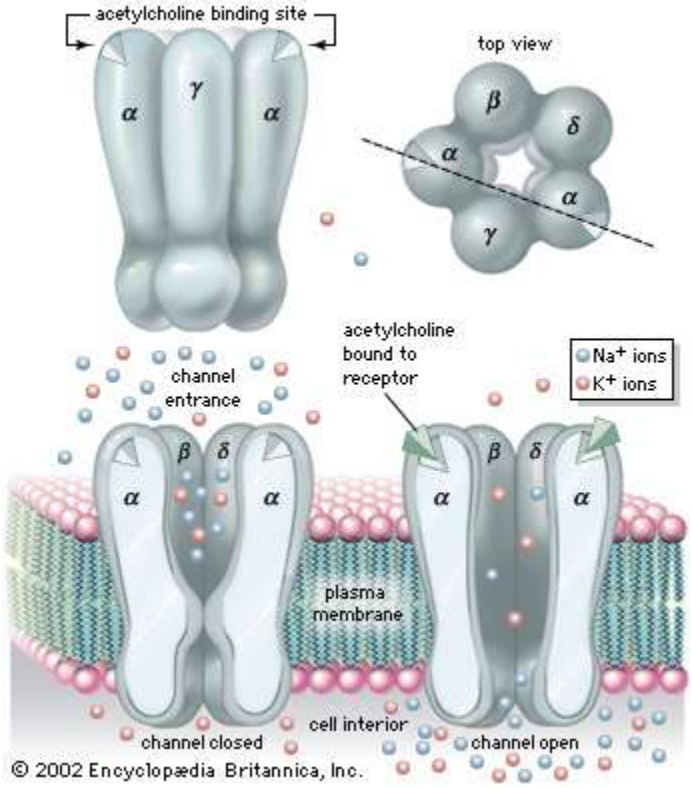
ophthalmic purpose

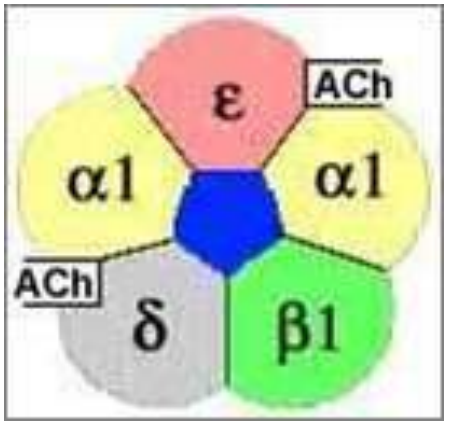
cosmetic procedure

Dose: 2.5 U (0.1 ml) max. 25 U

Effect: in 2-3 days, maximum in 5-6 weeks, until 12 weeks

Nicotinic acetylcholine receptors

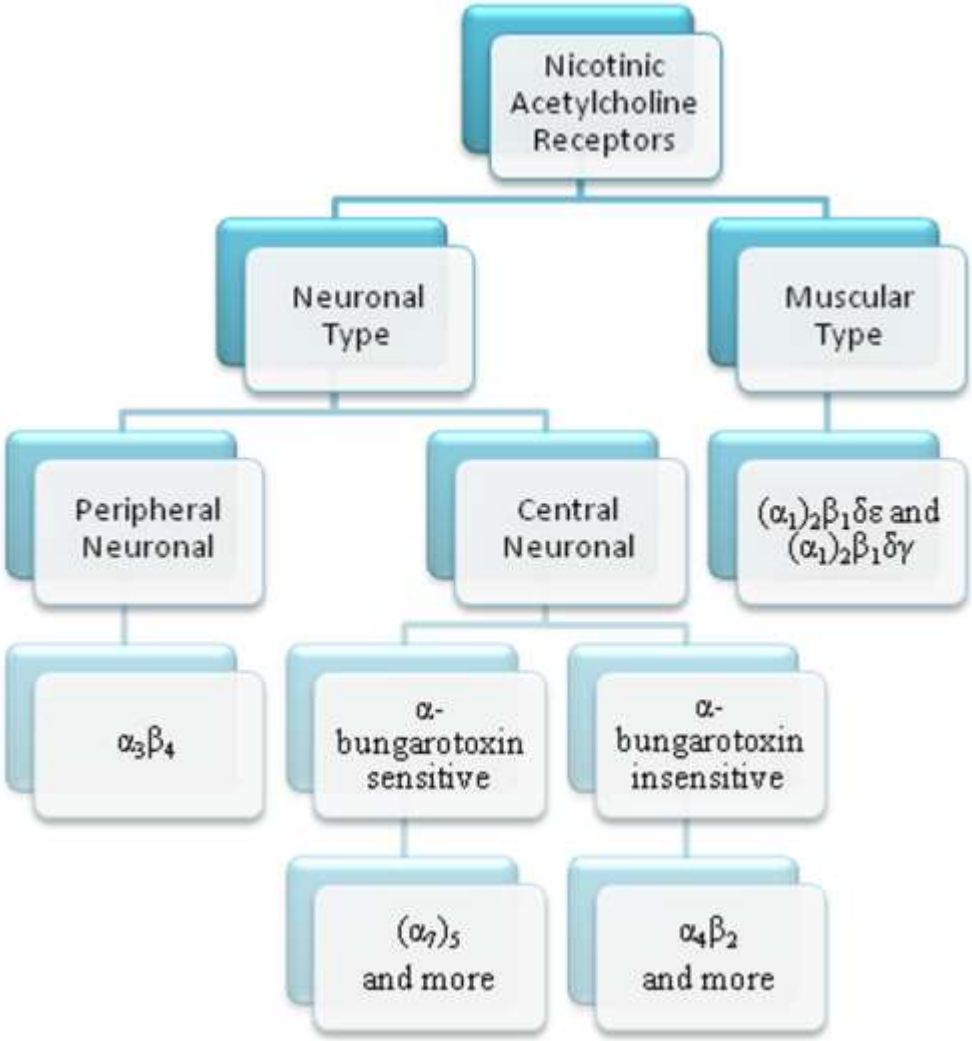




Heteromer receptor

- non-selective ligand-gated cation channels
- several different positively charged ions can cross through
- permeable to Na^+, K^+, with some subunit combinations also permeable to Ca^{2+}

