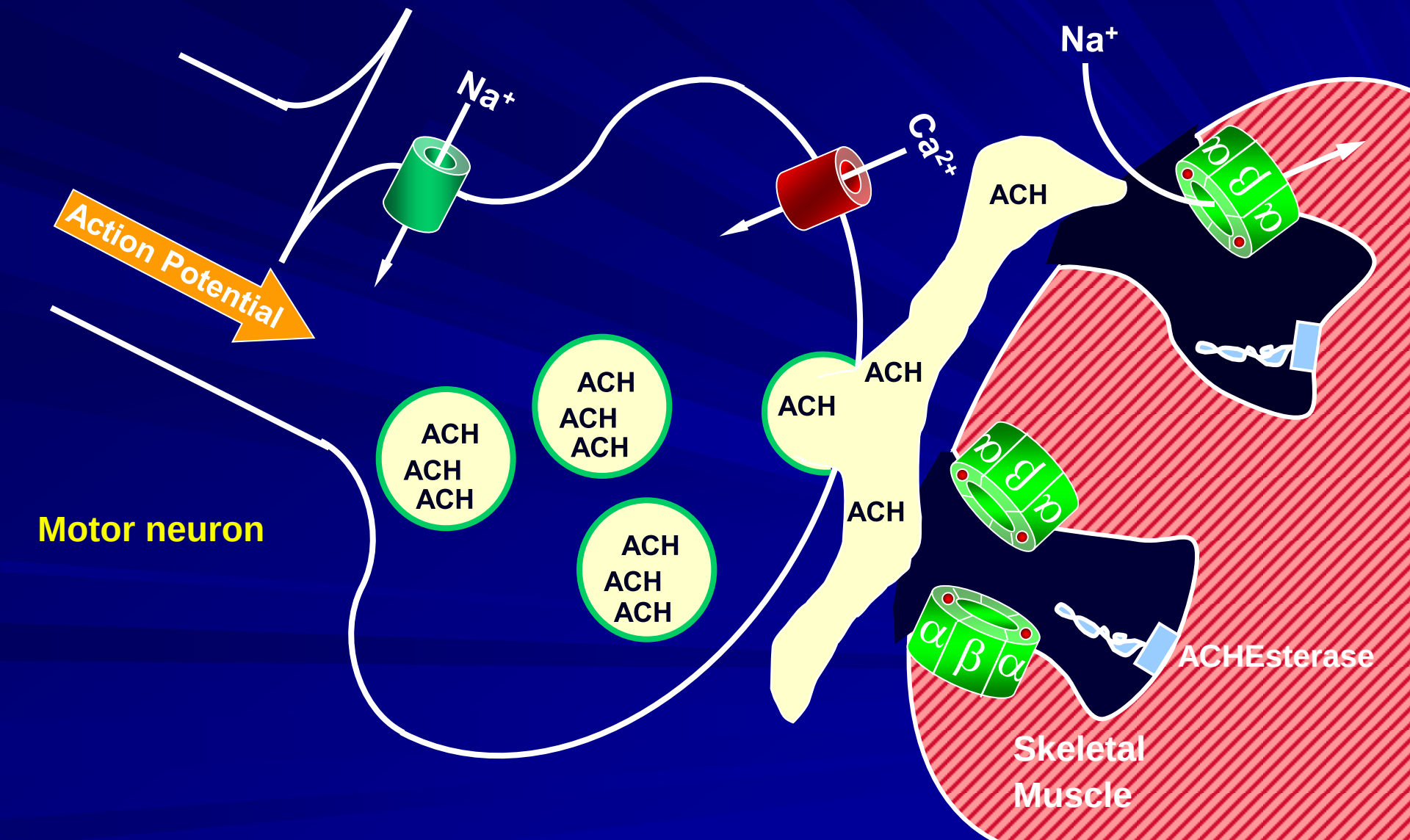
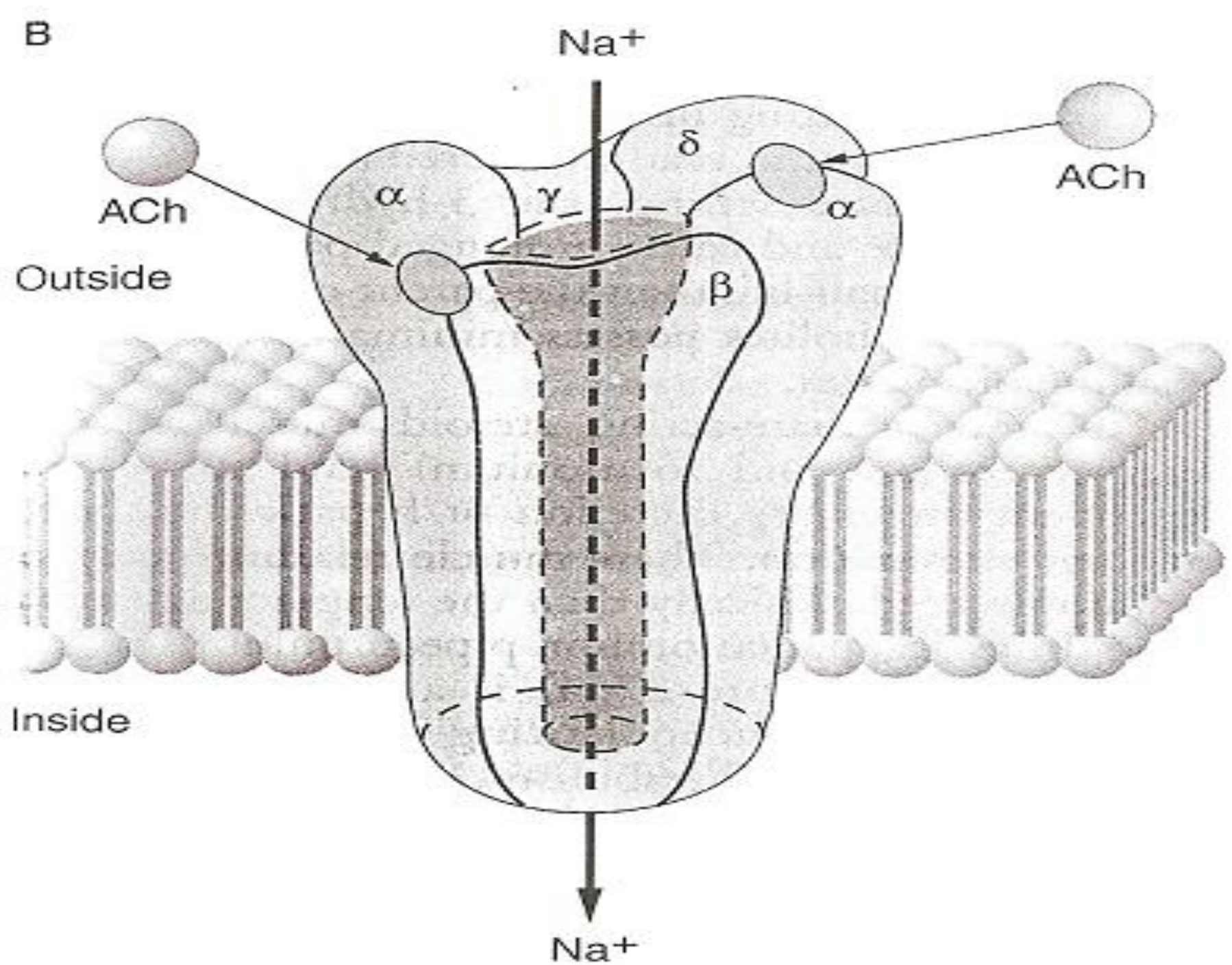
Skeletal Muscle Relaxants

