Skeletal Muscle Relaxants

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The nicotinic Acetycholine receptor

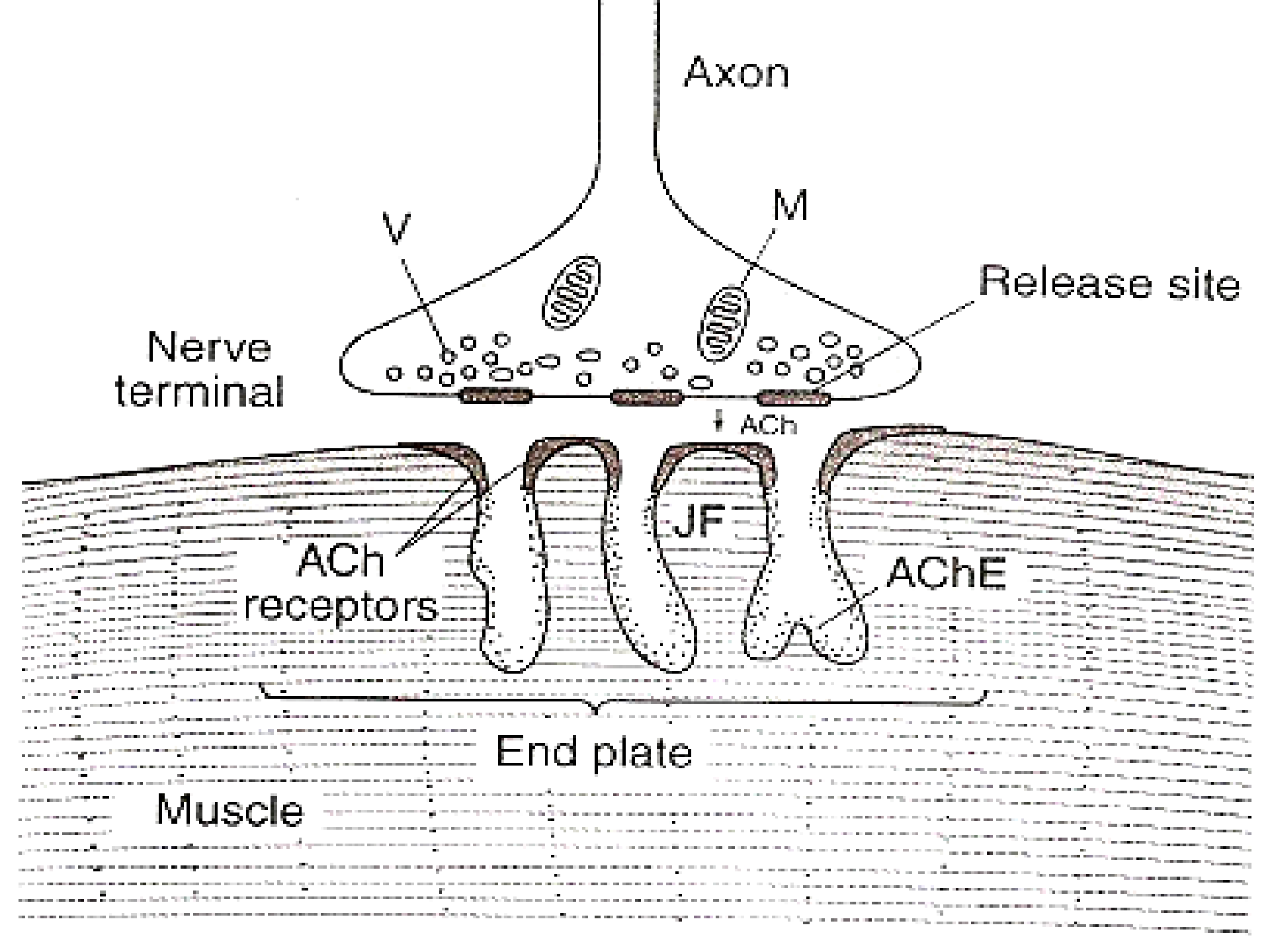
- Present at the neuromuscular junction, peripheral autonomic ganglia; and in the CNS.

- Distinct subtypes of nicotinic receptors exist at these sites.
- Several pharmacological agents discriminate between the receptor subtypes.

