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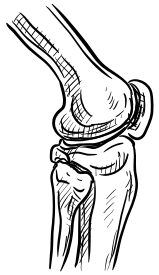

PHARMACOLOGY

MID | Lecture 3

Skeletal Muscle Relaxants

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وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم

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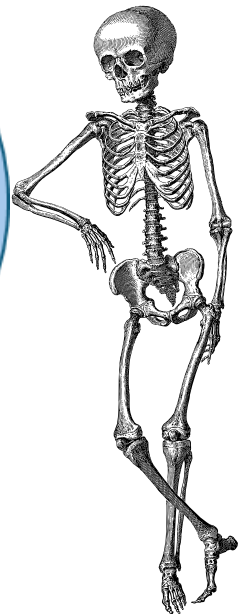


Skeletal Muscle Relaxants

Alia Shatanawi

Muscle relaxants affect skeletal muscle function and **decrease** muscle tone.
They are used to alleviate muscle spasms and pain.

Skeletal Muscle Relaxants

1. Neuromuscular Blockers:
   - Nondepolarizing Drugs
   - Depolarizing Drugs
2. Spasmolytics

- Both are directly Acting Drugs
- Neuromuscular blockers are used in many conditions, most importantly in surgical procedures and in the ICU. Their primary purpose is to facilitate intubation during anesthesia in the ICU.
- Additionally, reducing muscle tone makes it easier to dissect muscles during surgery. Neuromuscular blockers also enhance anesthetic safety because they reduce the amount of anesthetic required to achieve muscle relaxation.

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
- Due to their polar nature, neuromuscular blockers are poorly absorbed in the gastrointestinal (GI) tract. As a result, they are primarily administered via injection, most commonly intravenously (IV).

Neuromuscular Blockers

- Pharmacokinetics:
  - Must be given parenterally.
  - Nondepolarizing Drugs:
    - Excreted in the kidney or metabolized by the liver.
    - Mivacurium is metabolized by cholinesterases, leading to it having a very short half-life.
    - Atracurium is spontaneously broken down (HOFMAN ELIMINATION). It will also have a short half life compared to drugs metabolized in the liver.
- We will focus solely on the prototype of this drug class, while other drugs in the group vary in their half-life and 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, leading to variations in the plasma levels and half-life of these drugs.
    - 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).

Table Overview

- This table presents the properties of various neuromuscular blocking agents. Most are eliminated through the kidneys, while others are metabolized by plasma cholinesterases.
- There are differences in their half-life, which is measured by clearance. Additionally, they vary in their duration of action and potency.
- These agents are all compared to tubocurarine, the prototype neuromuscular blocker.

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. As a result, they prevent acetylcholine (ACh) from binding to nicotinic receptors at the muscle, thereby inhibiting muscle contraction.
    - Can also block prejunctional sodium channels to interfere with the mobilization of acetylcholine at the nerve ending.

