Skeletal Muscle Relaxants

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Skeletal Muscle Relaxants

- **Neuromuscular Blockers:**
  - **Nondepolarizing Drugs**
  - **Depolarizing Drugs**

- **Spasmolytics.**
- **Directly Acting Drug.**

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.

Neuromuscular Blockers

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

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.

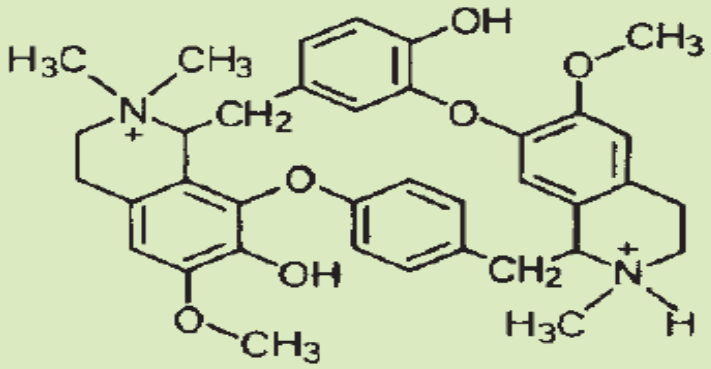
Drug	Elimination	Clearance (mL/kg/min)	Approximate Duration of Action (minutes)	Approximate Potency Relative to Tubocurarine
Isoquinoline derivatives				
Atracurium	Spontaneous[1]	6.6	20–35	1.5
Cisatracurium	Mostly spontaneous	5–6	25–44	1.5
Doxacurium	Kidney	2.7	> 35	6
Metocurine	Kidney (40%)	1.2	> 35	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).