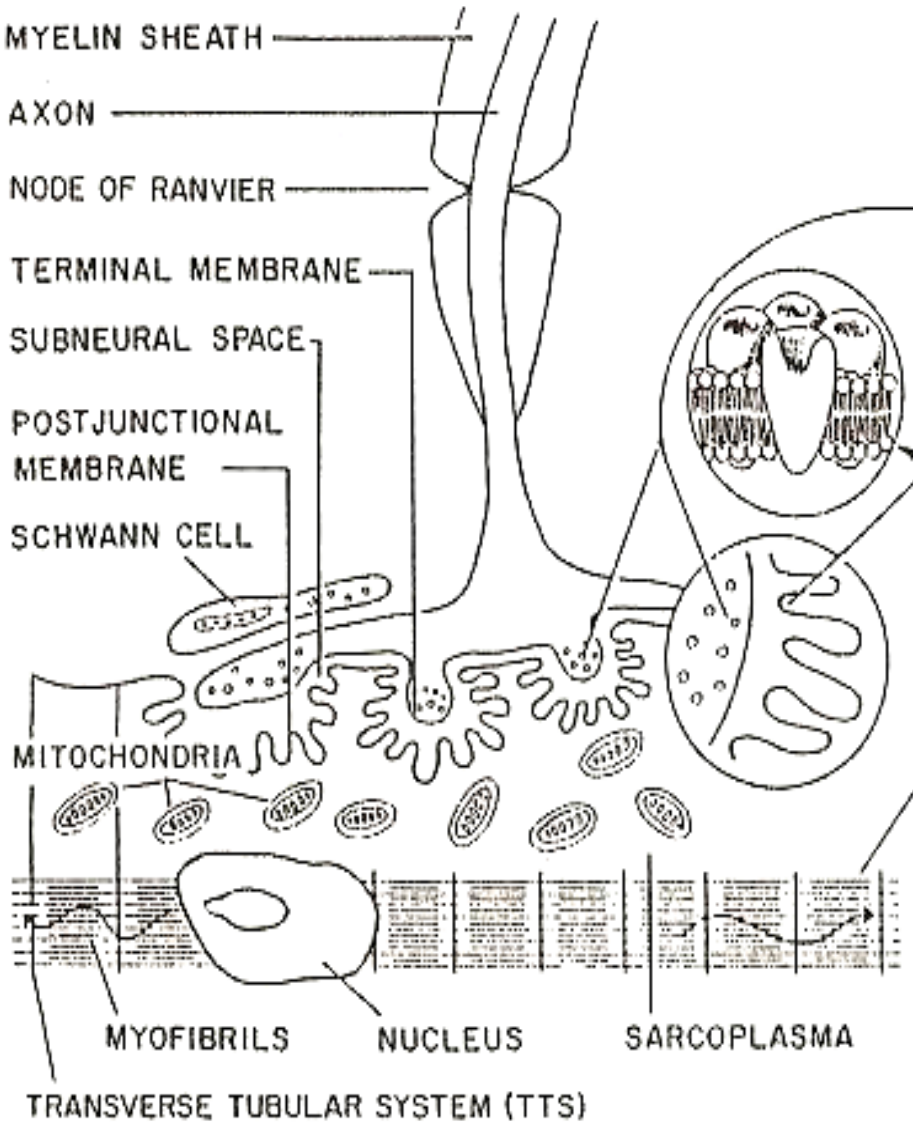
- The binding of ACh to the nicotinic ACh receptor initiates the end-plate potential (EPP) in muscle or an excitatory postsynaptic potential (EPSP) in peripheral ganglia.

- Classical studies of the actions of curare and nicotine defined the concept of the nicotinic ACh receptor over a century ago and made this the prototypical pharmacological receptor.

- Peripheral and then central nicotinic receptors were isolated and characterized.


Axon
V
M
Release site
Nerve terminal
ACh
JF
ACh receptors
AChE
End plate
Muscle

ANATOMY OF THE MOTOR END-PLATE



PHYSIOLOGY

NERVE ACTION POTENTIAL (AP)

↓

ACETYLCHOLINE RELEASE

↓

DEPOLARIZATION (EPP) (INCREASED PERMEABILITY TO Na^+ AND K^+)

↓

MUSCLE ACTION POTENTIAL (MAP)