Classes of nicotinic acetylcholine receptors

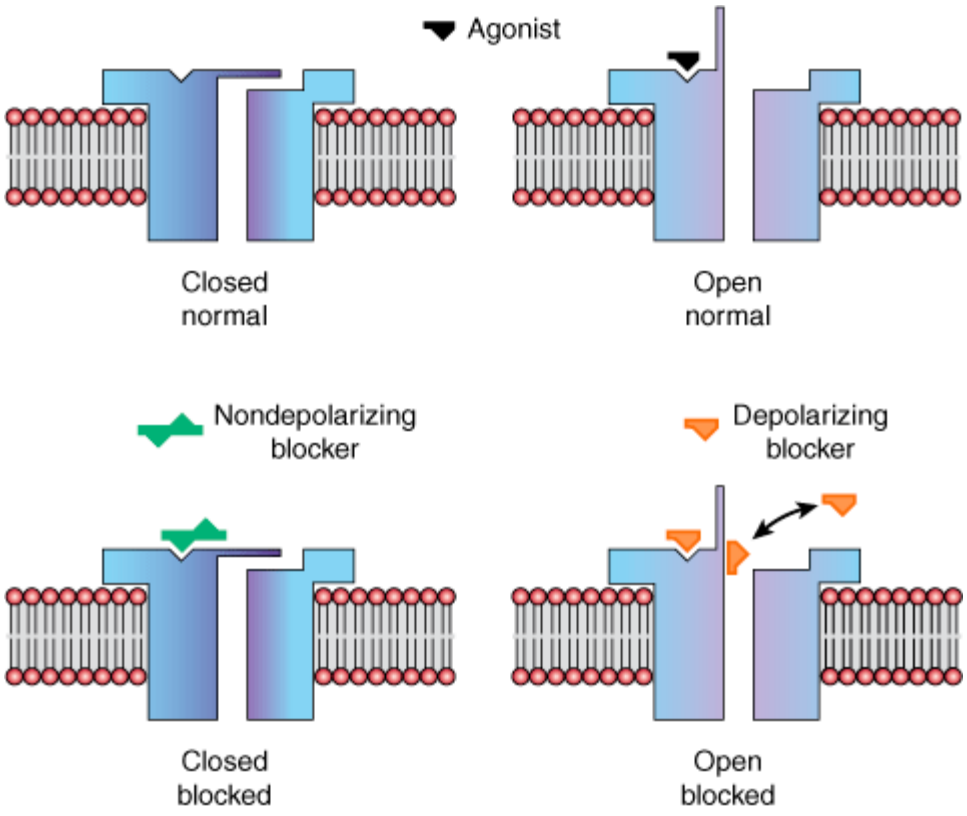


The action of the normal agonist, the non-depolarizing and the depolarizing blockers on the end plate channel

Top
- effect of the agonist (ACh)
- the ion-channel is opened

Bottom left
-non-depolarizing blockers after the binding to the receptor prevent opening of the channel

Bottom right
-after the initial depolarization they cause persistent depolarization of the channel, which leads to muscle relaxation block