Neuromuscular Blockers




B
Na+
ACh
ACh
α
γ
δ
α
β
Outside
Inside
Na+

Skeletal Muscle Relaxants

- Neuromuscular Blockers:
  - Nondepolarizing Drugs
  - Depolarizing Drugs

- Spasmolytics.
- Directly Acting Drug.

Neuromuscular blockers

- Non depolarizing agents
- Isoquinilone
  - Tubocurarine
  - Doxacurium
  - Atracurium
  - Metocurine
  - Mivacurium

Steriod

-Pancuronuium

-Pipecuronium

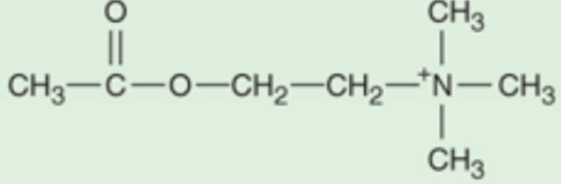
-Rapacuronium

-Rocuronium

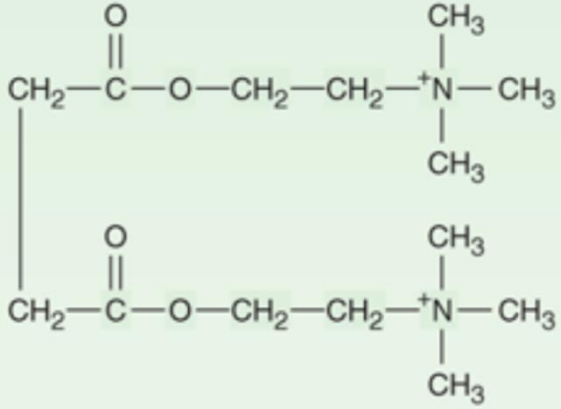
- Vecuronium

Neuromuscular Blockers

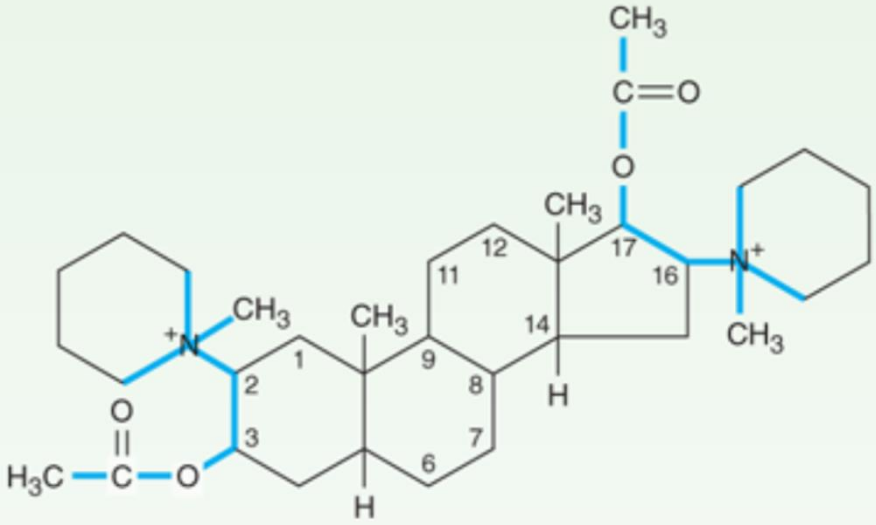
- **Chemistry:**
  - One or two quaternary nitrogen's, i.e. poorly lipid soluble or highly polar compounds.
  - Double acetylcholine molecules linked:
    - End to end.
    - Concealed, bulky semi- rigid ring systems.



Acetylcholine



Succinylcholine



Pancuronium

Neuromuscular Blockers

- **Pharmacokinetics:**
  - Must be given parenterally.
  - Nondepolarizing Drugs:
    - Excreted in the kidney metabolized by the liver.
    - Mivacurium is metabolized by cholinesterases.
    - Atracurium is spontaneously broken down (HOFMAN ELIMINATION)….Laudanosine

Depolarizing agents

- Suxamethonium (Succinylcholine)
- Decamethonium

These drugs are structural analogue pf acetylcholine .

These are used parentrally

Neuromuscular Blockers