↓

SPREAD OF EXCITATION IN MUSCLE VIA TTS

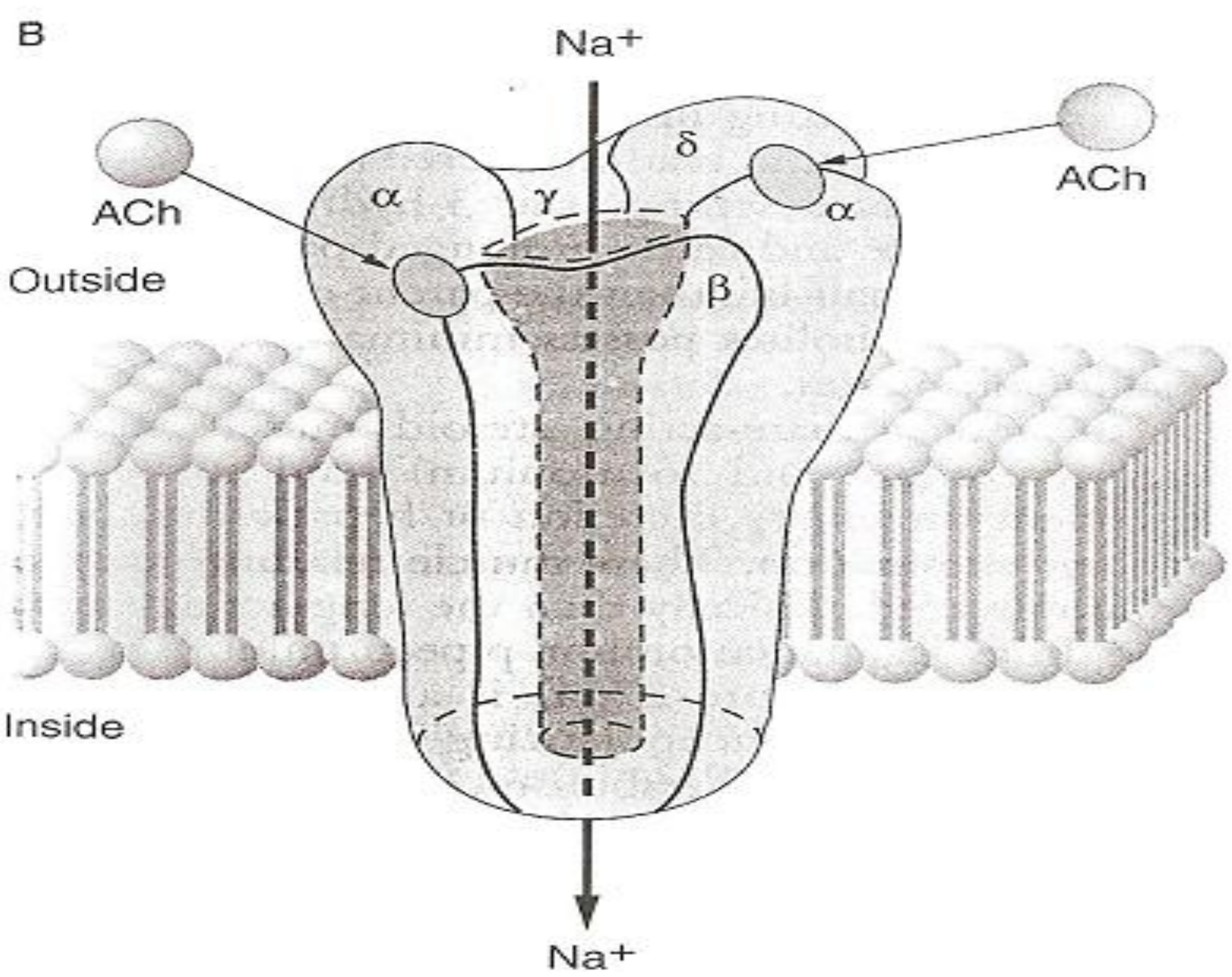
↓

MUSCLE CONTRACTION

PHARMACOLOGY

BLOCKADE
ENHANCEMENT

- TETRODOTOXIN, BATRACHOTOXIN, LOCAL ANESTHETICS → NERVE ACTION POTENTIAL (AP)
- HEMICHOLINIUM, BOTULINUS TOXIN, PROCAINE, Mg^{2+}, β-BUNGAROTOXIN, LACK OF Ca^{2+} → ACETYLCHOLINE RELEASE
- EXCESS OF Ca^{2+} → ACETYLCHOLINE RELEASE
- CURARE ALKALOIDS, SNAKE α-TOXINS → DEPOLARIZATION (EPP)
- SUCCINYLCHOLINE, DECAMETHONIUM → DEPOLARIZATION (EPP)
- NEOSTIGMINE, DFP, K^+ → DEPOLARIZATION (EPP)
- Ca^{2+}, VERATRINE → MUSCLE ACTION POTENTIAL (MAP)
- QUININE → MUSCLE ACTION POTENTIAL (MAP)
- METABOLIC POISONS, LACK OF Ca^{2+}, PROCAINE, DANTROLENE → MUSCLE CONTRACTION


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

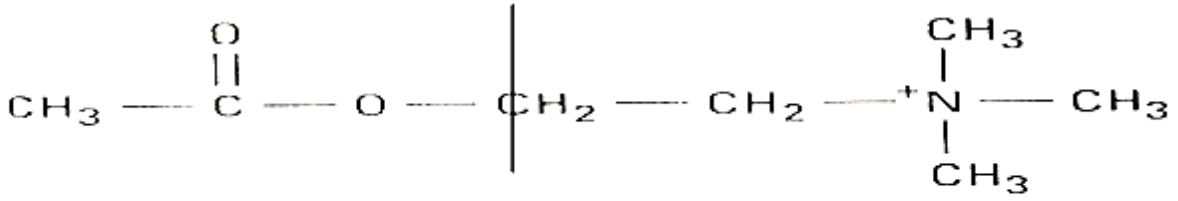
Skeletal Muscle Relaxants

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

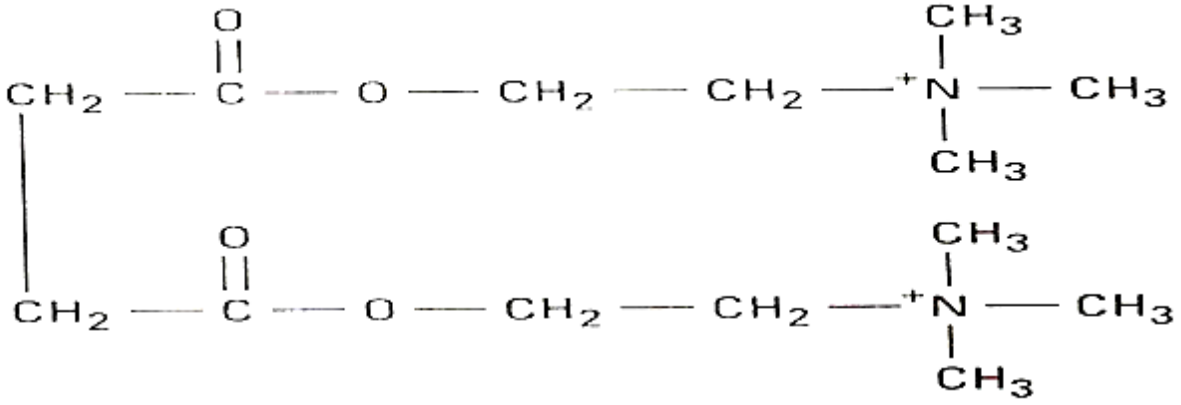
- **Spasmolytics.**
- **Directly Acting Drugs.**

