MSS

Pharmacology

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Skeletal Muscle Relaxants

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Muscle relaxants are drugs that affect skeletal muscle function and decrease the muscle tone, these agents can be used to relieve symptoms such as muscle spasms and pain.

Skeletal Muscle Relaxants

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

Note:The two main types of skeletal muscle relaxants are neuromuscular blockers (act at neuromuscular junctions), and spasmolytics (act on the central nervous system).

They are used during surgical procedures and intensive care unit. The purpose of muscle relaxation in these procedures is to facilitate the intubation process during anesthesia or in the ICU. Additionally, during surgical procedures, reduced muscle tone makes it easier to dissect through the muscle to perform the surgery. Moreover, neuromuscular blockers have increased the safety of anesthesia because less anesthetic is required to produce muscle relaxation.

- **Spasmolytics.**

Directly Acting Drug.

Neuromuscular Blockers

- **Chemistry:**
  - One or two quaternary nitrogen's, i.e. poorly lipid soluble or highly polar compounds.

Which is why they will not be absorbed through the G.I. system. Instead, they are given by intra-venous injection during different procedures.

  - Double acetylcholine molecules linked:
    - End to end.
    - Concealed, bulky semi - rigid ring systems.

An example is succinylcholine

Neuromuscular Blockers

- **Pharmacokinetics:**
  - Must be given parenterally.
  - Nondepolarizing Drugs:
    - Excreted in the kidney or metabolized by the liver.
    - Mivacurium is metabolized by cholinesterases. Short half-life
    - Atracurium is spontaneously broken down (HOFMAN ELIMINATION). It has a short half-life compared to drugs that are metabolized in the liver.

There are various kinds of these neuromuscular blockers, we are going to focus mainly on the prototype of these drugs. Different chemical structures have differences in their half-life or metabolism.

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 .

Which shows a variation in plasma levels and half-life of these drugs among patients, so we use dibucaine number.

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).

This table shows some of the properties of neuromuscular blocking agents. We can notice that the elimination is mostly through the kidneys while some, as mentioned earlier, get metabolized in the plasma by cholinesterase. There are differences in the half-life which can be measured by the clearance. Also, there are differences in the duration of action and the potencies. Then they are compared to tubocurarine, which is a prototype of these agents.

Neuromuscular Blockers

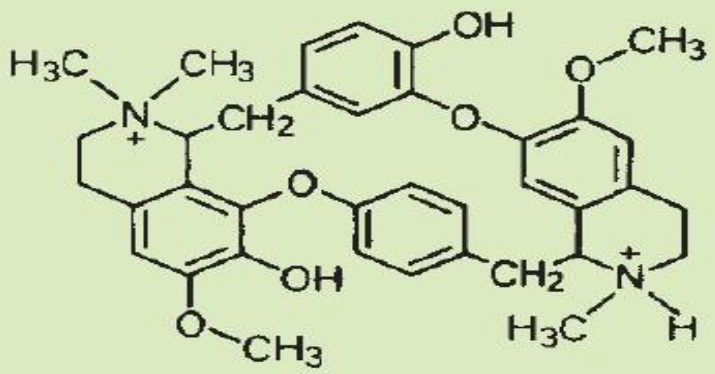
Mechanism of Action

- **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.**

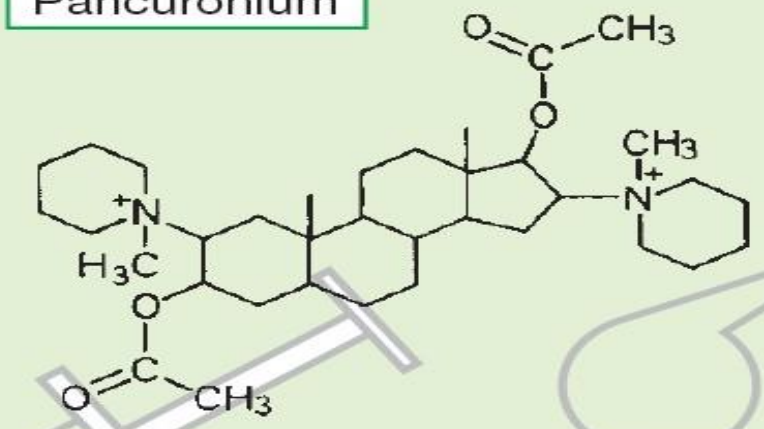
They will prevent the binding of acetylcholine to the nicotinic receptor of the muscle endplate, thereby inhibiting the action of acetylcholine on those muscles and inhibiting their contraction.