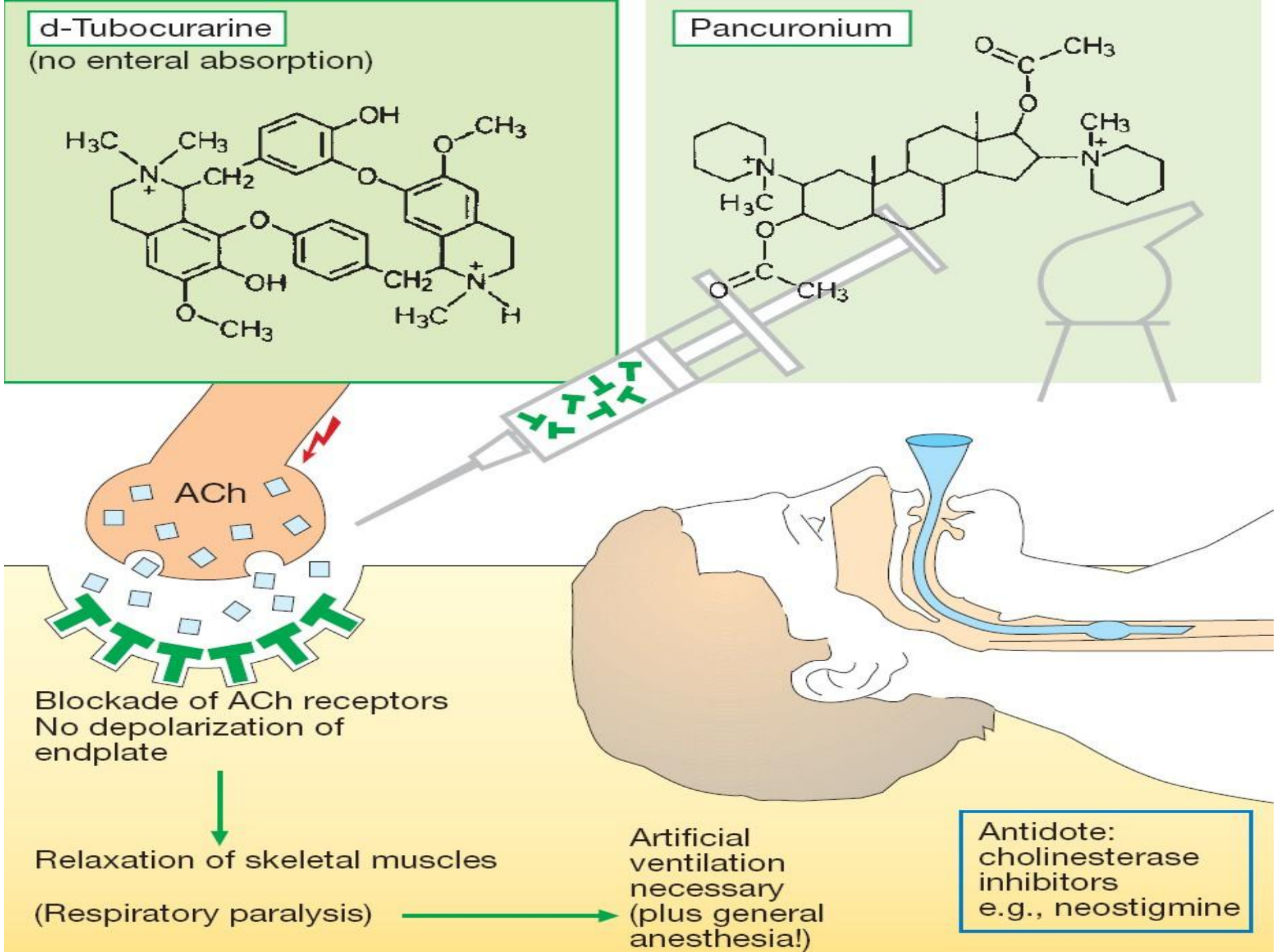
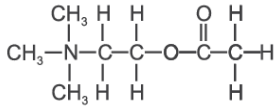

d-Tubocurarine
(no enteral absorption)
Pancuronium
ACh
Blockade of ACh receptors
No depolarization of endplate
Relaxation of skeletal muscles
(Respiratory paralysis)
Artificial ventilation necessary (plus general anesthesia!)
Antidote: cholinesterase inhibitors e.g., neostigmine

Image Interpretation

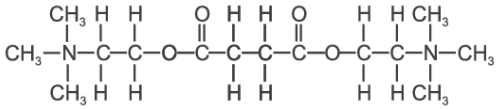
- Once injected into a patient, tubocurarine and pancuronium compete with acetylcholine (ACh) for binding to nicotinic receptors. As a result, they block ACh binding and inhibit skeletal muscle contraction.
- One example of affected skeletal muscles is the respiratory muscles. This inhibition induces muscle relaxation, facilitating ventilation during anesthesia.

