# 1. SKELETAL MUSCLE RELAXANTS

# (PERIPHERAL: DEPOLARIZING )

# +

## DIRECTLY ACTING

*DR SHAMS SULEMAN*

# LEARNING OBJECTIVES

- Classify skeletal muscle relaxants.
- Describe the mechanism of action of Non depolarizing and depolarizing neuromuscular blockers.
- Discuss the differences between depolarizing and non depolarizing skeletal muscle relaxants
- Describe the therapeutic uses and adverse effects of skeletal muscle relaxants
- Describe centrally acting skeletal muscle relaxants (Spasmolytics)

# LEARNING OBJECTIVES

- Name drugs causing malignant hyperthermia
- Discuss the rationale for use of Dantrolene in the treatment of malignant hyperthermia
- Discuss succinylcholine apnea and its management

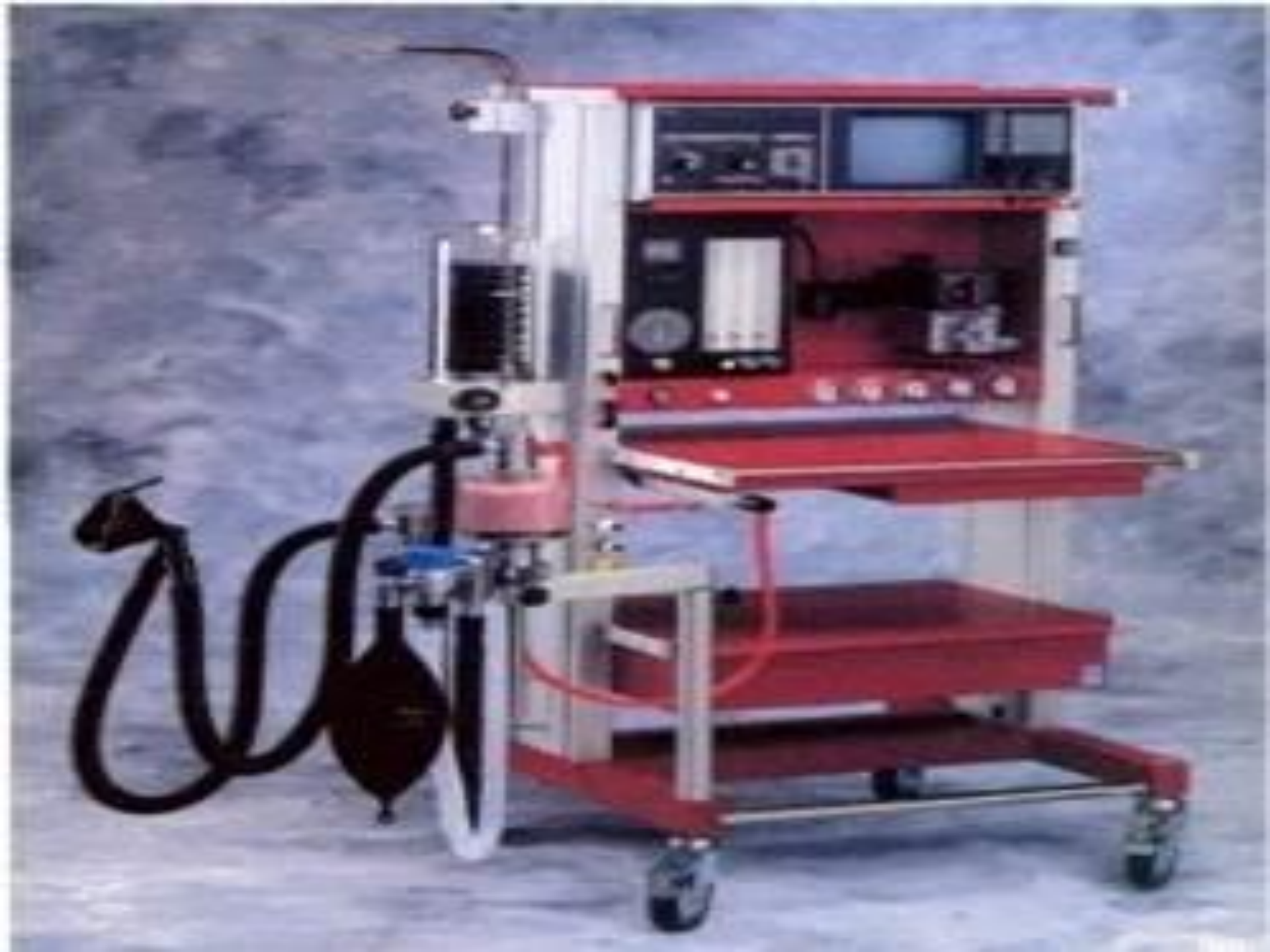
# Introduction

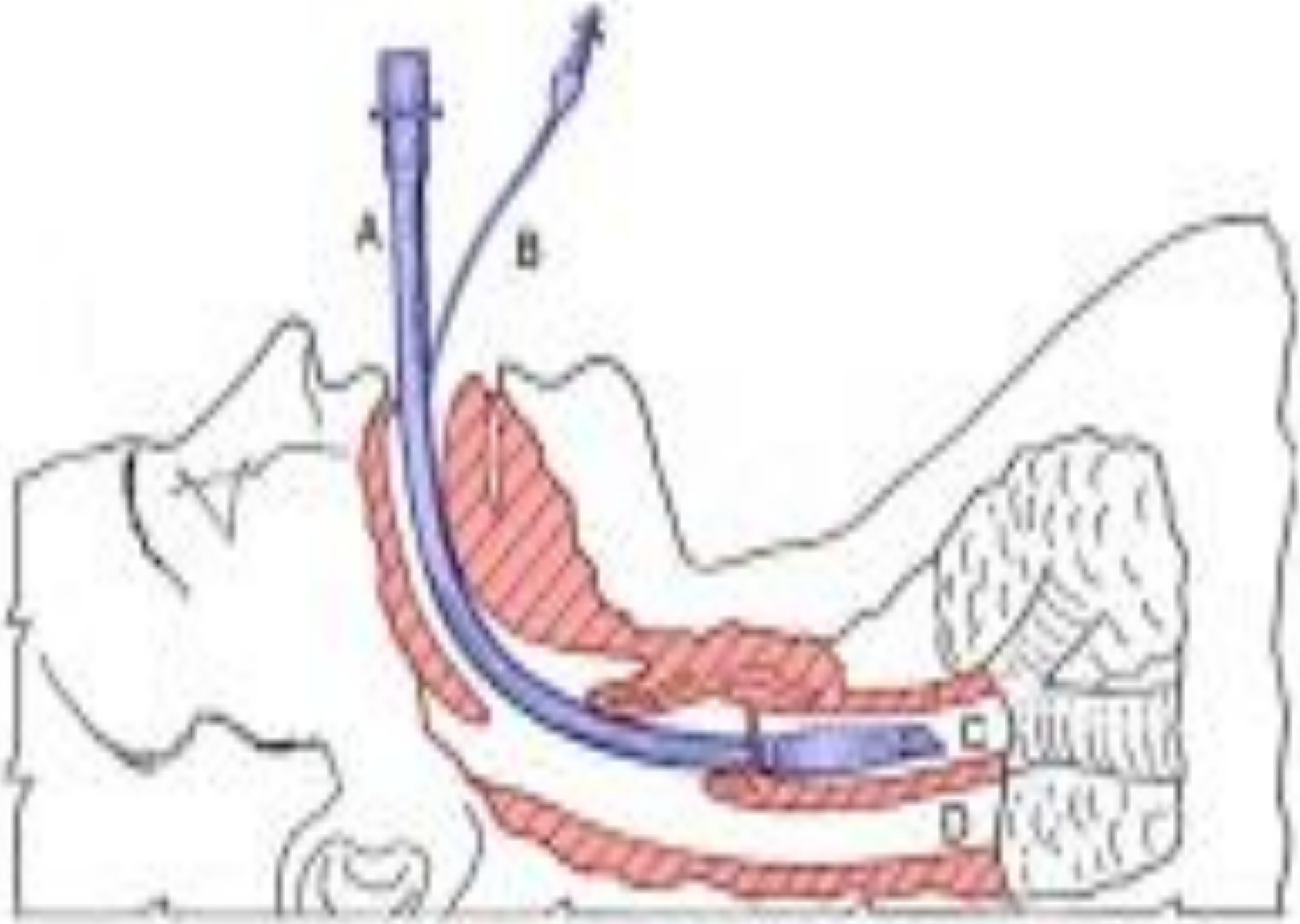
What are neuromuscular blocking drugs ?

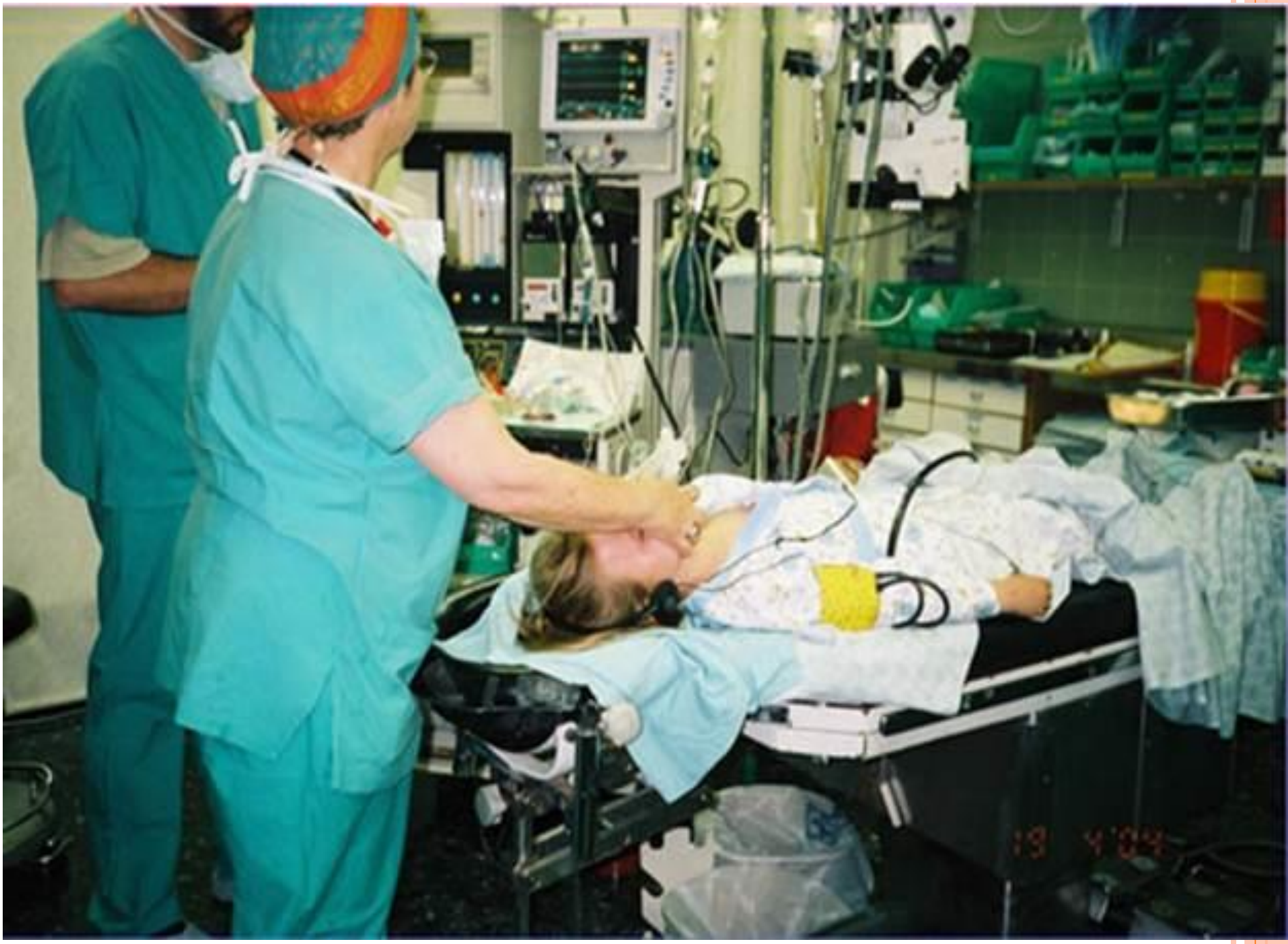
These are agents that act peripherally at neuromuscular junction/muscle fibre itself to block neuromuscular transmission.