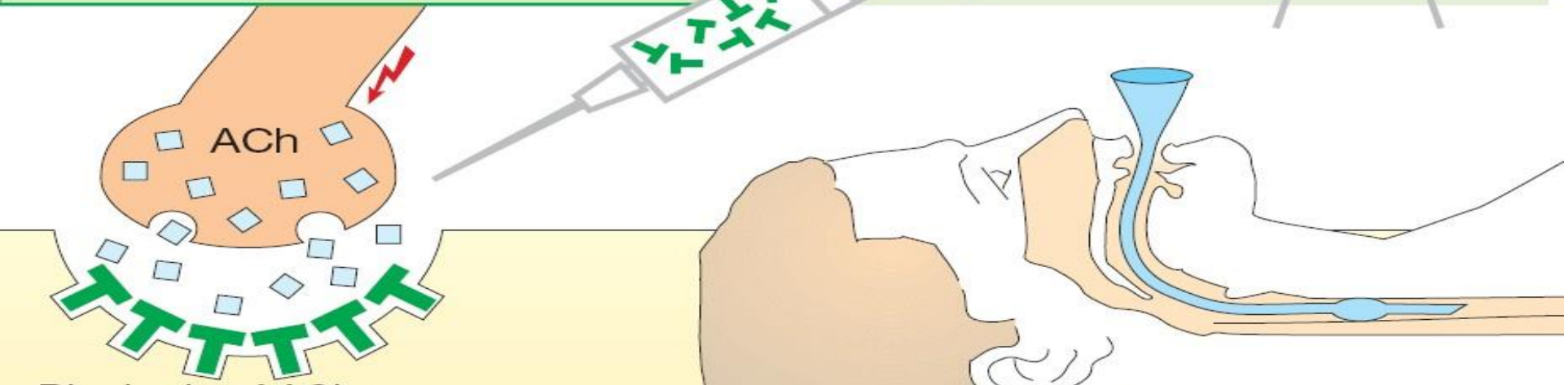
  - **Can also block prejunctional sodium channels to interfere with the mobilization of acetylcholine at the nerve ending.**

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

Explained in the next slide

As depicted in the previous image, drugs such as tubocurarine or pancuronium, when administered to the patient have the ability to compete with acetylcholine for binding sites on the nicotinic receptors. Consequently, they prevent acetylcholine from binding and initiating contraction of the skeletal muscle. An example of skeletal muscles affected by this phenomenon is the respiratory muscles. This inhibition of muscle contraction results in the relaxation of the respiratory muscles, which, as previously mentioned, facilitates artificial ventilation required during general anesthesia procedures.