Neuromuscular Blockers

Acetylcholine



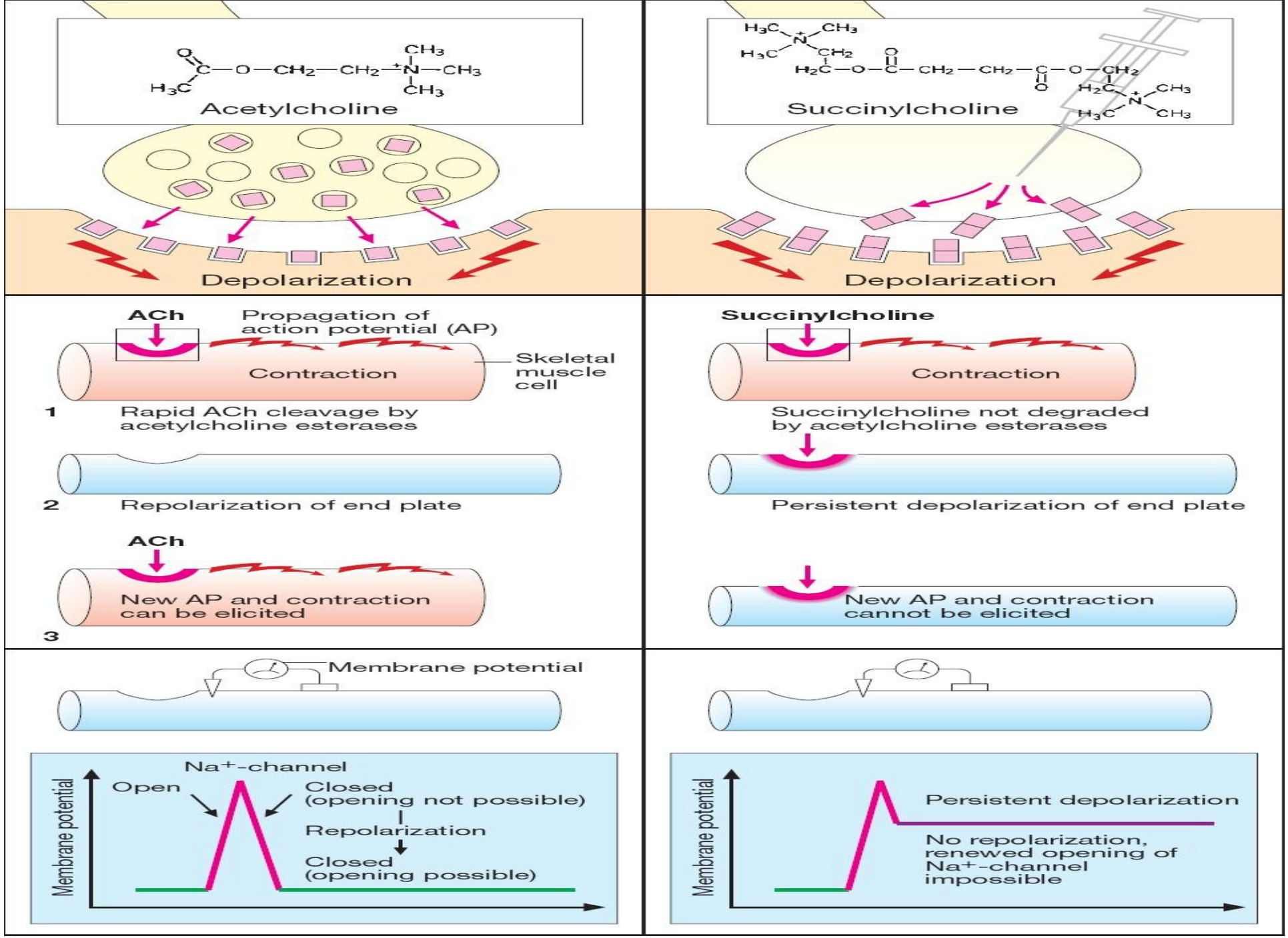
Succinylcholine



- Mechanism of Action:
- Depolarizing Drugs (Work at different phases):
  - Succinylcholine has a structure very similar to acetylcholine (ACh). Chemically, it consists of **two ACh molecules linked end to end.**
  - *Phase I Block (depolarizing):* succinylcholine reacts with nicotinic receptors to open the channel and cause depolarization of the motor end plate which will spread to adjacent membranes, initially 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.

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

Image Interpretation

- Here, we can see the difference between succinylcholine and acetylcholine (ACh). Both can depolarize the muscle. However, ACh is rapidly broken down by acetylcholinesterase, allowing the muscle to relax, repolarize, and contract again.
- In contrast, succinylcholine is not rapidly degraded, leading to prolonged depolarization and preventing repolarization of the sodium channels, resulting in sustained muscle paralysis.