1./ Non-depolarizing relaxant drugs

Competitive antagonist at nACh receptors

d-Tubocurarine - prototype

- it is now rarely used

alkaloids from Strychnos and Chondrodendrum

Strychnos toxifera

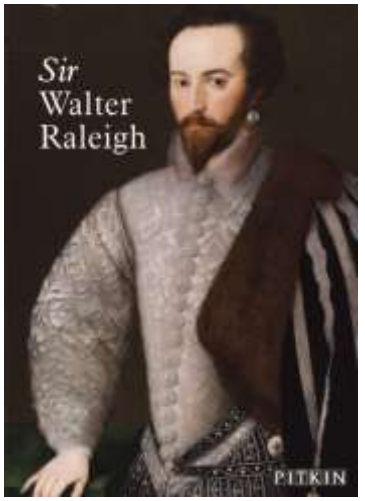
Curare

natives in the Amazon Basin of South America used curare as arrow poison

they tasted the extract to see if it was suitable for use

Curare

- Spanish writer - XVI. century –
  toxic arrow uses
- Sir Walter Raleigh 1595 and
  Acuna 1639 - effect of toxic arrow
- Leyden – 1744 - testing the effect
- Humboldt –
  detailed prescription of the poison
  preparation



Alexander von Humboldt
1769-1859

Claude Bernard – ligature (1857)

the beggining of the modern experimental pharmacology

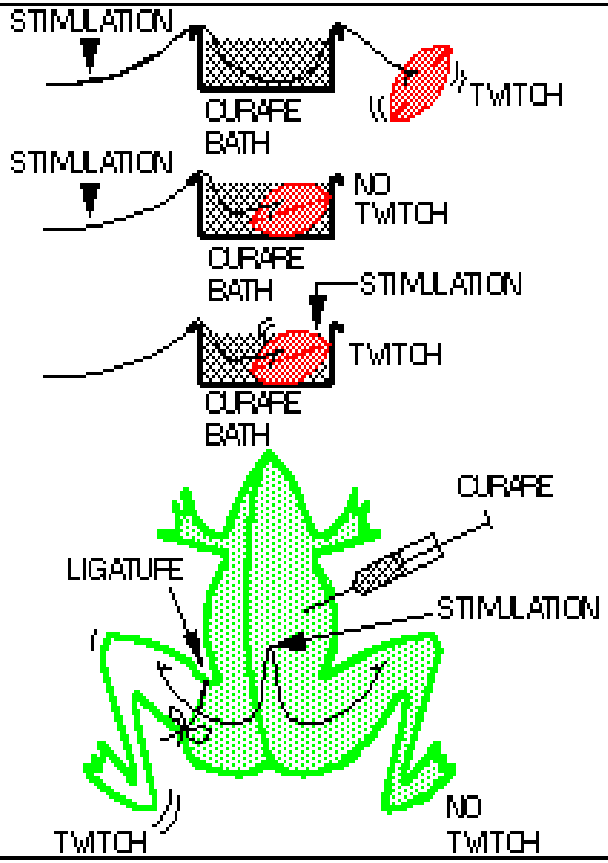
Hamilton - Timmons

A. Bathing the NERVE in a curare solution has no effect on the muscle contraction; the action potential travels through the solution unimpeded.

B. Bathing the MUSCLE in curare abolishes the contraction that would normally be produced by nerve stimulation.

C. Bathing the MUSCLE in curare does NOT prevent the contraction that results from the direct stimulation of the muscle; thus, the muscle fibers are not paralyzed by curare.

D. A tight ligature around the leg of an intact frog prevents injected curare from reaching that limb. Stimulation of the nerves that cause the legs to move results in no contraction of the leg that is affected by curare, but DOES cause twitching of the leg that has been protected from the curare by the ligature. This provides further confirmation that curare does not impair either the nerve or the muscle, but rather acts at the JUNCTION between the nerve and muscle.



History of the developent of the non-depolarizing relaxant

1935 Preparation of the crystalline D-tubocuraine

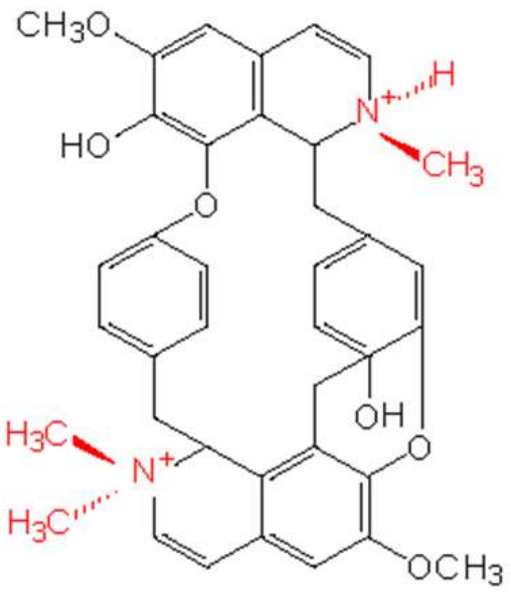
1942 First successful human application of D-tubocurarine
Harold Griffith (anesthetist)

1962 Pancuronium – first administration

1980 Vecuronium – new chemical structure (amino steroid and benzylisoquinoline)

1990 Mivacurium

d-Tubocurarine (dT)



dose: per os ineffective

5-10 mg subling.