- **Pharmacokinetics:**
  - Depolarizing Drugs:
    - Extremely short duration(5-10 minutes).
    - Metabolized by cholinesterases in the plasma and liver.
    - Only a small percentage reaches the neuromuscular junction, where it diffuse away into the extracellular fluid.
    - Some patients have a genetically abnormal variant of plasma cholinesterase.
    - *Dibucaine Number:* is a measure of the ability of a patient to metabolize succinylcholine.

Table 27–1. Some properties of neuromuscular blocking drugs.

Drug	Elimination	Clearance (mL/kg/min)	Approximate Duration of Action (minutes)	Approximate Potency Relative to Tubocurarine
Isoquinoline derivatives				
Atracurium	Spontaneous[1]	6.6	20–35	1.5
Cisatracurium	Mostly spontaneous	5–6	25–44	1.5
Doxacurium	Kidney	2.7	> 35	6
Metocurine	Kidney (40%)	1.2	> 35	4
Mivacurium	Plasma ChE[2]	70–95	10–20	4
Tubocurarine	Kidney (40%)	2.3–2.4	> 35	1
Steroid derivatives				
Pancuronium	Kidney (80%)	1.7–1.8	> 35	6
Pipecuronium	Kidney (60%) and liver	2.5–3.0	> 35	6
Rocuronium	Liver (75–90%) and kidney	2.9	20–35	0.8
Vecuronium	Liver (75–90%) and kidney	3–5.3	20–35	6
Depolarizing agent				
Succinylcholine	Plasma ChE[2] (100%)	>100	< 8	0.4

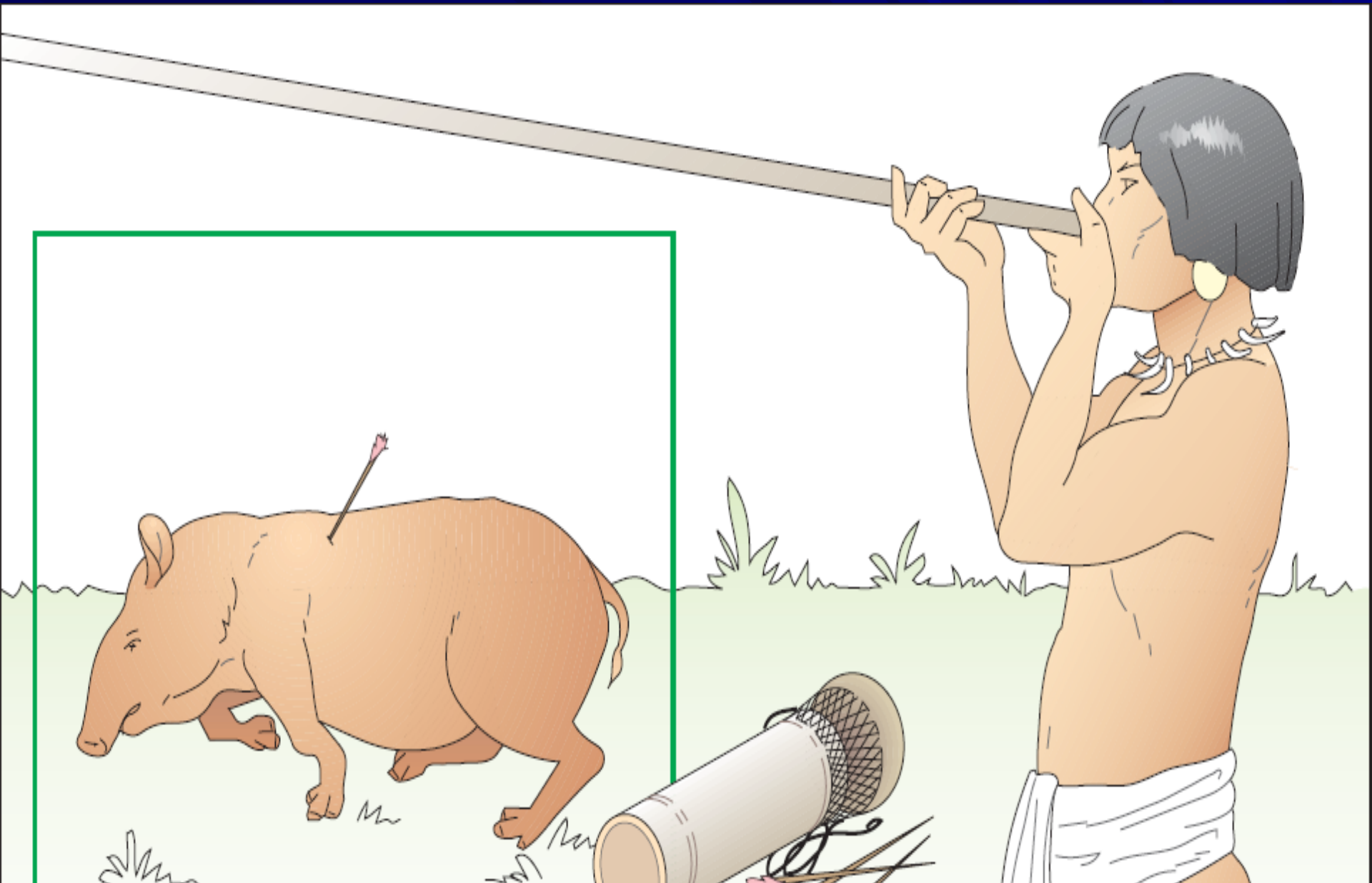
[1]Nonenzymatic and enzymatic hydrolysis of ester bonds.
[2]Butyrylcholinesterase (pseudocholinesterase).