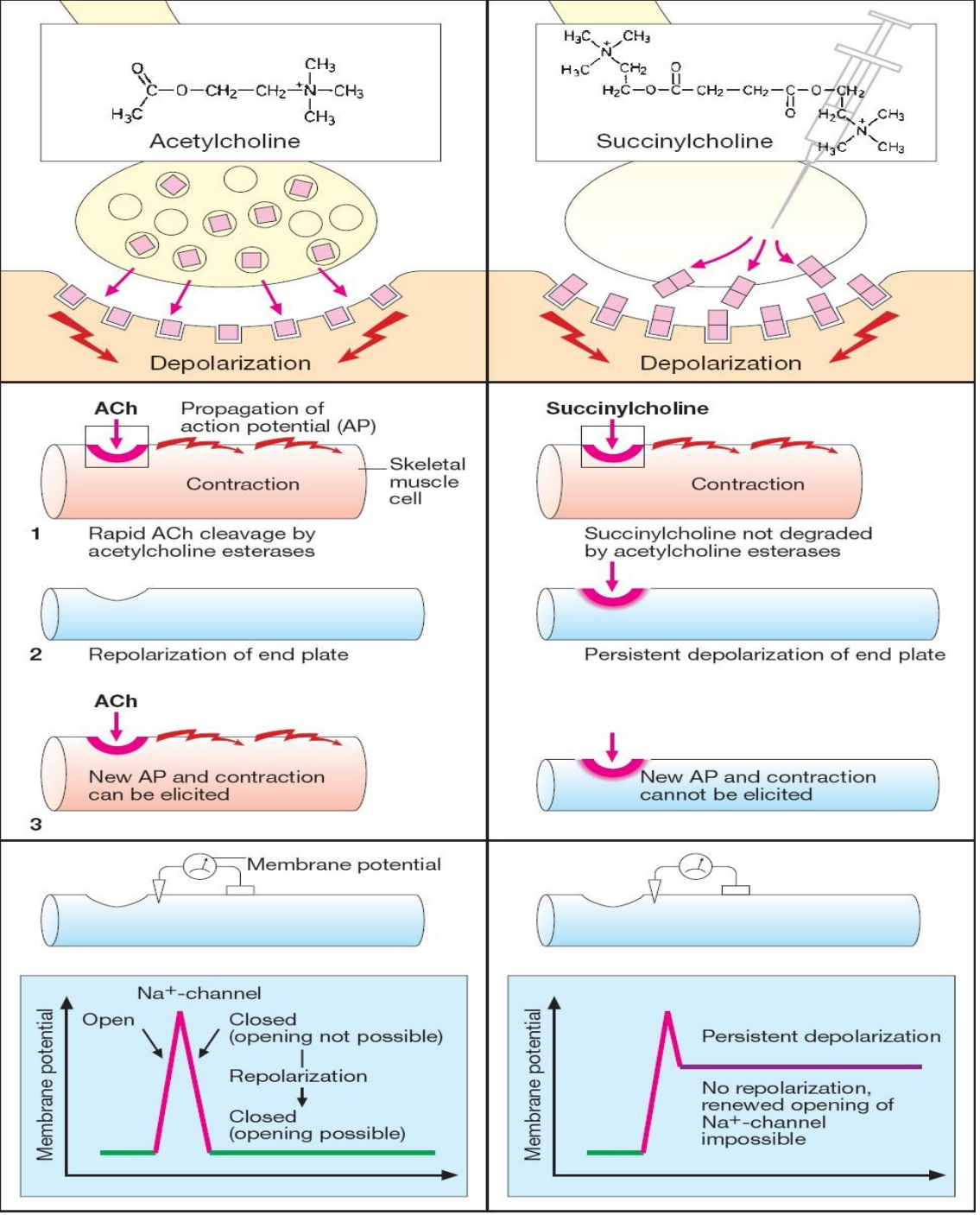
Neuromuscular Blockers

- **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 cholinesterase inhibitors.**

An example of depolarizing drugs is succinylcholine. Succinylcholine has a very similar structure to acetylcholine since its chemical structure is two ACh molecules bound H to H.
Depolarizing Agents work at multiple phases. The first one is depolarizing.

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 **acetylcholinesterase** inhibitors.



A. Action of the depolarizing muscle relaxant succinylcholine

In this image, we can see the difference between ACh and succinylcholine. Both cause initial depolarization of the muscle. However, ACh shows relaxation after a period of time which allows the muscle to repolarize, and we can perform activation or contraction again. In contrast, succinylcholine results in persistent depolarization with no repolarization, and reopening the sodium channels becomes impossible.