Neuromuscular Blockers

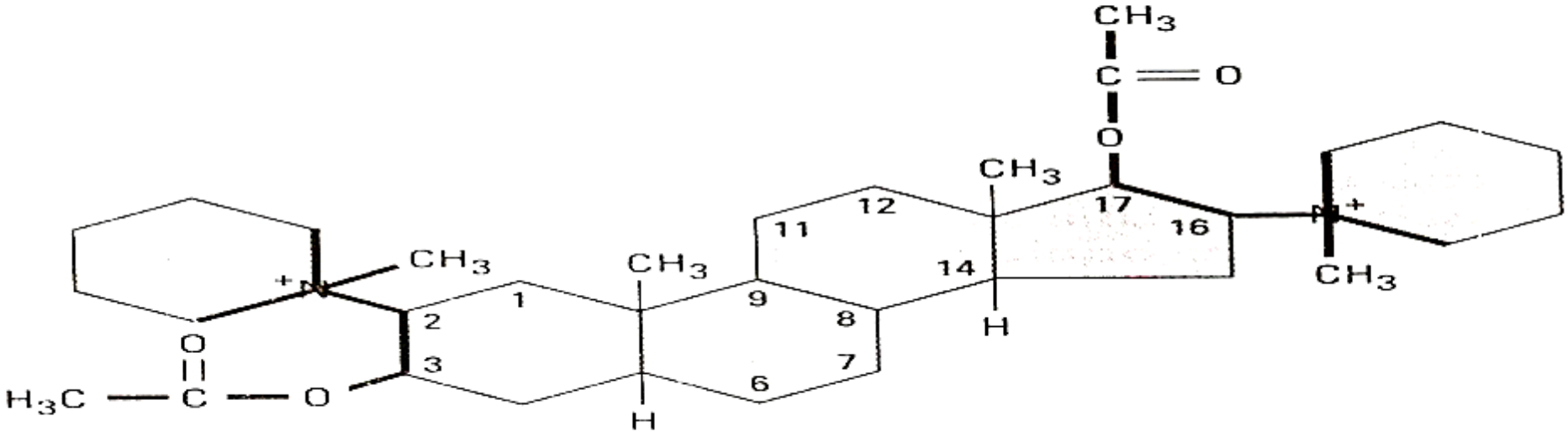
- **Chemistry:**
  - One or two quaternary nitrogens, i.e. poorly lipid soluble or highly polar compounds.
  - Double acetylcholine molecules linked:
    - End to end.
    - Concealed, bulky semi- rigid ring systems.



Acetylcholine



Succinylcholine



Pancuronium

Neuromuscular Blockers

- **Pharmacokinetics:**
  - **All given parenterally.**

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 diffuses 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.**