Properties of neuromuscular blockers

Drug	Elimination via	Duration of action (minutes)
Short-acting		
Succinylcholine	Plasma AChE	5-10
Mivacurium	Plasma AChE	10-20
Intermediate-acting		
Atracurium	Spontaneous	20-35
Vecuronium	Hepatic and renal	20-35
Rocuronium	Hepatic and renal	20-35
Long-acting		
Pancuronium	Renal	60

Neuromuscular Blockers

- **Mechanism of Action**
  - Nondepolarizing Drugs:
    - Compete with acetylcholine at the nicotinic receptor sites at the NMJ.
    - In high doses, can enter the pore of the ion channel to cause a more intense blockade.
    - Can also block prejunctional sodium channels to interfere with the mobilization of acetylcholine at the nerve ending.



non-depolarizing blockers
Tubocurarine

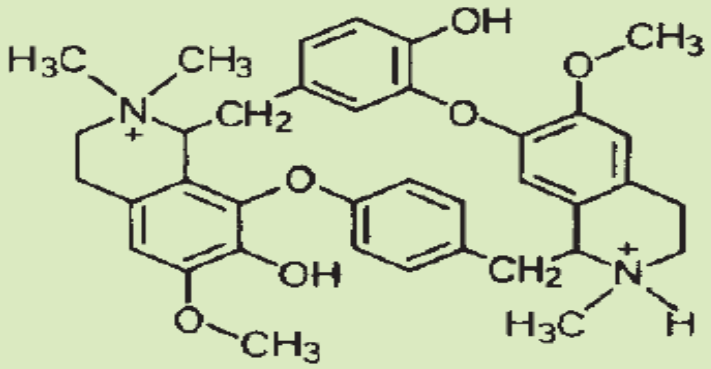
***Tubocurarine is given by i.v. injection*.**

Mechanism of action

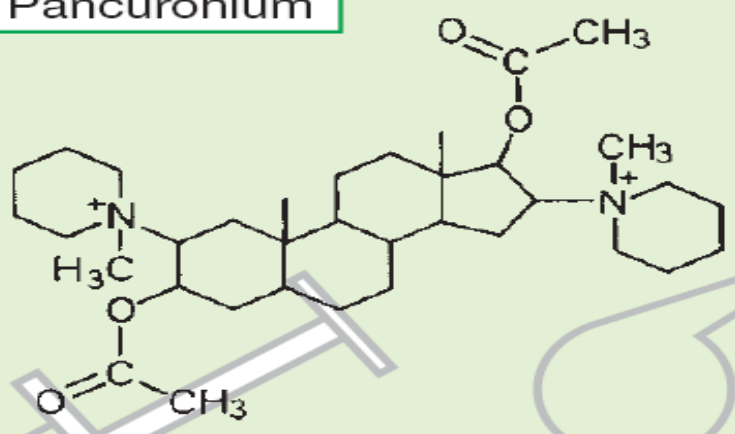
- **It binds to the endplate nicotinic cholinoceptors without exciting them, acting as a *competitive antagonist towards ACh.***
- **Muscular paralysis develops within about 4 min. *d-Tubocurarine does not* penetrate into the CNS.**