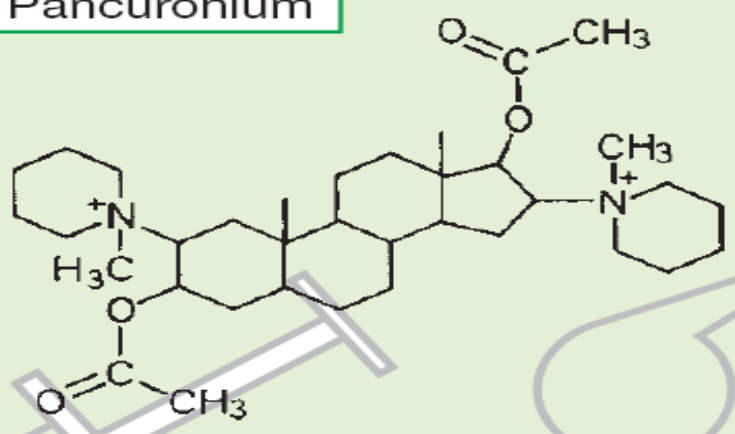
Neuromuscular Blockers

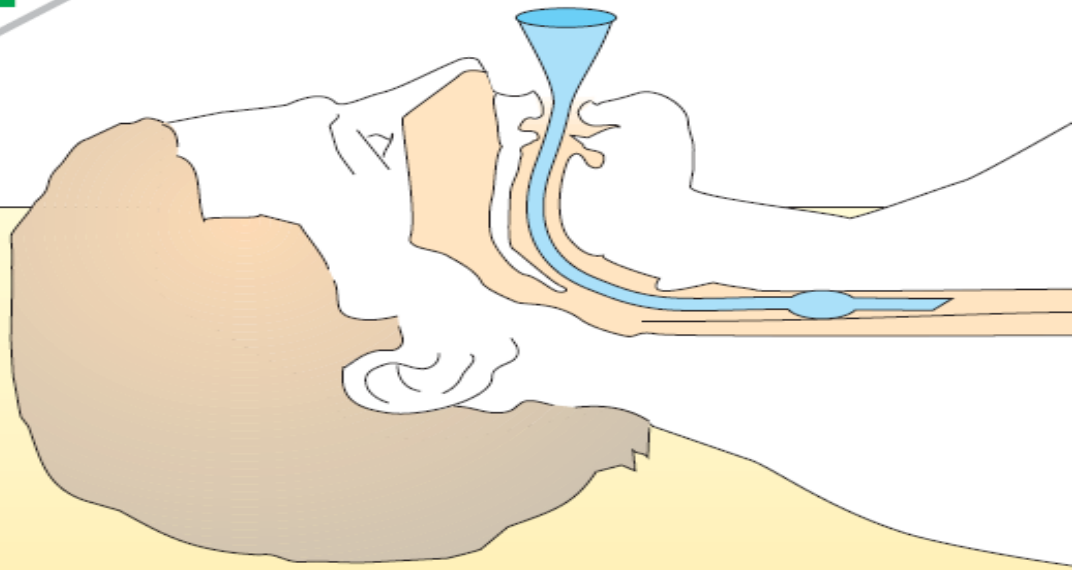
- **Mechanism of Action**
  - **Nondepolarizing Drugs:**
    - **Compete with acetylcholine at the nicotinic receptor sites at the NMJ.**
    - **In high doses, can enter the pore of the ion channel to cause a more intense blockade.**