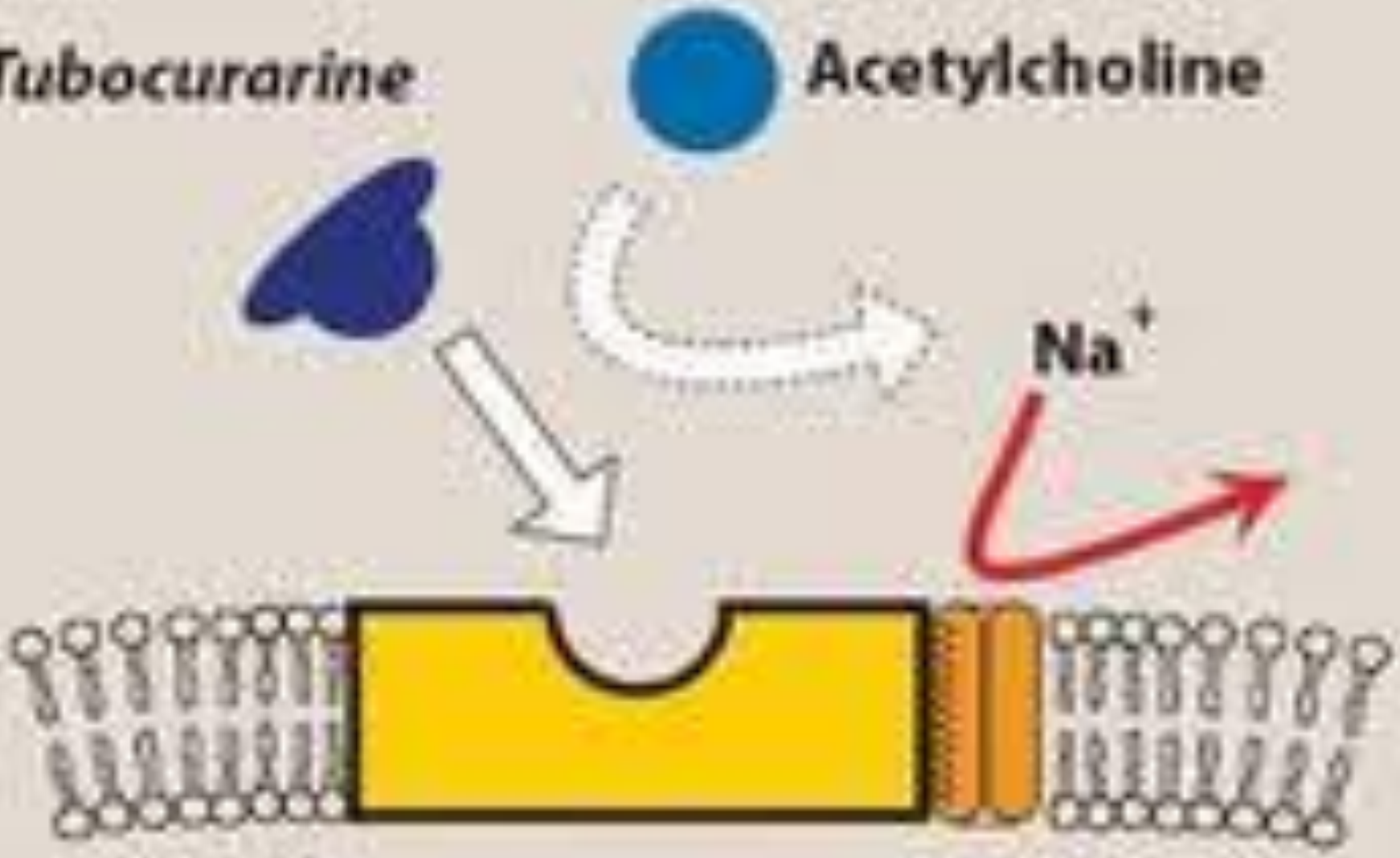
Table 27–1. Some properties of neuromuscular blocking drugs.

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

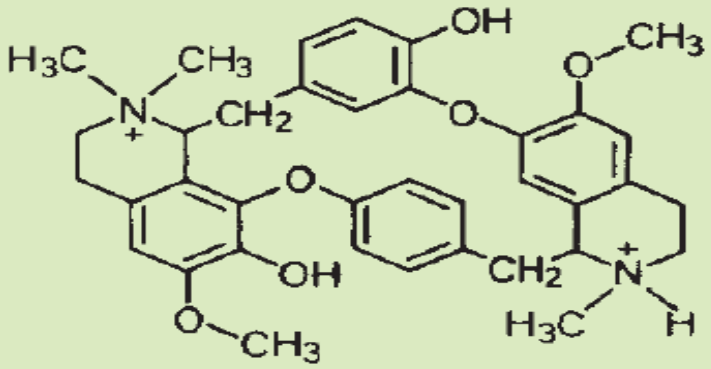
[1]Nonenzymatic and enzymatic hydrolysis of ester bonds.
[2]Butyrylcholinesterase (pseudocholinesterase).

Neuromuscular Blockers

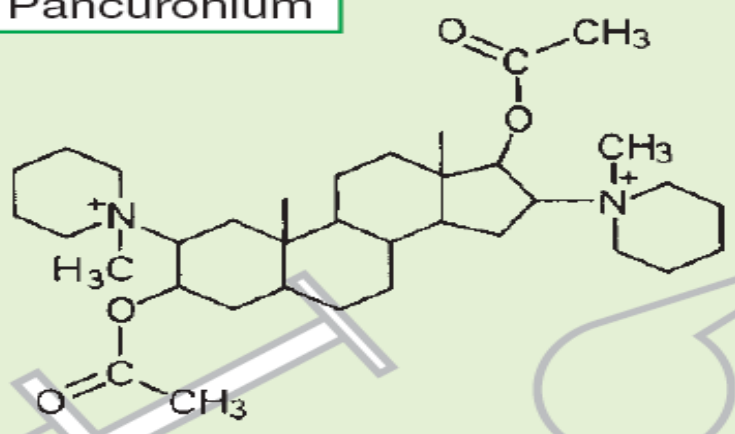
- **Mechanism of Action**
  - Nondepolarizing Drugs:
    - Compete with acetylcholine at the nicotinic receptor sites at the NMJ.
    - In high doses, can enter the pore of the ion channel to cause a more intense blockade.
    - Can also block prejunctional sodium channels to interfere with the mobilization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