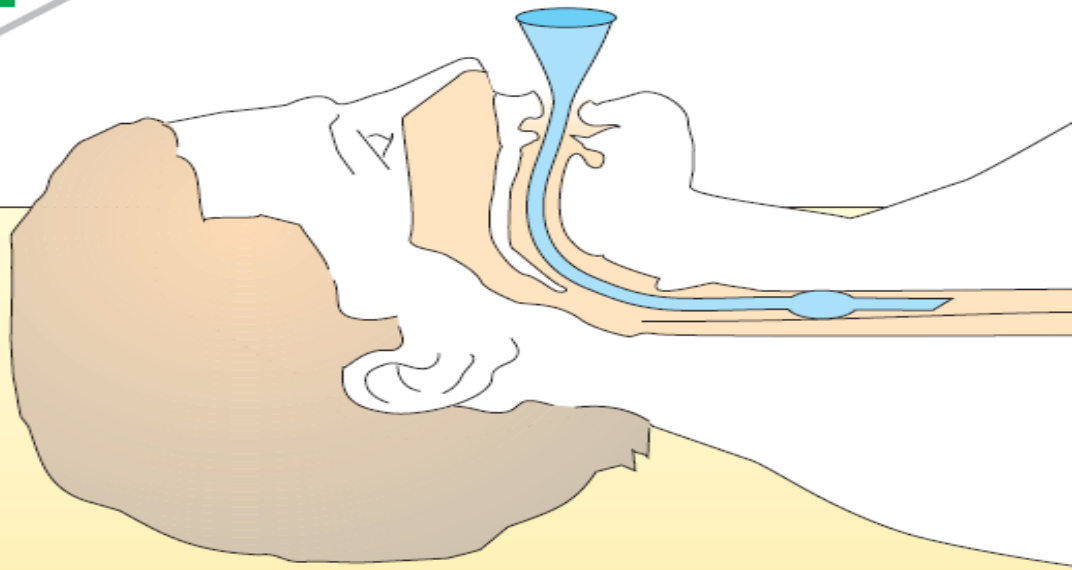
- **The patient would thus experience motor paralysis and inability to breathe, while remaining fully conscious but incapable of expressing anything**

d-Tubocurarine
(no enteral absorption)



Pancuronium





Blockade of ACh receptors
No depolarization of endplate

Relaxation of skeletal muscles

(Respiratory paralysis) → Artificial ventilation necessary (plus general anesthesia!)

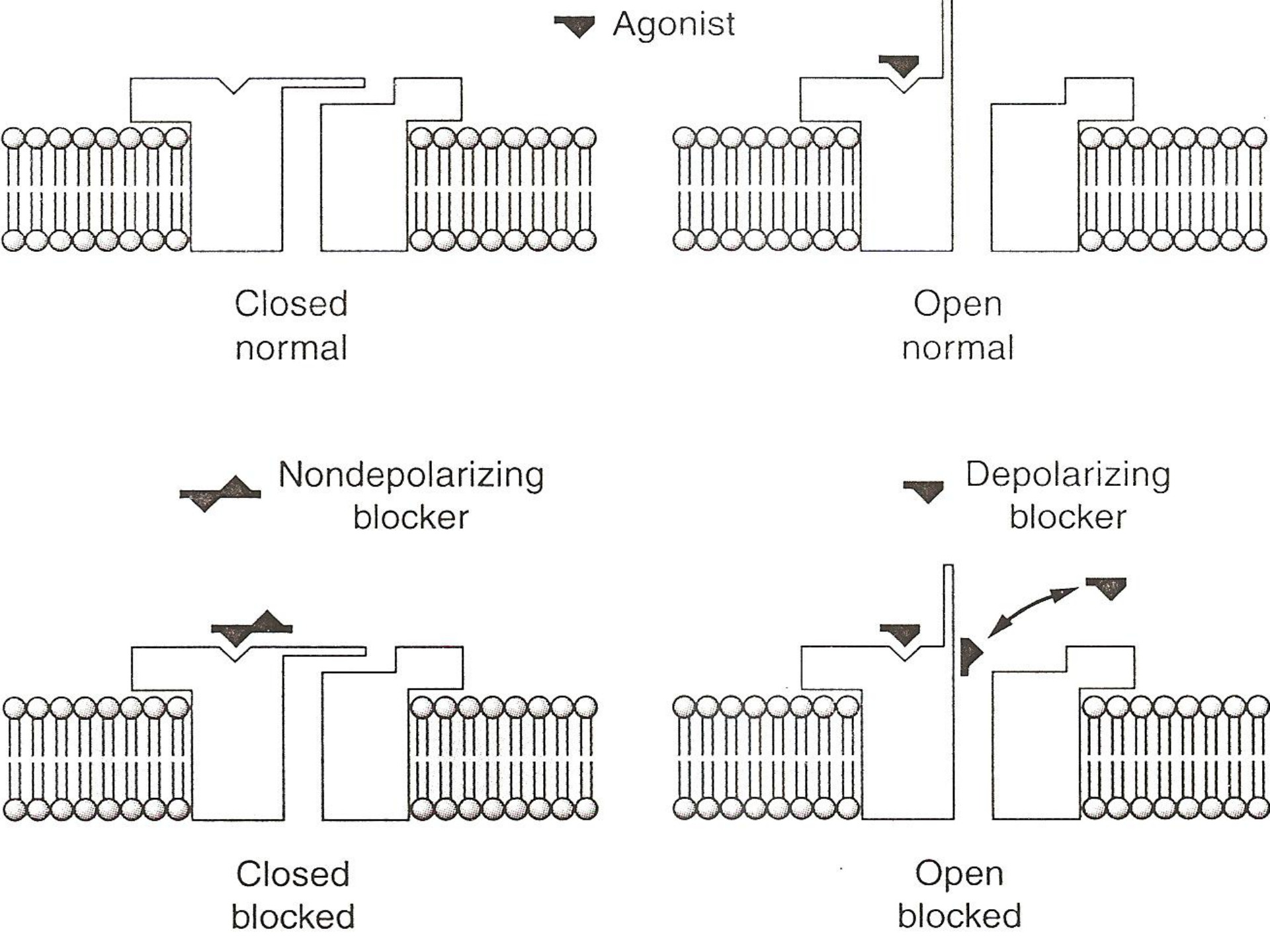
Antidote:
cholinesterase inhibitors
e.g., neostigmine