    - **Can also block prejunctional sodium channels to interfere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

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!)

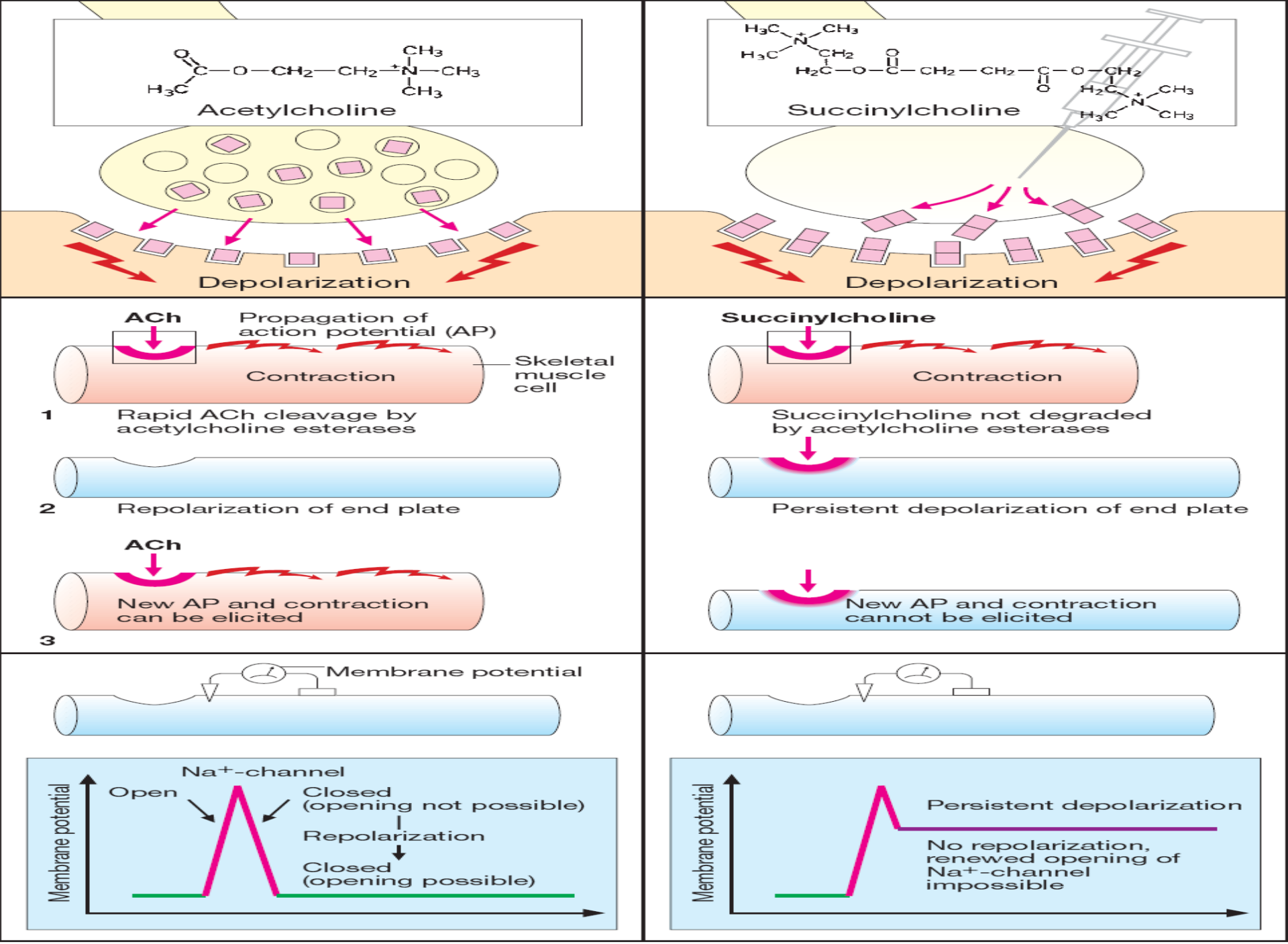
Antidote:
cholinesterase inhibitors
e.g., neostigmine