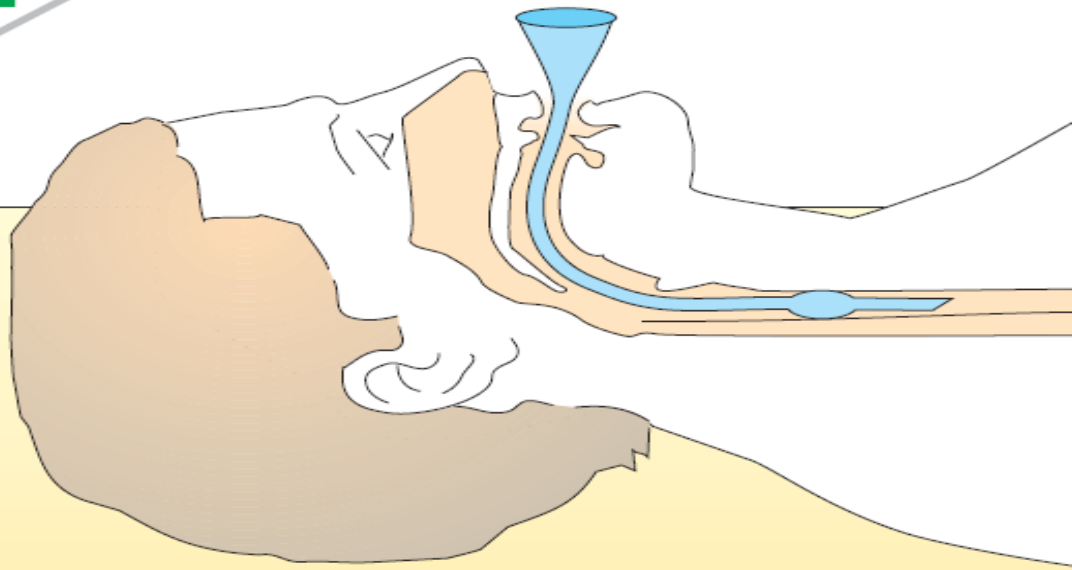

Tubocurarine
Acetylcholine
Na+
Nicotinic receptor at
neuromuscular junction

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!)

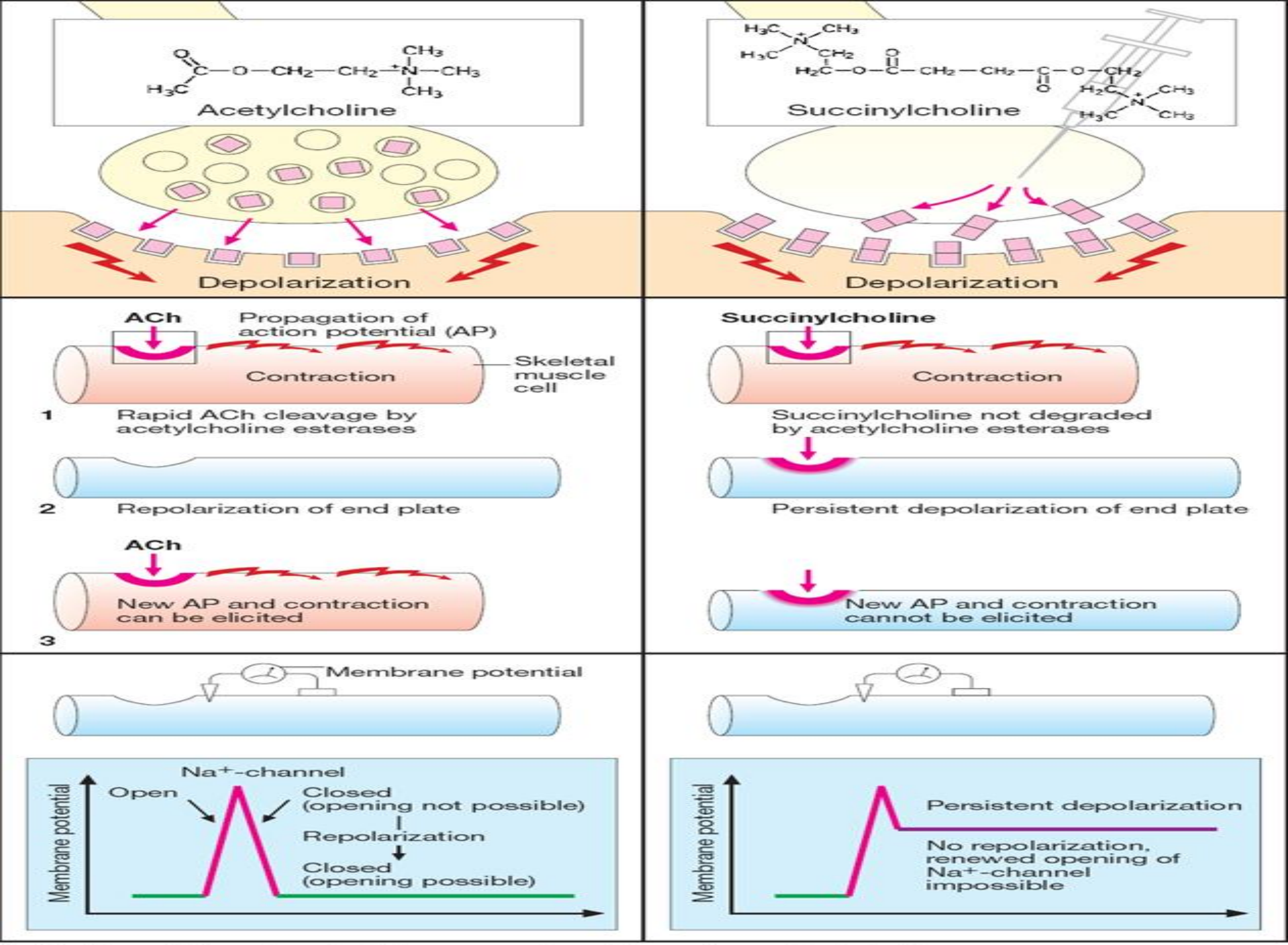
Antidote:
cholinesterase inhibitors
e.g., neostigmine