Neuromuscular Blockers

- **Mechanism of Action:**
  - **Depolarizing Drugs:**
    - ***Phase I Block(depolarizing):*** **succinycholine reacts with nicotinic receptors to opens the channel and cause depolarization of the motor end plate which will spread to adjacent membranes, causing contractions of muscle motor units.**
    - **Can enter the channel to produce a prolonged "flickering" of the ion conductance.**
    - **The depolarized membranes remain depolarized and unresponsive to subsequent impulses causing paralysis which is augmented by cholinesterse inhibitors.**

Neuromuscular Blockers

- **Mechanism of Action:**
  - **Depolarizing Drugs:**
    - ***Phase II Block(desensitizing):*** **with continued exposure, depolarization decreases and the membrane becomes repolarized and can not be depolarized again because it is desensitized. This may be due to blockade of ion channel, which might be more important than the action of the agonist at the receptor, i.e. the channels behave as if they are in a prolonged closed state.**
    - **This phase is reversed by acetylcholinesterse inhibitors.**


Agonist
Closed
normal
Open
normal
Nondepolarizing
blocker
Depolarizing
blocker
Closed
blocked
Open
blocked

Clinical use of neuromuscular blockers

- Muscle relaxation during surgical procedures
- Endotracheal intubation
- Maintain controlled ventilation

neuromuscular blockers interactions

- Potentiated by inhaled anesthetics (Isoflurane)
- Potentiated by aminoglycosides and calcium channel blockers
- Can block autonomic ganglia at higher doses
- Respiratory paralysis

Actions of Neuromuscular Blockers

- **Skeletal Muscle Paralysis:**
  - Nondepolarizing Drugs:
    - Onset of effect is very rapid.
    - Motor weakness followed by flaccidity.
    - Starts with small muscles, large muscles are more resistant to blockade and recover more rapidly. Diaphragm is last to be paralysed.
    - Effects lasts for 45-60 minutes.

Actions of Neuromuscular Blockers

- **Skeletal Muscle Paralysis:**
  - Nondepolarizing Drugs:
  - Depolarizing Drugs:
    - Action stars by transient muscle fasiculations over the chest and abdomen within 30 seconds.
    - Paralysis develops rapidly (within 90 seconds), the arm, neck, and leg muscles followed by the respiratory muscles.
    - Blockade lasts less than 10 minutes.

Actions of Neuromuscular Blockers

- **Skeletal Muscle Paralysis.**
- **Cardivascular Effects:**
  - Mediated by autonomic or histamine receptors.
  - Both sympathetic and parasympathetic ganglia and muscarinic receptors in the heart can be stimulated.
  - Usually cause hypotension, which can be attenuated by antihistamines.

Actions of Neuromuscular Blockers

- **Skeletal Muscle Paralysis.**
- **Cardivascular Effects.**
- **Hyperkalemia:**
  - In patients with burns, nerve damage, or neuromuscular disease, head injury, and other trauma.
  - Can result in cardiac arrest.

Actions of Neuromuscular Blockers

- **Skeletal Muscle Paralysis.**
- **Cardivascular Effects.**
- **Hyperkalemia:**
- **Increased Intraocular Pressure:**
  - Due to tonic contraction of myofibrils or transient dilation of ocular blood vessels.
- **Increased Intragastric Pressure:**
  - In obese, heavily muscled, diabetics, traumatic patients, fasiculations of succinylcholine can cause regurgitation and aspiration of gastric contents.
- **Muscle Pain:**
  - Due to unsynchronized contractions of adjacent muscle fibers just before the onset of paralysis.

Spasmolytics

- Chronic neurologic diseases
  - Multiple Sclerosis

- Acute Injury
  - Spinal cord damage, muscle inflammation

Goal of therapy: Reduce spasticity and pain, while retaining function

Spasmolytic Drugs

- **Diazepam:**
  - **Acts at $GABA_A$ receptors in the CNS.**
  - **Sedative.**

Spasmolytic Drugs

- **Baclofen:**
  - Acts at $GABA_B$ receptors, resulting in hyperpolarization and presynaptic inhibition through reducing calcium influx.
  - Can also reduce spasticity by inhibiting release of substance P in the spinal cord.
  - Less sedative, but can cause drowsiness.
  - Can be given intrathecally.
  - Can reduce craving in alcoholics and in migraine.