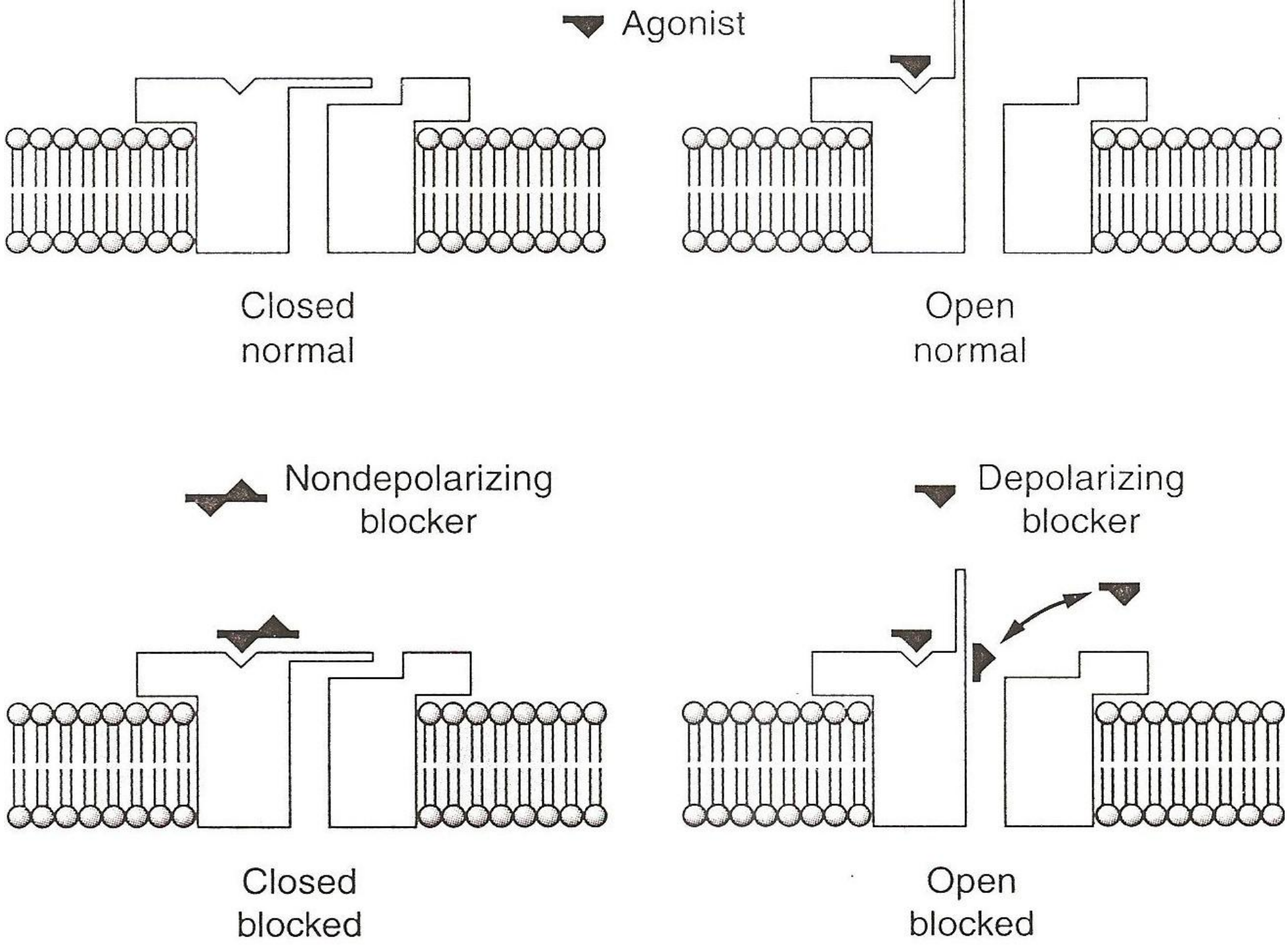

Agonist
Closed
normal
Open
normal
Nondepolarizing
blocker
Depolarizing
blocker
Closed
blocked
Open
blocked

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.