10-15 mg iv. (30-40 min)

Narrow margin between therapeutic dose and toxic dose

25-30 mg – respiratory (diaphragmatic) paralysis

d-Tubocurarine

Therapeutic indication

historically known and important,
it is rarely used because safer alternatives

Pharmacokinetics

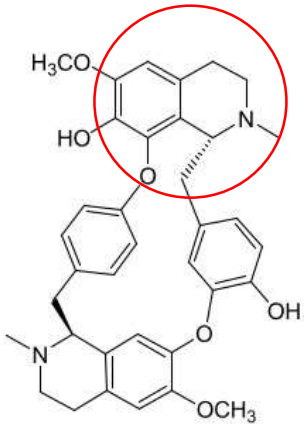
quaternary substance, does not cross the BBB
it is not metabolized

Side effects:

allergic reaction (histamine release from mast cells)
muscle weakness
headache

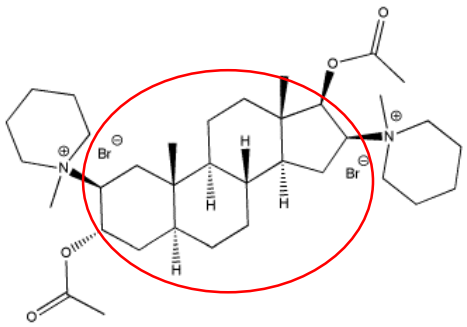
Isoquinoline derivatives

	relative potency to tubocurarine
Tubocurarine →	1
Atracurium	1,5
Doxacurium	6
Metocurine	4
Mivacurium	4



Aminosteroid derivatives

Pancuronium →	6
Pipecuronium	6
Rocuronium	0,8
Vecuronium	6



Classification of the non-depolarizing relaxant drugs according to the duration of action

- Long acting > 35 min
  - d-tubocurarine
  - pancuronium
  - pipecuronium
  - alcuronium
  - doxacurium
- Intermediate acting 20-35 min
  - vecuronium
  - atracurium
  - cisatracurium
  - rocuronium
- Short acting 10-20 min
  - mivacurium

Long acting non-depolarizing relaxants
(> 35 min)

Pancuronium - 5-6x stronger

40-50 min

there is no histamine-releaser and ggl-blocker effect

inhibit the cardiac muscarinic receptors - tachycardia

release of noradrenalin

Pipecuronium

there is no histamine-releaser effect - bradycardia

Alcuronium

60-80 min

natural alkaloid

Doxacurium

90-120 min

Metocurin 23x stronger

Gallamin – first synthetic compound – 1946 - Daniel Bovet

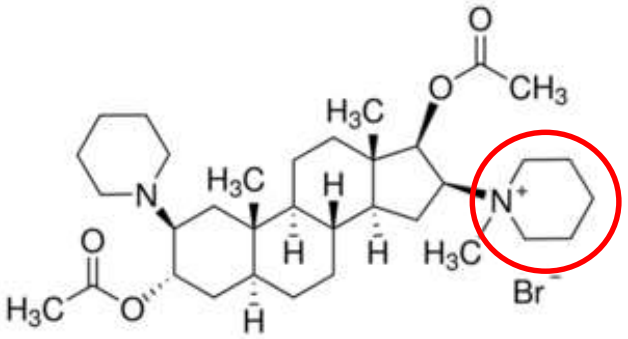
short and week effect, there is no ggl. blocker effect, atropin-like effect on the heart

it is not metabolized, crossed the placenta

Intermediate acting non-depolarizing relaxant (20-35 min)

Vecuronium

Clinically more commonly used



Atracurium

stronger than dT

the main breakdown product is laudanosine,
it has longer elimination half-life (150 min)
crosses the BBB and in high concentration cause seizure
cisatracurium – produces less laudanosine

Rocuronium

30-40 min, onset 1-2 min

Short-acting non-depolarizing relaxants (10-20 min)