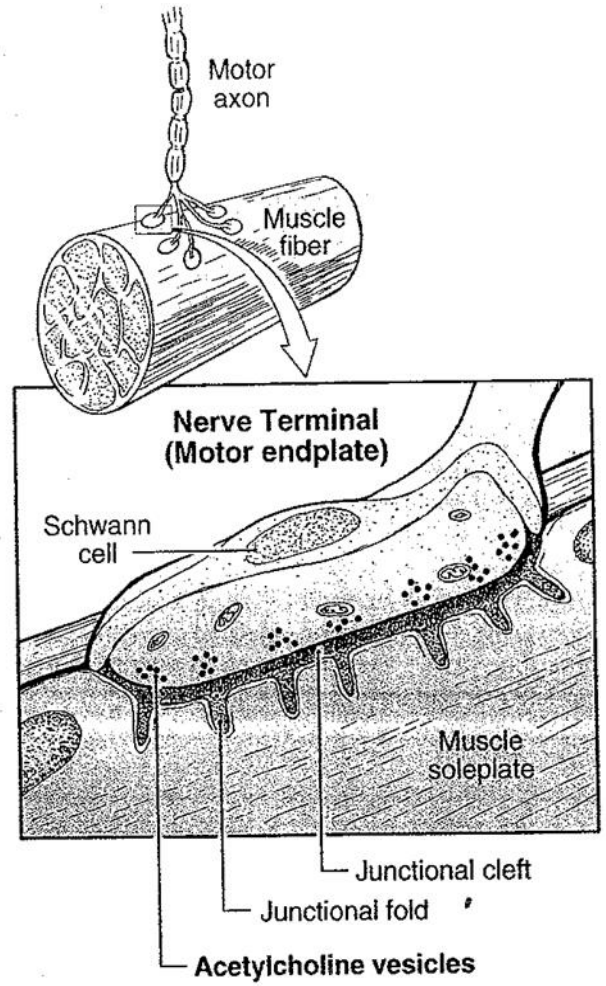
Why do we need them ?

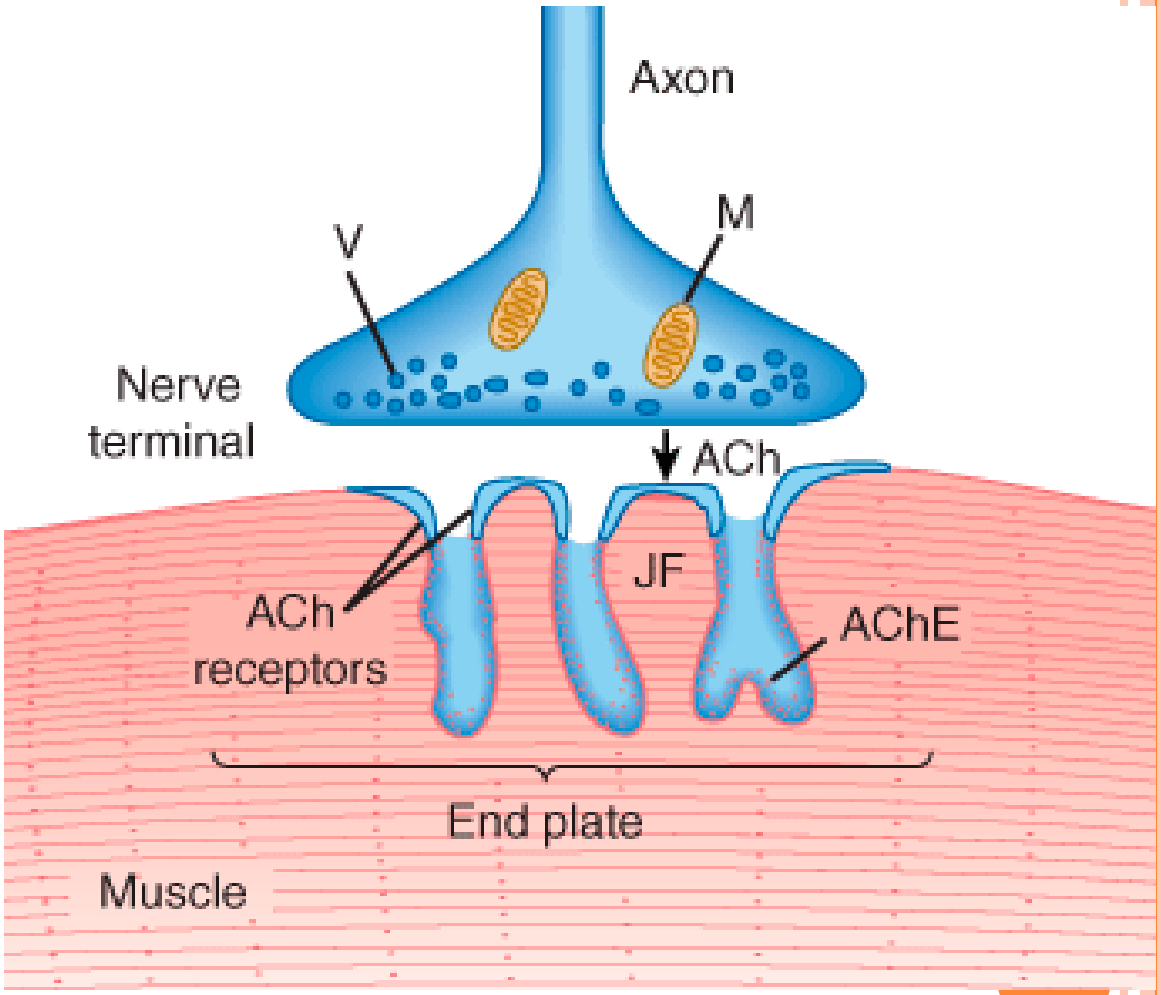
In order to facilitate muscle relaxation for surgery & for mechanical ventilation during surgery or in ICU