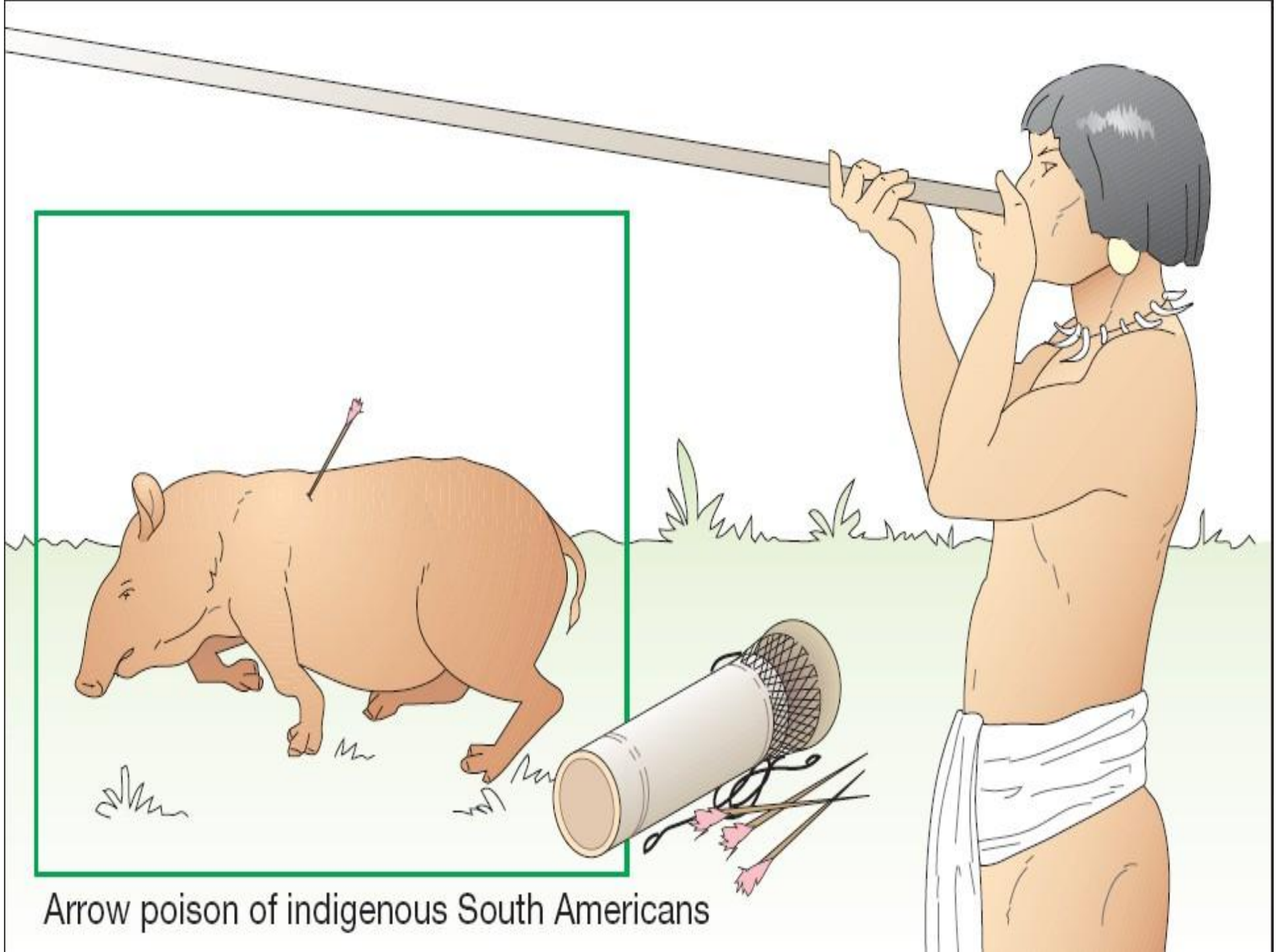
[3]The rate depends on the dose and on the completeness of neuromuscular blockade.

Table Interpretation

- Here, we compare a typical non-depolarizing muscle relaxant (rocuronium) to a depolarizing muscle relaxant (succinylcholine). These agents are often compared to tubocurarine, the prototype neuromuscular blocker.
- The comparison will continue in the following slides.

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 paralyzed.
    - Effects lasts for 45-60 minutes.



Arrow poison of indigenous South Americans

Image Interpretation

- One of the earliest uses of tubocurarine was for hunting animals.
- As mentioned earlier, this drug does not harm individuals when ingested because it cannot be absorbed in the gastrointestinal (GI) tract due to its polar nature.
- Tubocurarine has been used for centuries as a hunting poison, though the clinical use of these drugs started in the 1940's.

Actions of Neuromuscular Blockers

- Skeletal Muscle Paralysis
  - Depolarizing Drugs:
    - Action stars by transient muscle fasciculations 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.