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 flaccid 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.**



A. Action of the depolarizing muscle relaxant succinylcholine

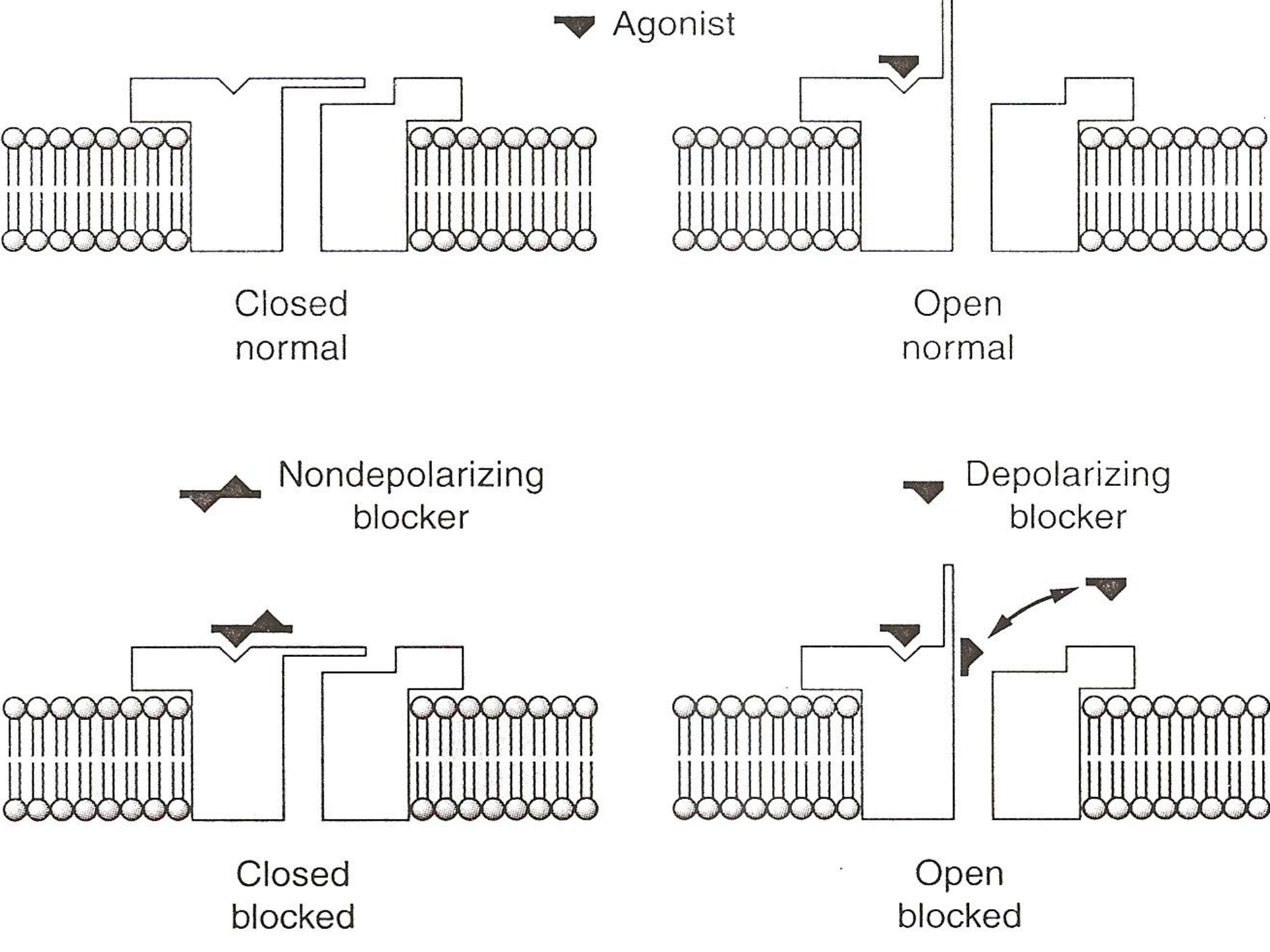

Agonist
Closed
normal
Open
normal
Nondepolarizing
blocker
Depolarizing
blocker
Closed
blocked
Open
blocked

Table 27–2. Comparison of a typical nondepolarizing muscle relaxant (rocuronium) and a depolarizing muscle relaxant (succinylcholine).

		Succinylcholine	
	Rocuronium	**Phase I**	**Phase II**
Administration of tubocurarine	Additive	Antagonistic	Augmented[1]
Administration of succinylcholine	Antagonistic	Additive	Augmented[1]
Effect of neostigmine	Antagonistic	Augmented[1]	Antagonistic
Initial excitatory effect on skeletal muscle	None	Fasciculations	None
Response to a tetanic stimulus	Unsustained (fade)	Sustained[2] (no fade)	Unsustained (fade)
Posttetanic facilitation	Yes	No	Yes
Rate of recovery	30–60 min[3]	4–8 min	> 20 min[3]