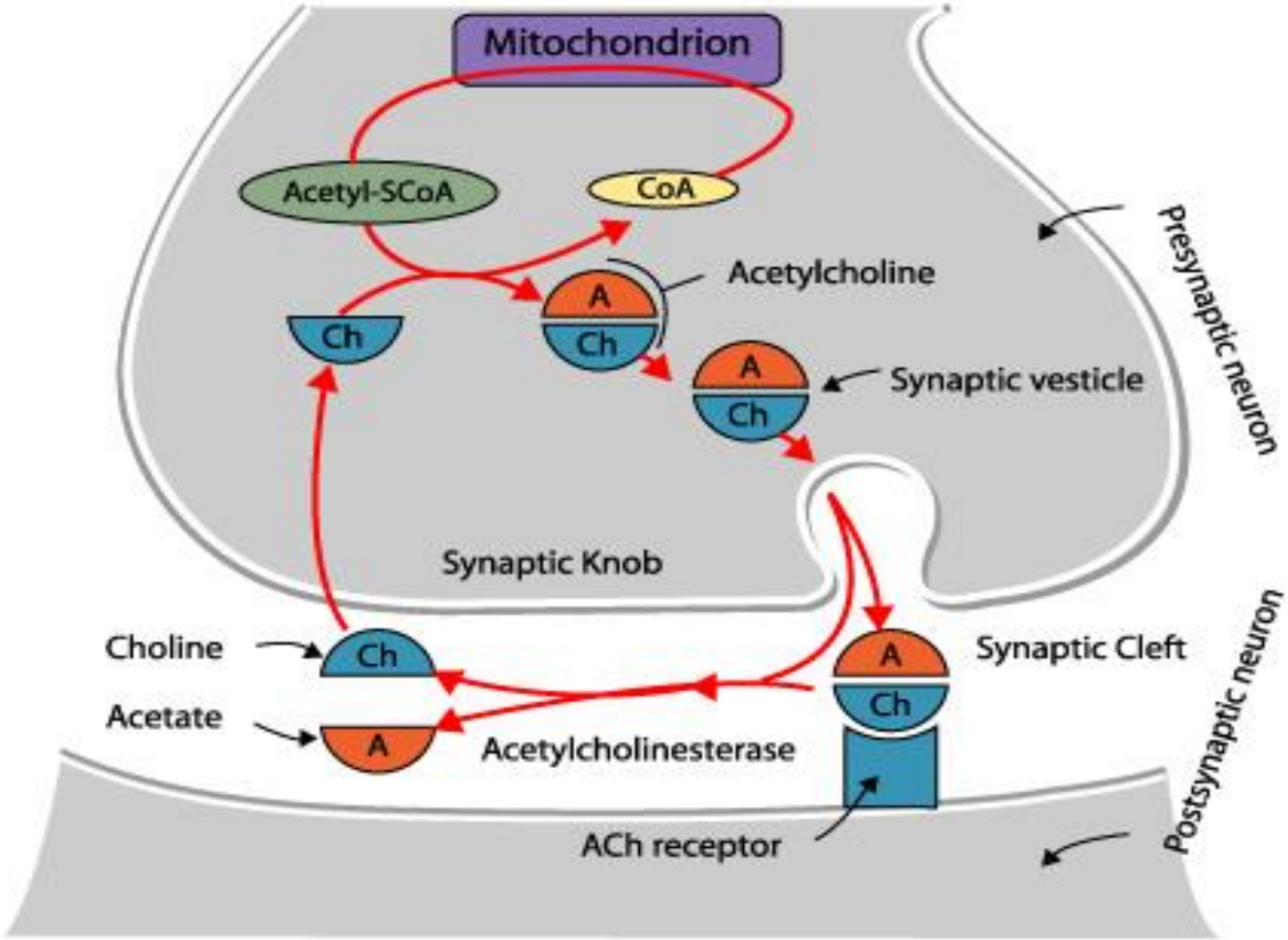



A
B
C
D

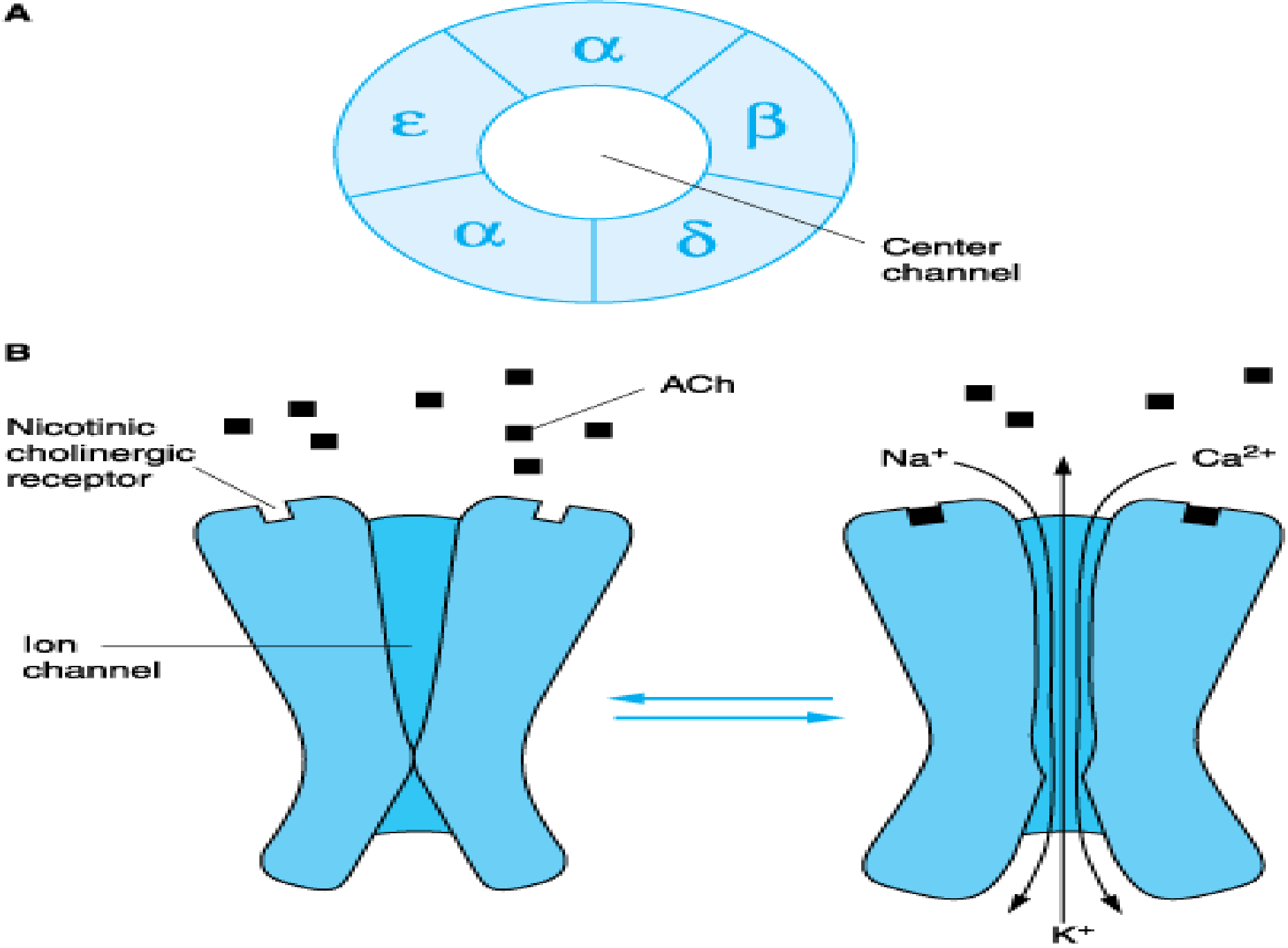


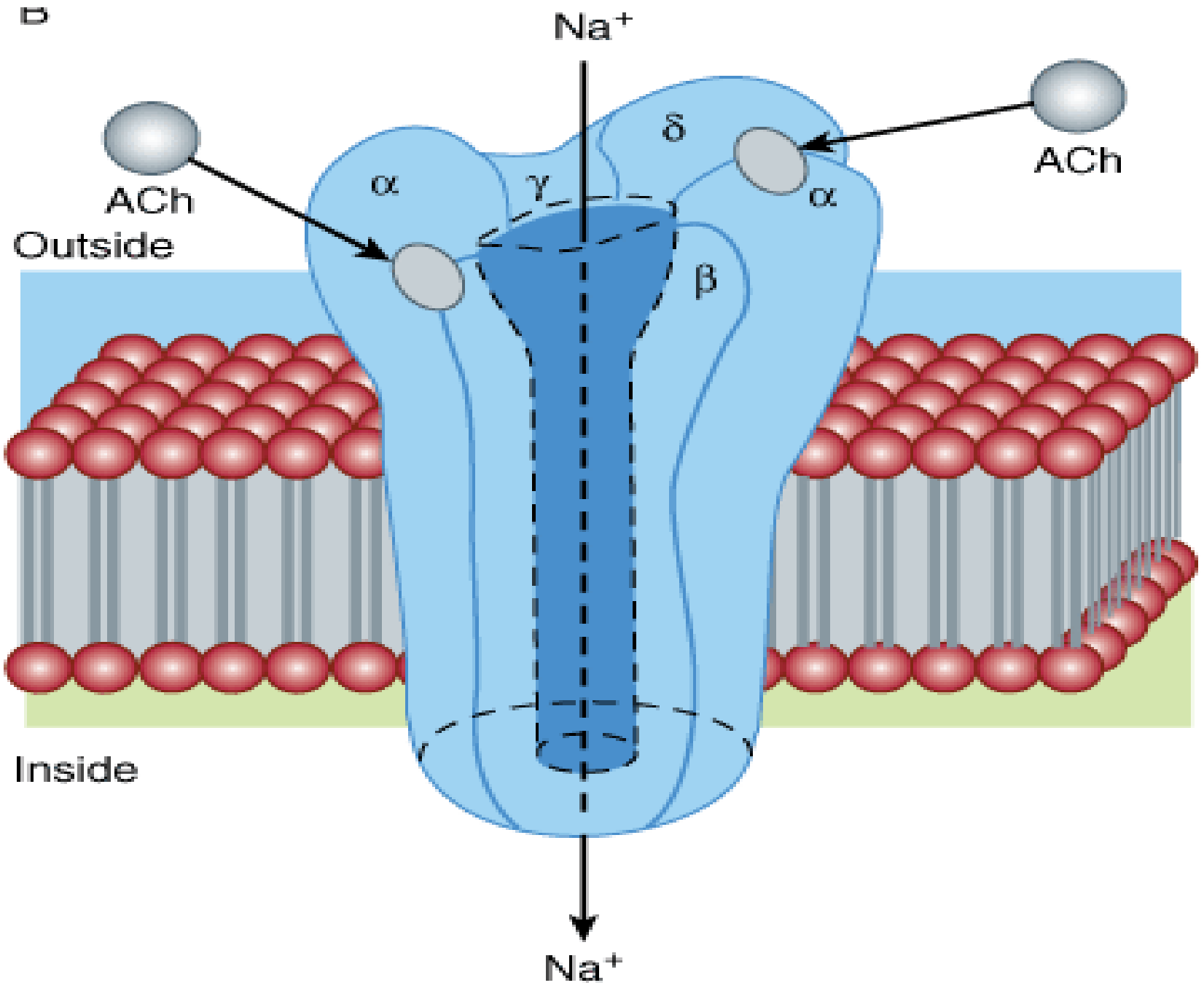

Motor axon
Muscle fiber
Nerve Terminal (Motor endplate)
Schwann cell
Muscle soleplate
Junctional cleft
Junctional fold
Acetylcholine vesicles