Action of Neuromuscular Blockers

- Skeletal Muscle Paralysis
- Cardiovascular Effects
  - Mediated by the autonomic nervous system 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
- Cardiovascular Effects
- Hyperkalemia (another side effect):
  - 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
- Cardiovascular Effects
- Hyperkalemia
- Increased Intraocular Pressure (Side Effect):
  - Due to tonic contraction of myofibrils or transient dilation of ocular chorodial blood vessels.
- Increased Intragastric Pressure (Side Effect):
  - Happens probably in obese, heavily muscled, diabetics, traumatic patients, fasiculations of succinylcholine can cause regurgitation and aspiration of gastric contents.
- Muscle Pain (Side Effect):
  - 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 (may also interact with neuromuscular blockers):
  - Depress release of acetylcholine due to blockade of specific P-type of calcium channels.
  - Additionally, aminoglycoside antibiotics such as gentamicin and tobramycin can inhibit acetylcholine (ACh) release from cholinergic nerves by competing with calcium ions. This interaction synergizes with tubocurarine and other competitive neuromuscular blockers, enhancing their effects.
- Local anesthetics and antiarrhythmic Drugs
- Other Neuromuscular Blockers.

Malignant Hyperthermia: Causes and Treatment

- Anesthetic Interaction: For example, when halothane (an anesthetic) is administered with succinylcholine, malignant hyperthermia may occasionally occur. This condition is associated with muscle rigidity and hyperpyrexia. It occurs especially in genetically susceptible individuals.
  One of the most important treatments for malignant hyperthermia is the administration of dantrolene, a directly acting muscle relaxant. Dantrolene blocks calcium release from the sarcoplasmic reticulum of muscle cells, thereby reducing heat production and relaxing muscle tone.

Spasmolytic Drugs

Agents used in conditions of spasticity

- Diazepam:
  - Acts at $GABA_A$ receptors in the CNS.
  - Benzodiazepines facilitate the action of GABA in the central nervous system.
  - It reduces spasticity at least partially mediated in the spinal cord, because it is effective with patients with cord transection.
  - Sedative.
  - Cause tolerance and dependance.
- 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. These notes should be given to the patient when using these agents.
- Other benzodiazepines, such as midazolam, have been used as spasmolytic agents, but clinical experience with them remains 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 than benzodiazepines but can cause drowsiness.
  - Can be given intrathecally.
  - Can reduce craving in alcoholics and in migraine.