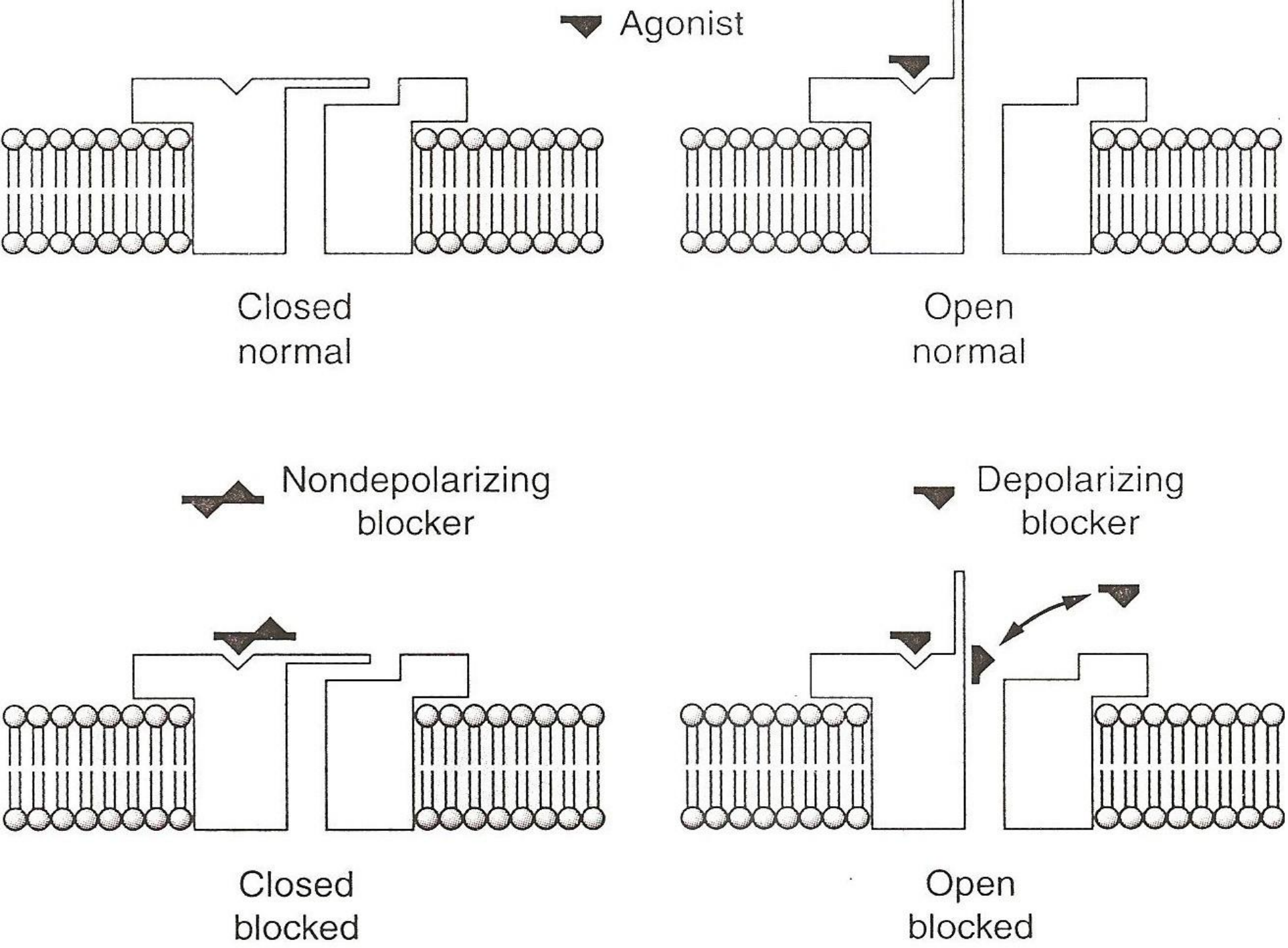

Agonist
Closed
normal
Open
normal
Nondepolarizing
blocker
Depolarizing
blocker
Closed
blocked
Open
blocked