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




AnaesthesiaUK




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

# Physiologic of Muscle Contraction

Arrival of an action potential at the motor nerve terminal

↓

Influx of calcium

↓

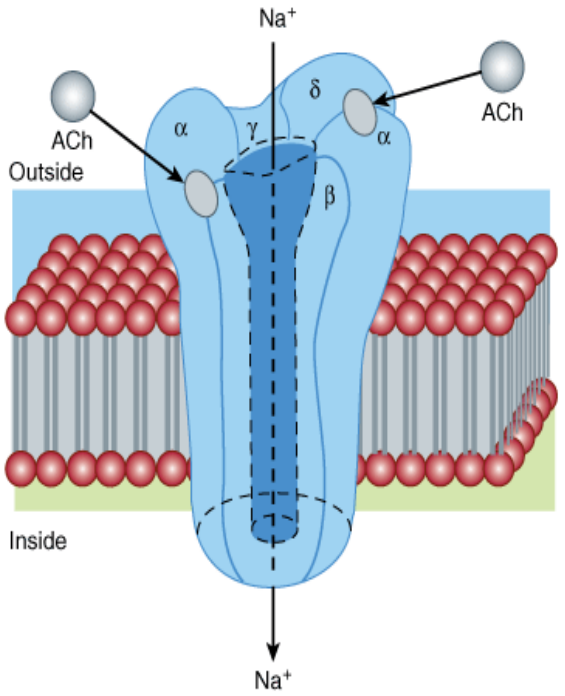
Release of acetylcholine

↓

Diffusion of acetylcholine across the synaptic cleft

↓

Activation of nicotinic receptors on motor end plate



Muscle contraction is then initiated by excitation-contraction coupling

AP depolarizes muscle membrane + travels deeply within the muscle fiber

SR release $Ca^{++}$

$Ca^{++}$ initiates attractive forces between Actin & Myosin filaments

$Ca^{++}$ pumped back into SR

Released acetylcholine is quickly removed from the end plate region

Diffusion & enzymatic destruction by the local acetylcholinesterase enzyme

# Mechanisms of Neuromuscular Blockade

**Blocking the effect of physiological agonist**

**Non-depolarizing blockade**

- **Tubocurarine**

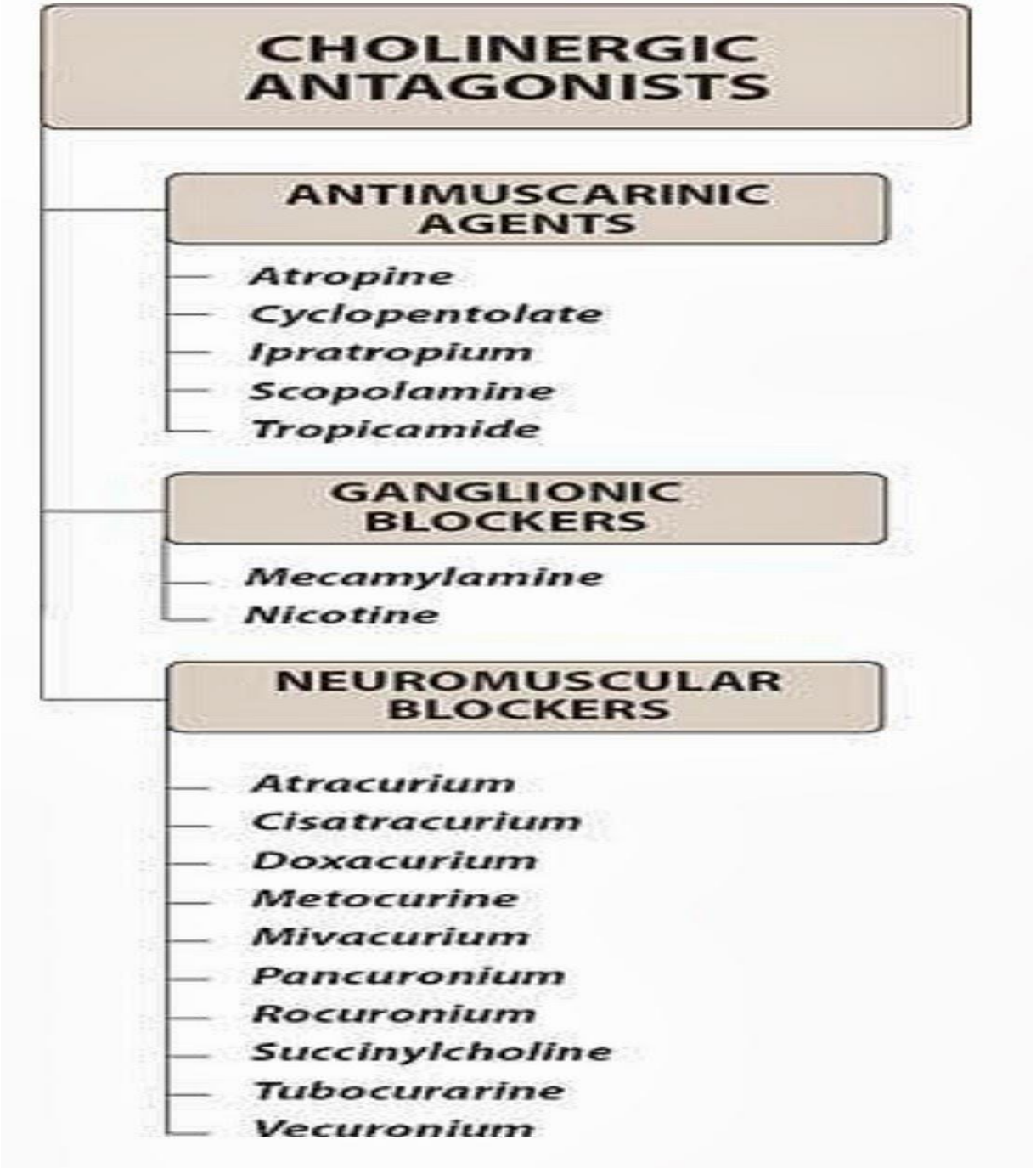
**Excess of depolarizing agonist**

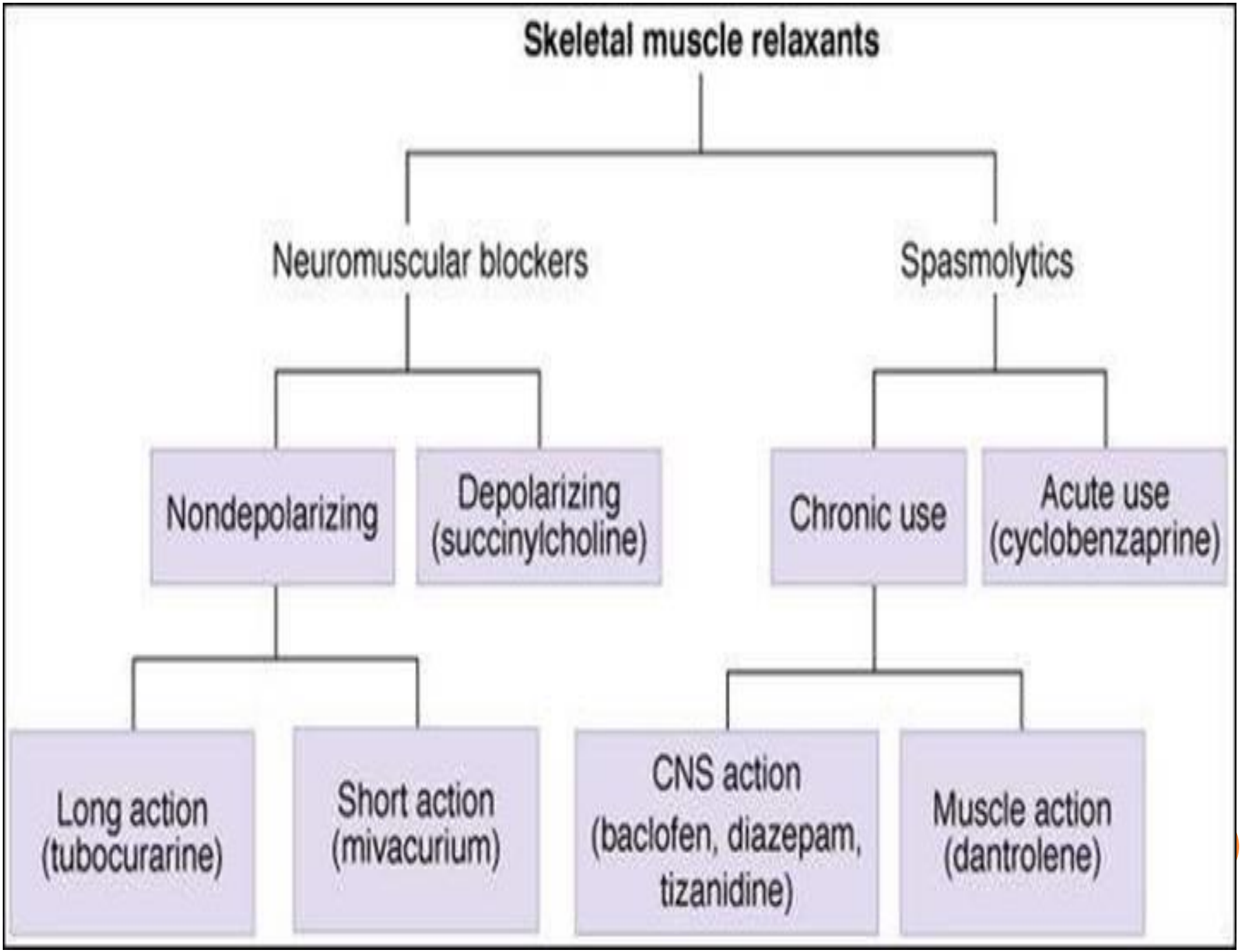
**Depolarizing blockade**

- Acetylcholine
- **Succinylcholine**

# SEQUENCE OF PARALYSIS OF SKELETAL MUSCLES

- Motor muscle weakness to total flaccid paralysis
- Muscles capable of rapid movement like eye, jaw, larynx are paralyzed first
- Then neck, limbs, trunk are paralyzed
- Diaphragm and other respiratory muscles are last to be paralyzed
- Recovery occurs in reverse order ie diaphragm to be the first to recover and facial muscles are last of all