Neuromuscular Blockers

- **Mechanism of Action:**
  - Depolarizing Drugs:
    - ***Phase I Block(depolarizing):*** succinycholine reacts with nicotinic receptors to open 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
    - This phase 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

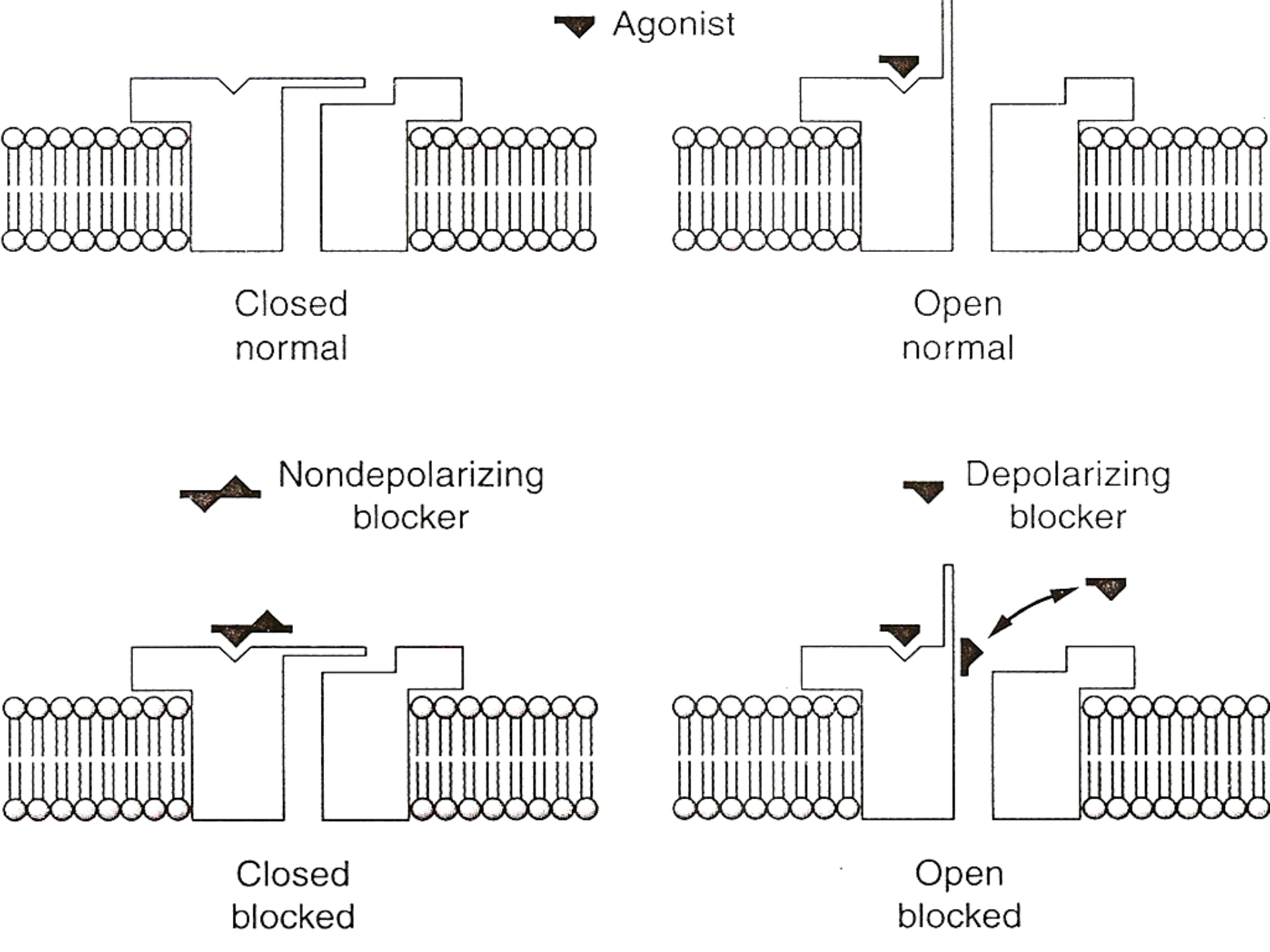

Agonist
Closed
normal
Open
normal
Nondepolarizing
blocker
Depolarizing
blocker
Closed
blocked
Open
blocked