Mivacurium

shortest duration of action

pseudo-cholinesterase break down quickly

4x more effective than dT

TIVA (total iv. anesthesia)

antidote: neostigmine

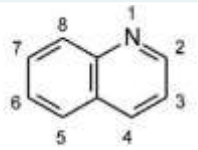
Gantacurium

new class of non-depolarizing relaxants

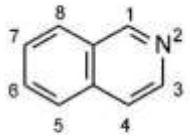
rapid onset

Classification of non-depolarizing relaxant according to the chemical structure

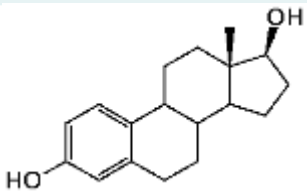
Isoquinoline derivatives	Steroid derivatives	Miscellenous
Tubocurarine	Pancuronium	Gallamin
Atracurium	Vecuronium	Alcuronium
Cisatracurium	Pipecuronium	Fazadinium
Doxacurium	Rocuronium	
Mivacurium		
Metocurium		
Gantacurium		

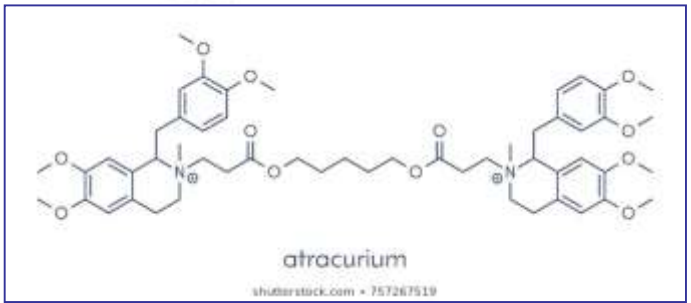


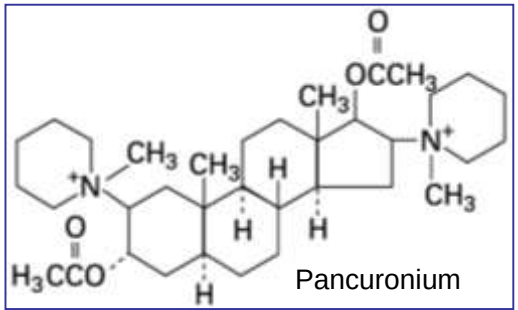
kinolin

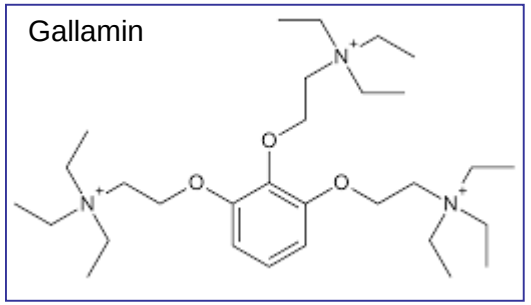


izokinolin

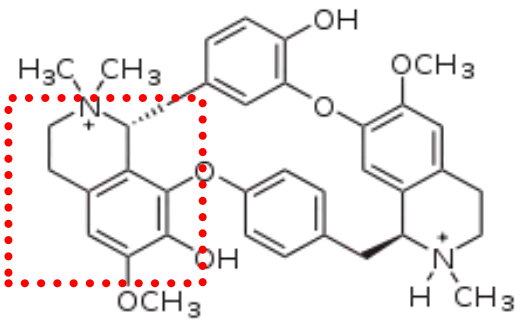








Isoquinolin derivatives

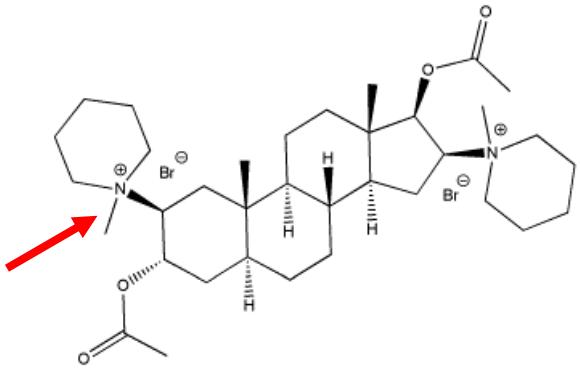


- the main breakdown product is laudanosine, Lipophilic – epileptiform seizure (ciszatracurium- produses less laudanosine)

	Effect on the ganglion	Release of histamine	During of action (min)
tubocurarin	weak	moderate	> 35
atracurium/ cisatracurium#	Ø	weak	20-35
alcuronium	Ø	Ø	20-35
doxacurium	Ø	Ø	> 35
mivacurium*	Ø	weak	10-20 min dose-dependent

* - cholinesterase metabolises, repeted administration (TIVA)

Steroid derivatives



	Effect on the ganglion	Release of the histamine	Duration of action (min)
Pancuronium*	**Ø**	**Ø**	**> 35**
pipecuronium	**weak**	**Ø**	**> 35**
rocuronium#	**Ø**	**Ø**	**20-35**
vecuronium	**Ø**	**Ø**	**20-35**

TIVA

* - increased NA release + vagolytic effect – tachycardia

\# - week vagolytic effect

2./ Depolarizing neuromuscular blocking drug

They act like nicotinic agonists

1st phase – initial depolarization

2nd phase – desensitization

Indications:

- adjunct to anasthesia

(facilitating tracheal intubation, improves intraoperative surgical conditions)

- treatment of convulsion (associated with epilepsy or local anesthetic toxicity)
- respiratory distress syndrome

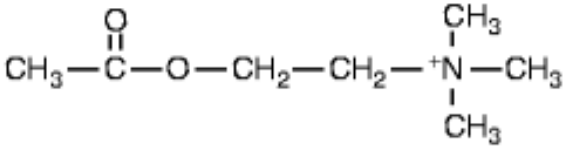
2./ Depolarizing neuromuscular blocking drug

Suxamethonium/Succinylcholine

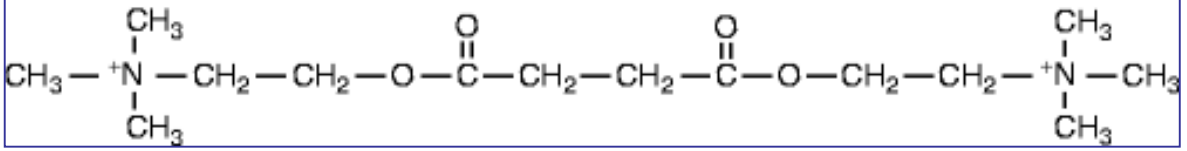
Daniel Bovet developed – 1949

ultra short acting, 5-10 min (only iv.)
two linked acetylcholine molecule

Acetylcholine



Succinylcholine
(= Diacetylcholine)



Depolarizing neuromuscular blocking drug

Succinylcholine

- metabolized by plasma cholinesterase

Therapeutic indication

rarely – placement of endotracheal tube at start of anesthetic procedure
control of muscle contractions in status epilepticus

Side effects:

-malignant hyperthermia (43ºC) treatment: DANTROLENE
-arrhythmia (bradycardia, tachycardia)
-increased intraocular pressure
-prolonged respiratory depression
-hypersensitive reactions
-myalgia (postoperative)

Indications

Non-depolarizing relaxant

prolonged relaxation for surgical procedure

antagonist: acetylcholinesterase inhibitors
(e.g. neostigmine)

Depolarizing relaxant

placement of endotracheal tube at start of anesthetic procedure

There is no antagonist!

Interactions with other drugs

Non-depolarizing relaxants

Anesthetics – inhaled anesthetics (isoflurane)
strongly potentiate and prolong NMJ blockade

Antibiotics – aminoglycosides produce increased blocking effect

Local anesthetics

in low dose - enhancement of blockade

in high dose – inhibit ACh release, complete NMJ blockade

Antiarrhythmic drugs – increased blockade (lidocaine, quinidine)

Depolarizing relaxants

Esther derivative local anesthetics can prolong the effect of suxamethonium because of the competition for the pseudo-cholinesterase binding site