CHOLINERGIC ANTAGONISTS
ANTIMUSCARINIC AGENTS
Atropine
Cyclopentolate
Ipratropium
Scopolamine
Tropicamide
GANGLIONIC BLOCKERS
Mecamylamine
Nicotine
NEUROMUSCULAR BLOCKERS
Atracurium
Cisatracurium
Doxacurium
Metocurine
Mivacurium
Pancuronium
Rocuronium
Succinylcholine
Tubocurarine
Vecuronium


Skeletal muscle relaxants
Neuromuscular blockers
Spasmolytics
Nondepolarizing
Depolarizing (succinylcholine)
Chronic use
Acute use (cyclobenzaprine)
Long action (tubocurarine)
Short action (mivacurium)
CNS action (baclofen, diazepam, tizanidine)
Muscle action (dantrolene)

# CLASSIFICATION

- **PERIPHERALLY ACTING**

<u>Neuromuscular blocking agents</u>

- 1. Depolarizing agents
- 2. Non Depolarizing agents

<u>Directly acting</u>

- Dantrolene sodium
- Quinine Sulphate
- Others: Botulinium toxin

- **CENTRALLY ACTING** (SPASMOLYTICS)

# PERIPHERALLY ACTING…….

## ***Depolarizing agents***

Action lasts less than 08 minutes

- Succinylcholine (Suxamethonium)
- Suxethonium
- Decamethonium

***Succinylcholine may stimulate***

- ✓ ***ganglionic nicotinic receptors***
- ✓ ***cardiac muscarinic receptors***

# PERIPHERALLY ACTING…….

## NEUROMUSCULAR BLOCKING AGENTS

### *Non depolarizing agents*

- ✓ **Isoquinolone derivatives (IQ)**
- ✓ **Steroid derivatives (SD)**

# PERIPHERALLY ACTING…….

## ***Non depolarizing agents*** ……..

a):- ***LONG ACTING:*** 30 to 100 minutes

- D Tubocurarine; also ganglion blocker
- Gallamine; anticholinergic
- Pancuronium (SD)
- Doxacarium (ID)
- Pipecuronium (SD)
- Metocurine (ID)