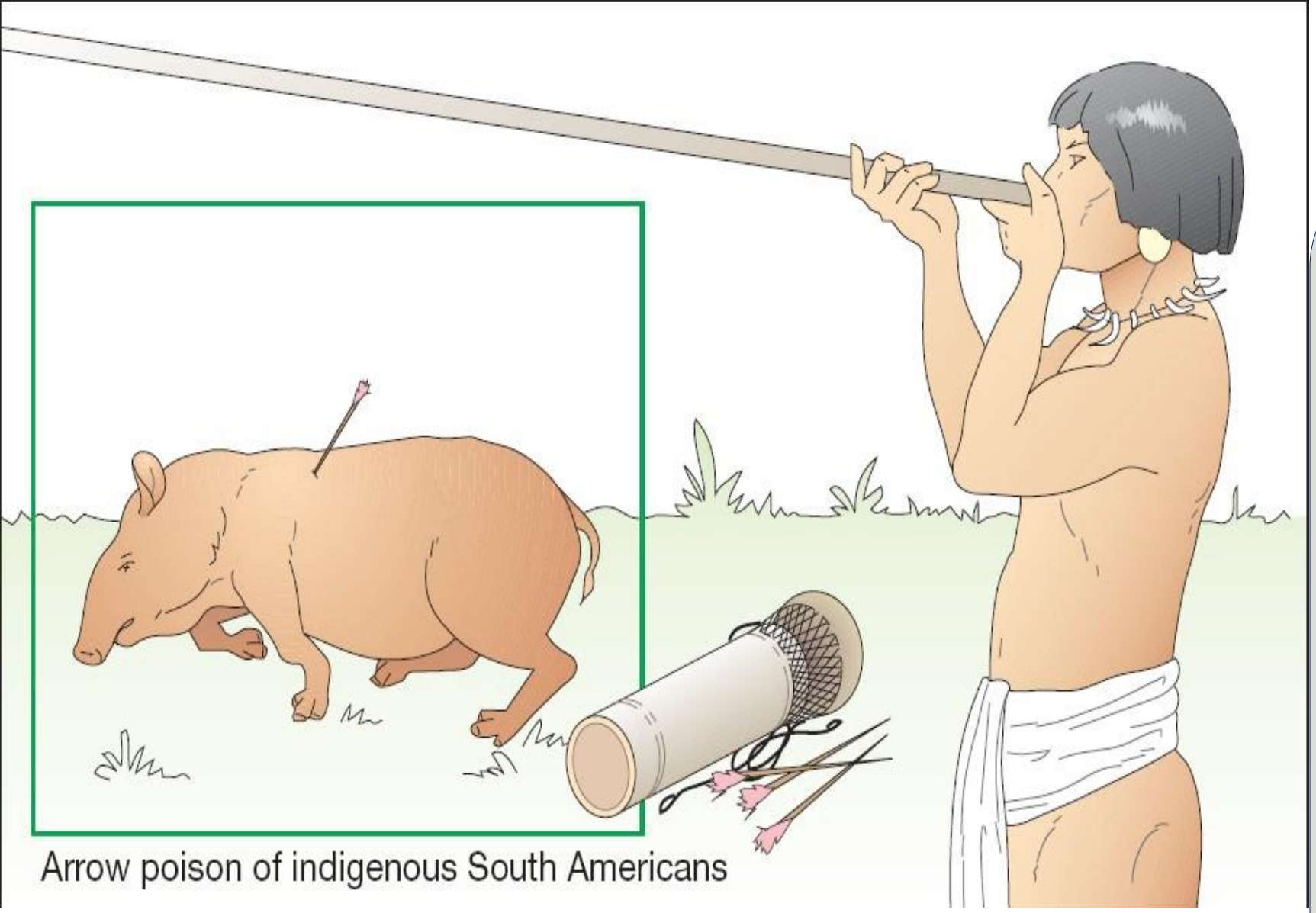
Table 27–2. Comparison of a typical nondepolarizing muscle relaxant (rocuronium) and a depolarizing muscle relaxant (succinylcholine).