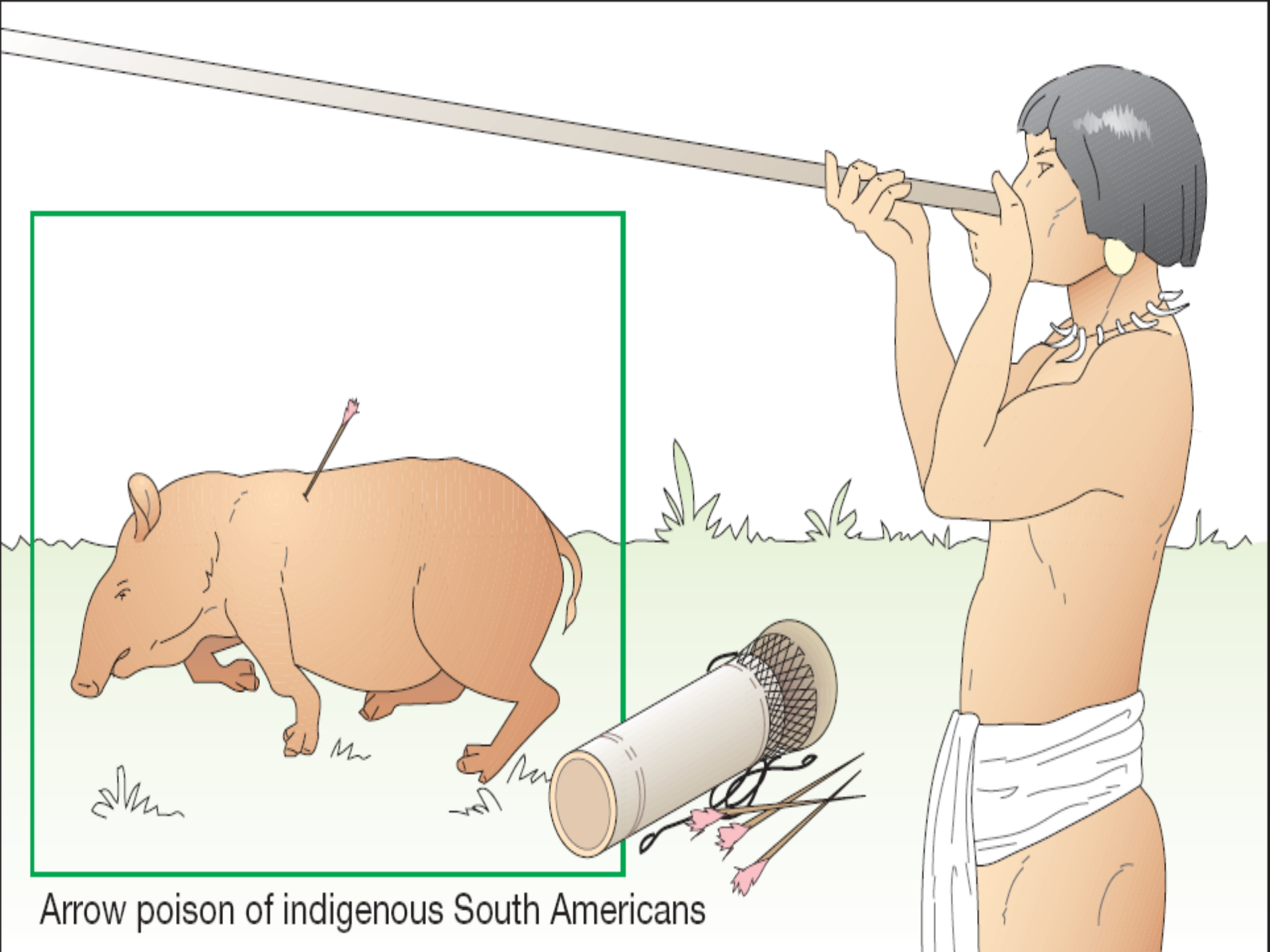
[1]It is not known whether this interaction is additive or synergistic (superadditive).

[2]The amplitude is decreased, but the response is sustained.

[3]The rate depends on the dose and on the completeness of neuromuscular blockade.

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.



Arrow poison of indigenous South Americans

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 choroidal blood vessels.
- **Increased Intragastric Pressure:**
  - Inobese, 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.