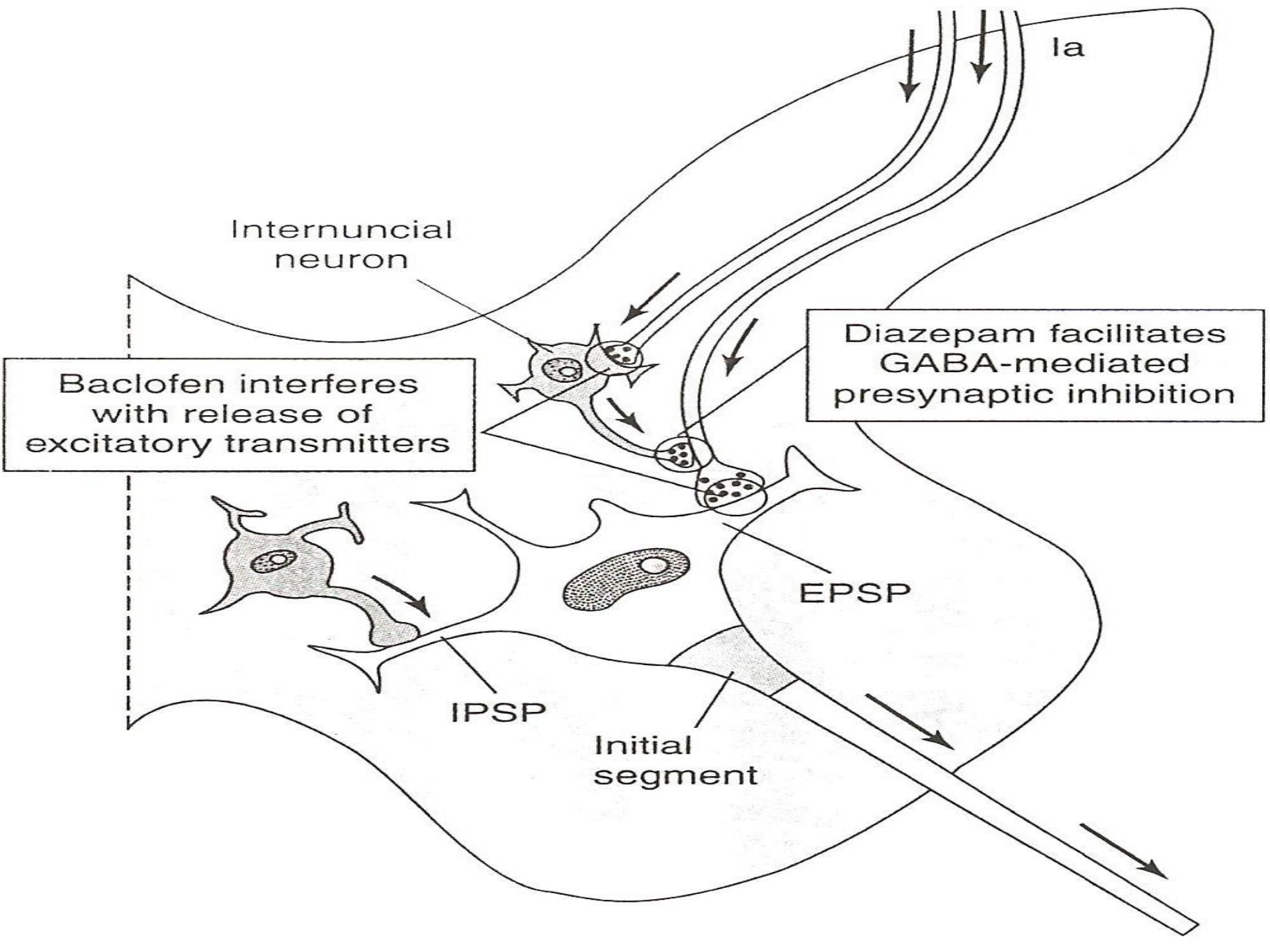
Spasmolytic Drugs

- **Tizanidine:**
  - **Related to clonidine.**
  - **α2-Adrenoceptor agonist**
  - **Presynaptic and postsynaptic inhibition of reflex motor output**

  Indications: Spasm due to multiple sclerosis, stroke, amyotrophic lateral sclerosis

  Pharmakokinetics: Renal and hepatic elimination • duration, 3–6 h •

  Toxicities: Weakness, sedation • hypotension
- **Gabapentin:**
  - **An antiepileptic Glycine.**


Ia
Internuncial neuron
Baclofen interferes with release of excitatory transmitters
Diazepam facilitates GABA-mediated presynaptic inhibition
EPSP
IPSP
Initial segment

Directly Acting Drugs

- **Dantrolene:**
  - Related to phenytoin, an antiepileptic.
  - Interferes with excitation-contraction coupling in the muscle fibers by interfering with the release of activator calcium by binding with the ryanodine receptor (RyR) channel of the sarcoplasmic reticulum.
  - Useful in treatment of malignant hyperthermia

Malignant Hyperthermia

- Rare heritable disorder triggered by a variety of stimuli, including general anesthetics and neuromuscular blockers.
- Patients have a hereditary impairment of the sarcoplasmic reticulum to sequester calcium.
- The trigger can causes sudden and prolonged release of calcium, with massive contraction, lactic acidosis, and increased body temperature.
- Treatment is by cooling, correcting acidosis, and dantrolene to reduce calcium release.