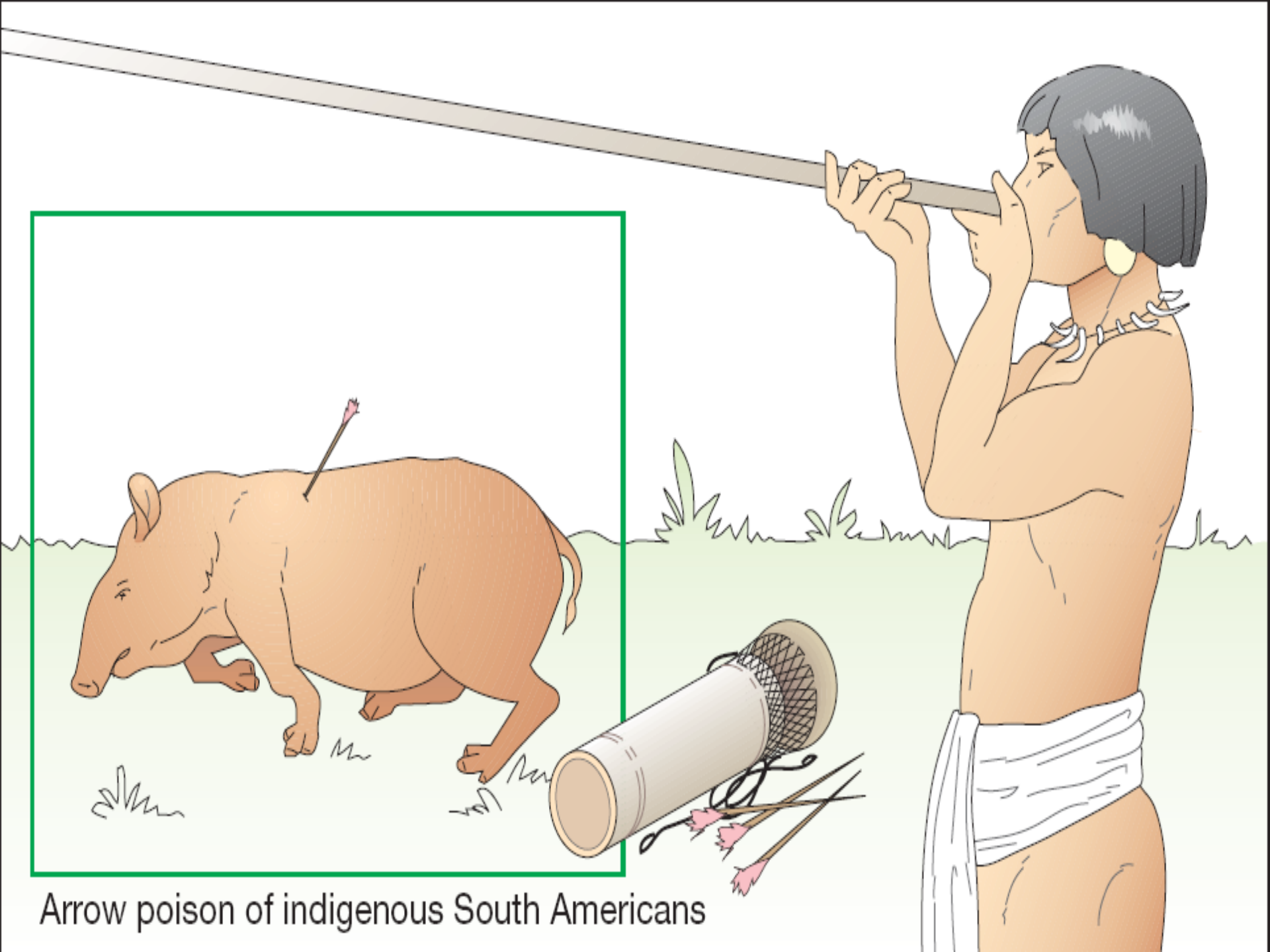
Table 27–2. Comparison of a typical nondepolarizing muscle relaxant (rocuronium) and a depolarizing muscle relaxant (succinylcholine).

		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 starts 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.

Difference	Depolarizers	Non-Depolarizers
Mechanism of Action	These reach the neuromuscular junction, block receptors and cause depolarization Persistently.	Also called stabilizers. These compete with receptors to cause them not to depolarize and action potential is stopped.
Effects	First paralyze large muscles (Abdominal & Limb) then Short muscles (Face, ear, nose) and respiratory muscles in the end.	First paralyze short muscles followed by larger ones and respiratory muscles in the end.
	Effect can not be antagonized.	Effect can be antagonized by reversible inhibitors.
	These directly lead to flaccid paralysis (no tone in muscles).	These stimulate action potential initially for a short while then flaccid paralysis is followed.

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:**
  - In obese, heavily muscled, diabetics, traumatic patients, fasciculations 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 by blocking specific P-type calcium channels.
- **Local anesthetics and antiarrhythmic Drugs**
- **Other Neuromuscular Blockers.**

Spasmolytic Drugs

- **Diazepam:**
  - **Acts at $GABA_A$ receptors in the CNS.**
  - **Facilitates GABA- mediated presynaptic inhibition.**
  - **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 and other excitatory transmitters .
  - Less sedative, but can cause drowsiness.
  - Can be given intrathecally.
  - Can reduce craving (التوق الشديد); in alcoholics and in migraine.

Spasmolytic Drugs

- **Tizanidine:**
  - **Related to clonidine.**
- **Gabapentin:**
  - **An antiepileptic.**
- **Others**

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 used for opthalmic 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.

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.