Centrally acting spasmolytic

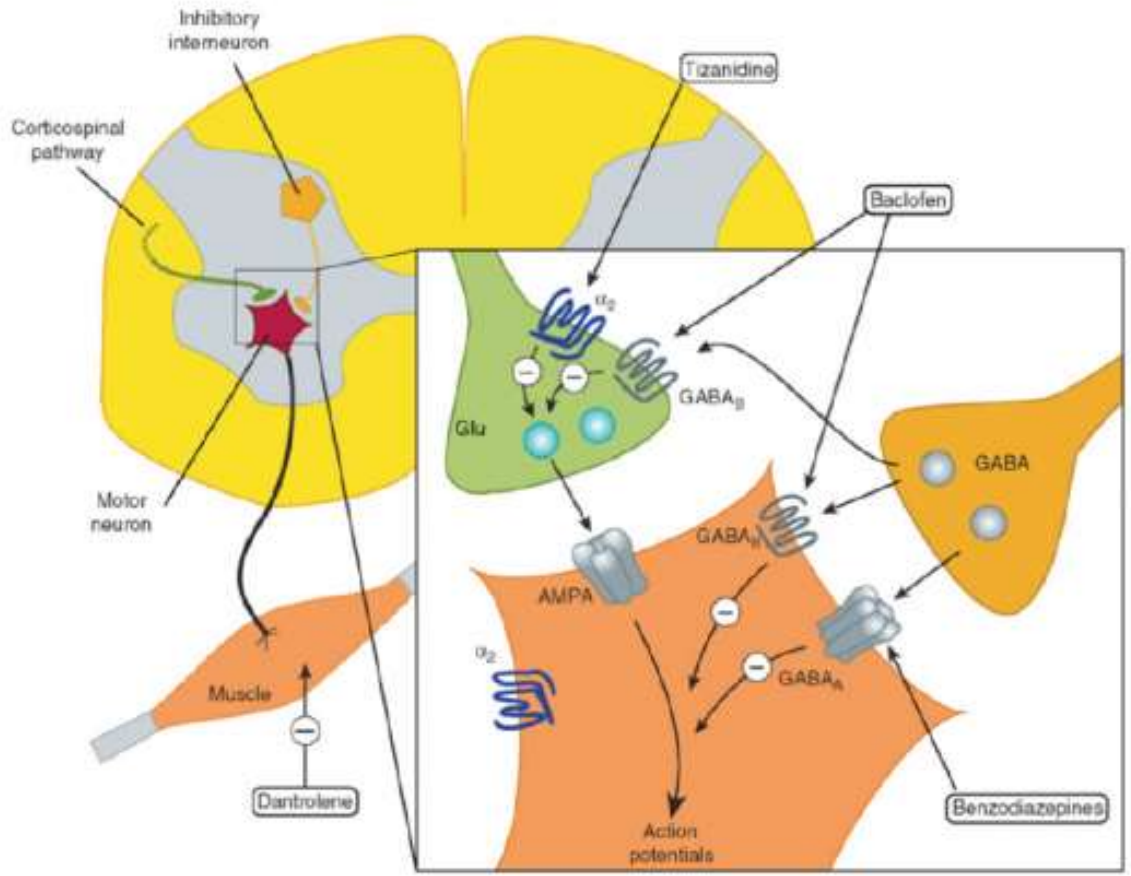


Figure 3. Two binding locations of antispasticity agents.
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; **GABA**, gamma-aminobutyric acid; **Glu**, glutamate

Centrally acting pasmolytic drugs

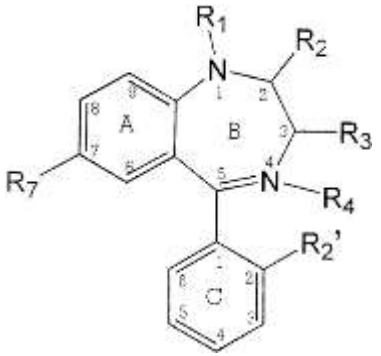
- **Diazepam** – GABAa agonist
- **Baclofen** – $GABA_B$ agonist
- **Tizanidine**

- Other -

  riluzole – possibly inhibit glutamatergic transmission

  antiepileptics - gabapentin and progabide

Benzodiazepines



Diazepam, tetrazepam

Reduces spasticity in the spinal cord

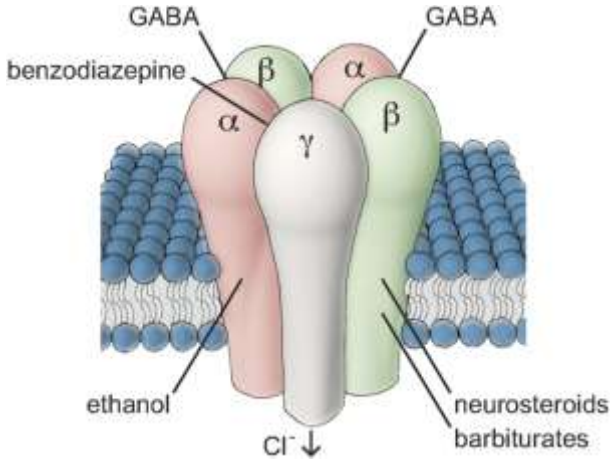
Mechanism of action

Acts at GABA-erg interneurons - $GABA_A$ receptor agonist

Anxiolytic effect

Side effects

sedation, tolerance and dependence

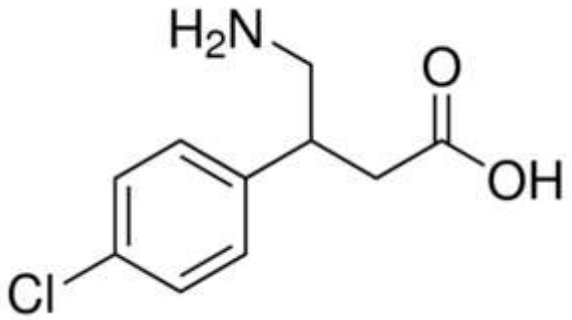


Baclofen

Inhibit the monosynaptic and polysynaptic reflexes

Mechanism of action:

$GABA_B$ mimetic agent, selective **agonist (Gi)**



Orally active

Crosses BBB

Side effects

Increased seizure activity, hallucination

Tizanidin

Per os - „first pass" metabolism (30%) – CYP1A2

Mechanism of action - α2-agonist such as clonidine

Indication

Stroke, SM, amyotrophic lateral sclerosis

Side effects

Sedation, hypotonia, bradycardia,

rarely hepatotoxicity

Other spasmolytics

- Dantrolene

  inhibit Ca++ release from the sarcoplasmatic reticulum

- Botulinum toxin

  Ach – exocytosis inhibition – SNAP 25 break down

Dantrolene

Direct muscle effect

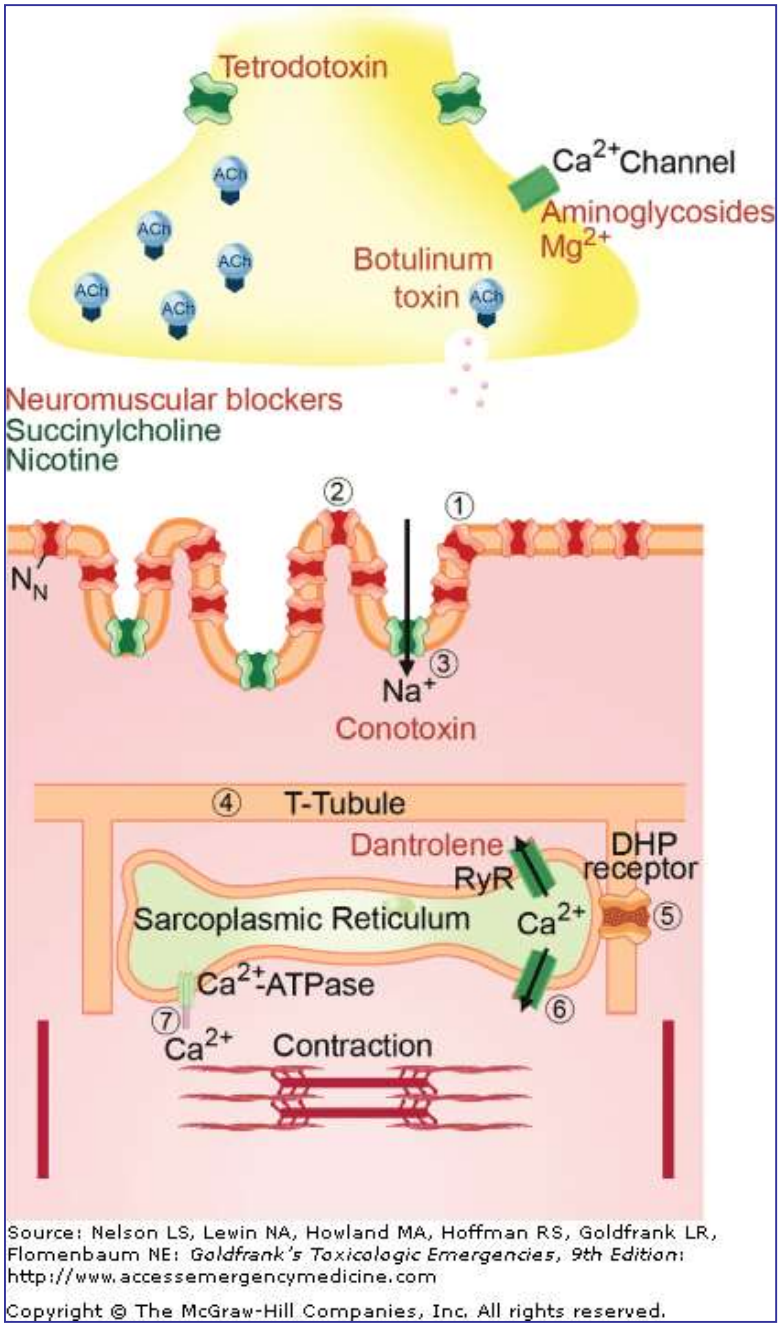
hydantoin derivative

Indication

malignant hyperthermia
spasms

Side effects

Muscle weakness,
sedation, euphoria
Rarely severe hepatotoxic effect



Source: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE: *Goldfrank's Toxicologic Emergencies, 9th Edition*: http://www.accessemergencymedicine.com

Neurolept malignant syndrome (NMS), malignant hypertermia (MH), versus serotonin malignant syndrome

NMS

Antipsychotic

Haloperidol, chlorpromazine, thioridazine

Antiemetics

Clozapine, risperidone

Side effects :mental disturbances, muscle rigidity, hyperthermia >40^{o}C, tachycardia

Therapy - Dantrolene,
Benzodiazepines
Dopamine agonists

Malignant hypertermia

Ryanodine receptor mutation

Neuromuscular junction relaxants

Succinylcholine

Inhalational narcotics

Halothane

Side effects

Muscle rigidity

Hyperthermia

Tachycardia

Therapy – dantrolene – hyperthermia

benzodiazepines – agitation

dopaminerg transmission does not included

Serotonin malignant syndrome

SSRI, Opioids, TCA, MAO inhibitors, Serotonin releaser