Botulinum Toxin

- Produced by *Botulinum* bacteria.
- Inhibits acetylcholine release.
- Food poisoning caused by this bacteria can result, within 12-36 hours, in diplopia, dysphagia, dysarthria, and dyspnea.
- Toxin is use for opthalmic purposes, local muscle spasms, and in the cosmetic treatment of facial wrincles around the eyes and mouth, as well as for generalized spastic disorders like cerebral palsy.

Basic & Clinical Pharmacology, 13e, 2015 > Skeletal Muscle Relaxants

Bertram G. Katzung, Anthony J. Trevor

SUMMARY Skeletal Muscle Relaxants

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
DEPOLARIZING NEUROMUSCULAR BLOCKING AGENT				
• Succinylcholine	Agonist at nicotinic acetylcholine (ACh) receptors, especially at neuromuscular junctions • depolarizes • may stimulate ganglionic nicotinic ACh and cardiac muscarinic ACh receptors	Initial depolarization causes transient contractions, followed by prolonged flaccid paralysis • depolarization is then followed by repolarization that is also accompanied by paralysis	Placement of endotracheal tube at start of anesthetic procedure • rarely, control of muscle contractions in status epilepticus	Rapid metabolism by plasma cholinesterase • normal duration, ~5 min • *Toxicities:* Arrhythmias • hyperkalemia • transient increased intra-abdominal, intraocular pressure • postoperative muscle pain
NONDEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS				
• *d*-Tubocurarine	Competitive antagonist at nACh receptors, especially at neuromuscular junctions	Prevents depolarization by ACh, causes flaccid paralysis • can cause histamine release with hypotension • weak block of cardiac muscarinic ACh receptors	Prolonged relaxation for surgical procedures • superseded by newer nondepolarizing agents	Renal excretion • duration, ~40–60 min • *Toxicities:* Histamine release • hypotension • prolonged apnea
• Cisatracurium	Similar to tubocurarine	Like tubocurarine but lacks histamine release and antimuscarinic effects	Prolonged relaxation for surgical procedures • relaxation of respiratory muscles to facilitate mechanical ventilation in intensive care unit	Not dependent on renal or hepatic function • duration, ~25–45 min • *Toxicities:* Prolonged apnea but less toxic than atracurium
• Rocuronium	Similar to cisatracurium	Like cisatracurium but slight antimuscarinic effect	Like cisatracurium • useful in patients with renal impairment	Hepatic metabolism • duration, ~20–35 min • *Toxicities:* Like cisatracurium
• *Vecuronium: intermediate duration; metabolized in liver*				
CENTRALLY ACTING SPASMOLYTIC DRUGS				
• Baclofen	$GABA_B$ agonist, facilitates spinal inhibition of motor neurons	Pre- and postsynaptic inhibition of motor output	Severe spasticity due to cerebral palsy, multiple sclerosis, stroke	Oral, intrathecal • *Toxicities:* Sedation, weakness
• Cyclobenzaprine	Poorly understood inhibition of muscle stretch reflex in spinal cord	Reduction in hyperactive muscle reflexes • antimuscarinic effects	Acute spasm due to muscle injury • inflammation	Hepatic metabolism • duration, ~4–6 h • *Toxicities:* Strong antimuscarinic effects
• *Chlorphenesin, methocarbamol, orphenadrine, others: Like cyclobenzaprine with varying degrees of antimuscarinic effect*				
• Diazepam	Facilitates GABAergic transmission in central nervous system (see Chapter 22)	Increases interneuron inhibition of primary motor afferents in spinal cord • central sedation	Chronic spasm due to cerebral palsy, stroke, spinal cord injury • acute spasm due to muscle injury	Hepatic metabolism • duration, ~12–24 h • *Toxicities:* See Chapter 22
• Tizanidine	α_2-Adrenoceptor agonist in the spinal	Presynaptic and postsynaptic	Spasm due to multiple sclerosis,	Renal and hepatic elimination •

• Succinylcholine	Agonist at nicotinic acetylcholine (ACh) receptors, especially at neuromuscular junctions • depolarizes • may stimulate ganglionic nicotinic ACh and cardiac muscarinic ACh receptors	Initial depolarization causes transient contractions, followed by prolonged flaccid paralysis • depolarization is then followed by repolarization that is also accompanied by paralysis	Placement of endotracheal tube at start of anesthetic procedure • rarely, control of muscle contractions in status epilepticus	Rapid metabolism by plasma cholinesterase • normal duration, ~5 min • *Toxicities:* Arrhythmias • hyperkalemia • transient increased intra-abdominal, intraocular pressure • postoperative muscle pain
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DIRECT-ACTING MUSCLE RELAXANT				

Other agents

- Tolperisone
- Orphenadrine