		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

This is one of the earliest uses of tubocurarine, which was used by indigenous hunters of the Amazons in South America. They used it as a hunting toxin to capture animals. As mentioned earlier, because of this poison's or drug's inability to be absorbed through the G.I. tract, it would not harm the individuals consuming the poisoned meat of the animal. While this drug had been utilized for hunting purposes long ago, its clinical use began in the early 1940s.

Actions of Neuromuscular Blockers

- **Skeletal Muscle Paralysis:**
  - 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

- **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

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

Actions of Neuromuscular Blockers

- **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

They have important drug interactions in general anesthesia especially with halogenated anesthetics

- **Anesthetics:**
  - Mostly with isoflurane, and least with nitrous oxide.
  - May be due to a central action, increased muscle blood flow.
  - Can cause *Malignant Hyperthermia.* 1
- **Antibiotics:**
  - Depress release of acetylcholine due to blockade of specific P-type of calcium channels. 2
- **Local anesthetics and antiarrhythmic Drugs**
- **Other Neuromuscular Blockers.**

1) For instance, when using Halothane as an anesthetic alongside succinylcholine, there's occasionally malignant hyperthermia. It's characterized by muscle rigidity and hyperoxia, particularly in individuals that are genetically susceptible to this condition. One key treatment for this is administration of a directly acting muscle relaxant called dantrolene. It works by blocking the release of calcium from sarcoplasmic reticulum. This action reduces heat production and relaxes muscle tone.
2) Similarly, aminoglycoside antibiotics like gentamicin or tobramycin can impede acetylcholine release from cholinergic nerves by competing with calcium ions. This effect synergizes with tubocurarine, another competitive blocker, thereby enhancing the blocking action.

Spasmolytic Drugs

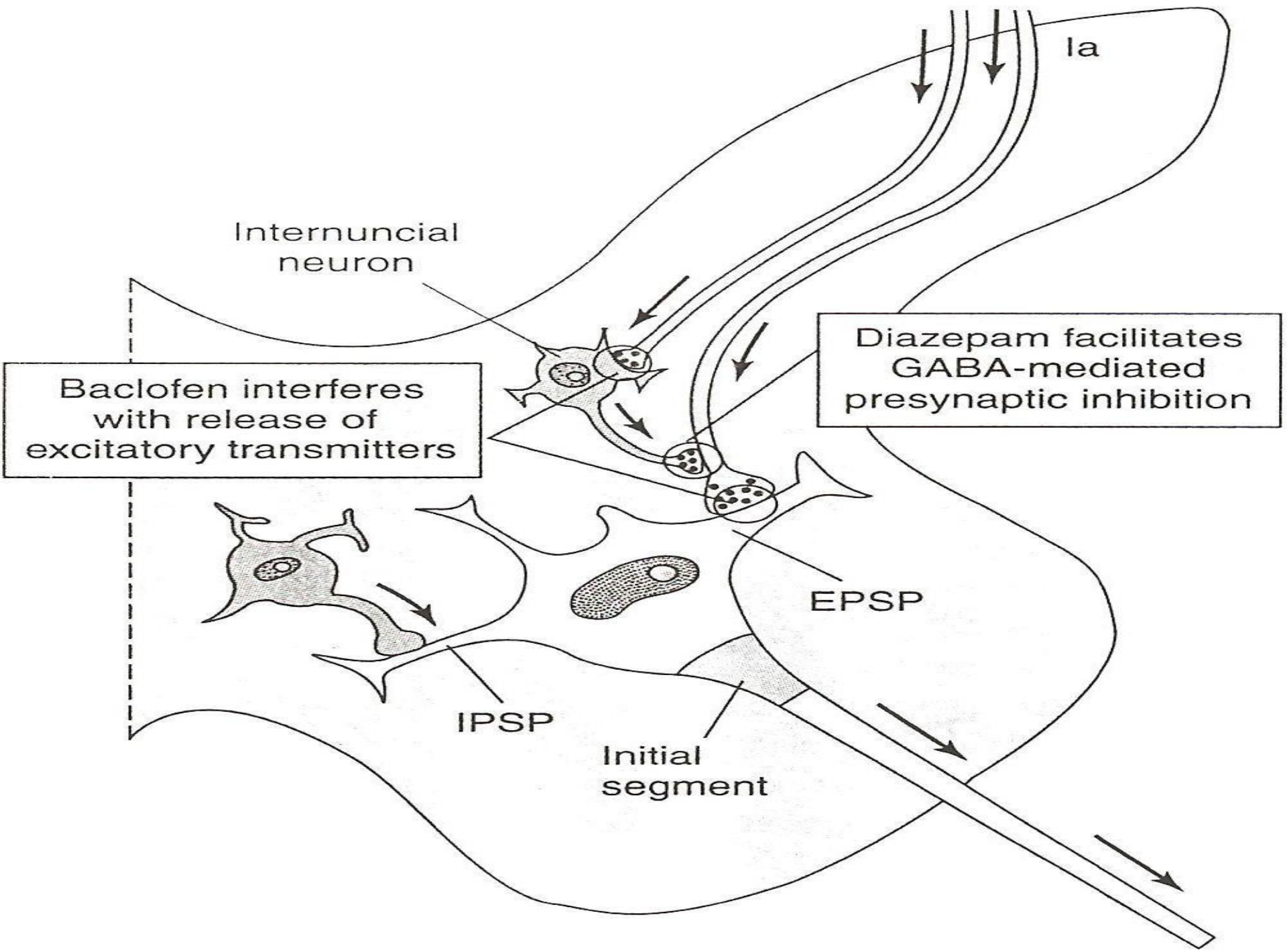
- **Diazepam:**
  - **Acts at $GABA_A$ receptors in the CNS.**
  - **Benzodiazepines facilitate the action of GABA in the central nervous system.**
  - **Sedative.**