Drug Interactions of Neuromuscular Blockers

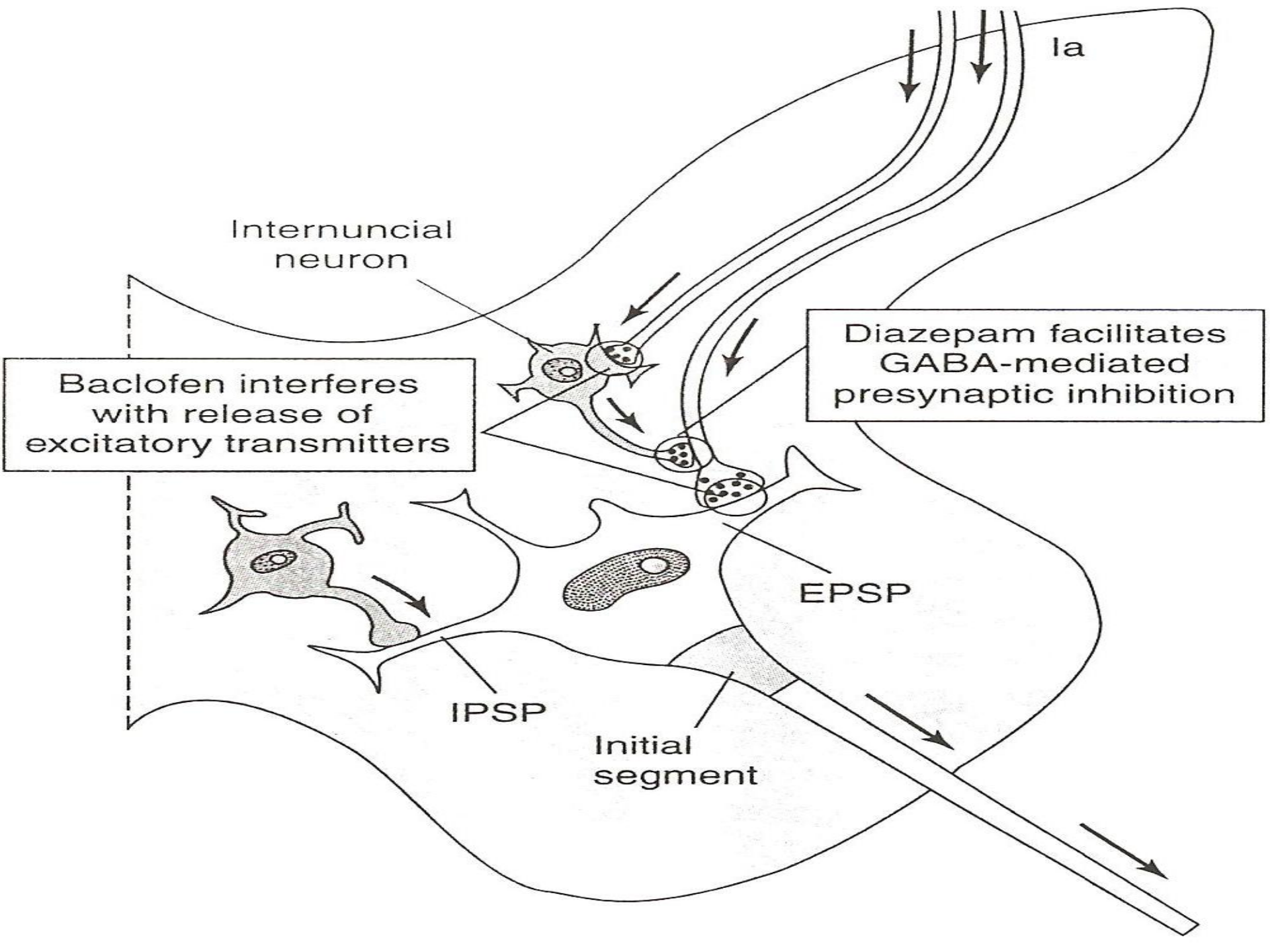
- **Anesthetics:**
  - Mostly with isoflurane, and least with nitrous oxide.
  - May be due to a central action, increased muscle blood flow.
  - Can cause *Malignant Hyperthermia.*
- **Antibiotics:**
  - Depress release of acetylcholine due to blockade of specific P-type of calcium channels.
- **Local anesthetics and antiarrhythmic Drugs**
- **Other Neuromuscular Blockers.**

Spasmolytic Drugs

- **Diazepam:**
  - **Acts at $GABA_A$ receptors in the CNS.**
  - **Benzodiazepines facilitate the action of GABA in the central nervous system.**
  - **Sedative.**
- **Although diazepam can be used in patients with muscle spasm of almost any origin (including local muscle trauma), it also produces sedation at the doses required to reduce muscle tone .**

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.


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

Spasmolytic Drugs

- **Tizanidine:**
  - Related to clonidine.
  - Used to treat muscle spacticity
  - due to spinal cord injury or multiple sclerosis
  - Alpha 2 agonist.
  - BP loweing ???
  - Side effects: dizziness, weakness, depression, hallucinations
  - dry mouth
- **Gabapentin:**
  - An antiepileptic Glycine.

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.
  - Can cause weakness, sedation, and hepatitis.

Malignant Hyperthermia

- Rare heritable disorder triggered by a variety of stimuli, including general anesthetics and neuromuscular blockers.
- Patieents 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 .