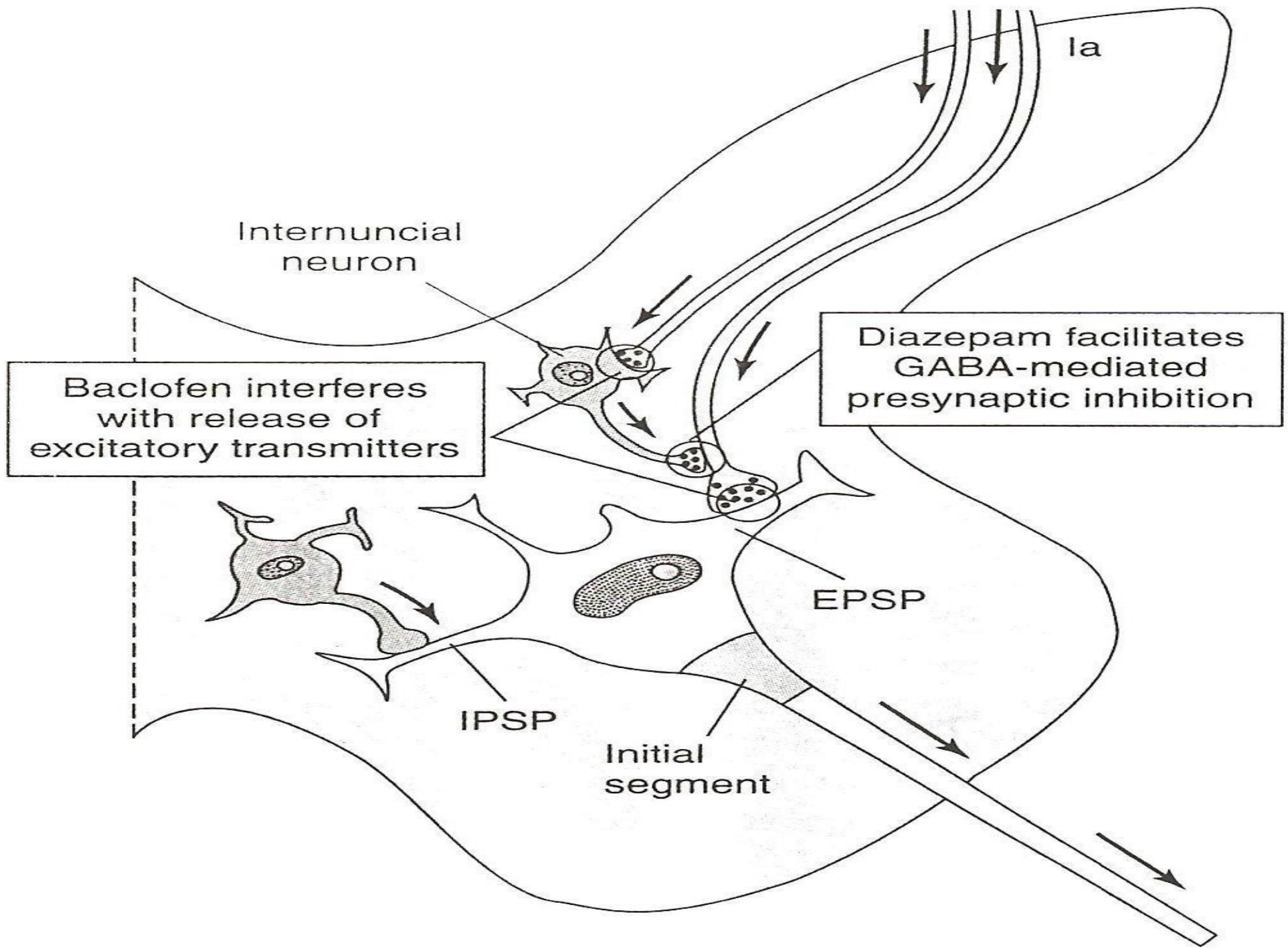

Ia
Internuncial neuron
Baclofen interferes with release of excitatory transmitters
Diazepam facilitates GABA-mediated presynaptic inhibition
EPSP
IPSP
Initial segment

Image Interpretation

- This image illustrates the sites of action of diazepam, which facilitates GABA-mediated presynaptic inhibition. In contrast, baclofen inhibits the release of excitatory neurotransmitters in the central nervous system and spinal cord.

Spasmolytic Drugs

- Tizanidine:
  - Related to clonidine.
  - Used to treat muscle spasticity, especially due to spinal cord injury or multiple sclerosis
  - Alpha 2 agonist
  - BP lowering ???
    - Although clonidine lowers blood pressure, tizanidine has significantly weaker effects, approximately one-tenth that of clonidine.
  - Side effects: dizziness, weakness, depression, hallucinations, sedation related to the CNS, dry mouth.
  - Some patients experience constipation while others experience diarrhea with these agents
- Gabapentin:
  - An antiepileptic Glycine.
  - Will be talked about more next year in the CNS lectures.

Directly Acting Drugs

- Dantrolene:
  - Structure is 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; thus, preventing further release of calcium from the SER in the muscle cell, reducing excessive muscle contraction.
  - This is why dantrolene is used as an antidote for patients experiencing malignant hyperthermia, which is triggered by the combination of succinylcholine and anesthetic agents such as halothane.
  - This condition is associated with a genetic mutation in the ryanodine receptor (RyR), making affected individuals more susceptible to excessive calcium release and muscle rigidity.
  - Can cause weakness, sedation, and hepatitis.

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 cause 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 ophthalmic purposes, local muscle spasms, and in the cosmetic treatment of facial wrinkles around the eyes and mouth, as well as for generalized spastic disorders like cerebral palsy .

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	#33, Second point	Thus, enhancing, …, cell.	Thus, preventing, …, contraction.
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

ربّ اشرح لى صدري، ويسّر لى أمري، واحلل عقدة من لسانى يفقه قولي،اللهم لا سهل إلا ما جعلته سهلا، فإنك إن شئت تجعل الصعب سهلا يا أرحم الراحمين.

ادعوا لأهلنا في غزة