- **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 .**

The effect of diazepam reduces spasticity caused by spinal cord trauma, although it could be a somewhat weak effect. Benzodiazepines like diazepam facilitate the action of GABA in the central nervous system. However, one significant side effect of this agent is sedation, so caution is necessary. Additionally, there is a tendency for tolerance and dependence to develop with these agents.
Other benzodiazepines such as midazolam have been used as spasmolytic agents but clinical experience with them is very limited.

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.



For clarification: Diazepam and Baclofen act as GABA agonists and have similar mechanisms of action, but baclofen can also inhibit the release of excitatory transmitters in the pre synaptic neuron.

Spasmolytic Drugs

- **Tizanidine:**
  - Related to clonidine.
  - Used to treat muscle spacticity
  - due to spinal cord injury or multiple sclerosis
  - Alpha 2 agonist.
  - BP loweing ??? 1
  - Side effects: dizziness, weakness, depression, hallucinations 2
  - dry mouth
- **Gabapentin:**
  - An antiepileptic Glycine.

1) As you recall, we discussed the use of clonidine as an antihypertensive agent. Tizanidine, however, is significantly less effective than clonidine, with an efficacy ratio ranging from approximately 1:10 to 1:15 compared to clonidine.
2) All that and sedation are effects related to the central nervous system, it can also cause dry mouth, and some patients experience constipation while others experience diarrhea.

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.**

Thus enhancing further release of calcium from the sarcoplasmic reticulum in the muscle cell, this is why dantrolene is used as an antidote for patients exhibiting malignant hyperthermia induced by the combination of succinylcholine with anesthetic agents such as halothane. We mentioned that a genetic mutation appears in patients who exhibit the side effects, this genetic mutation is related to the ryanodine receptor.

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. Therefore, flaccid paralysis.

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 .


طوفان الأقصى
اللهم إنا نستودعك فلسطين وأهلها
سمائها وأرضها رجالها ونسائها اطفالها
وشبابها اللهم انصرهم وثبت أقدامهم

V2

- Cholineestrase instead of cholinesterse slide 11+12