# PERIPHERALLY ACTING…….

***Non depolarizing agents*……..**

b):- **INTERMEDIATE ACTING**; 20 to 60 minutes

- Vecuronium (SD)
- Atracurium (ID)
- Cisatracurium (ID)
- Rocuronium (SD); fastest onset of action

# PERIPHERALLY ACTING…….

## ***Non depolarizing agents*……..**

c):- **SHORT ACTING;** 10 to 20 minutes

- Mivacurium (ID)

OVERALL CLASSIFICATION

# BASED ON DURATION OF ACTION

- Ultra short acting: Succinylcholine (Dep)
  Gantacurium (investigational)
- Short acting: Mivacurium
- Intermediate acting: Vecuronium, atracurium, cisatracurium, rocuronium
- Long acting: D-Tubocurarine, metocurine, pancuronium, doxacurium

# PHARMACOKINETICS OF NEUROMUSCULAR BLOCKERS

- Neuromuscular blockers contain quaternary ammonium groups.
- They are highly polar and poorly soluble in lipid.
- Inactive if given by mouth.
- Penetrate membranes very poorly.
- Do not enter cells or cross the BBB.
- Always given IV or IM.

# CLINICAL USES

- Surgical Relaxation
- Tracheal Intubation
- Control of Ventilation
  - For critically ill patients

    *(Involving trauma  surgery, CPDD, pneumonia etc. on ventilators in ICUs)*
- Treatment of Convulsions
  - Status epilepticus or local anesthetic toxicity

    *(Effective in eliminating the muscular manifestations of the seizures)*

# CLINICAL USES

- Facilitate laryngoscopy, bronchoscopy, esophagoscopy
- In Modified ECT: to prevent fractures
- As a treatment of crush injures of chest
- Rx of poisoning due to convulsant drugs e.g. strychnine

**Spasmolytics (centrally acting muscle relaxants)**

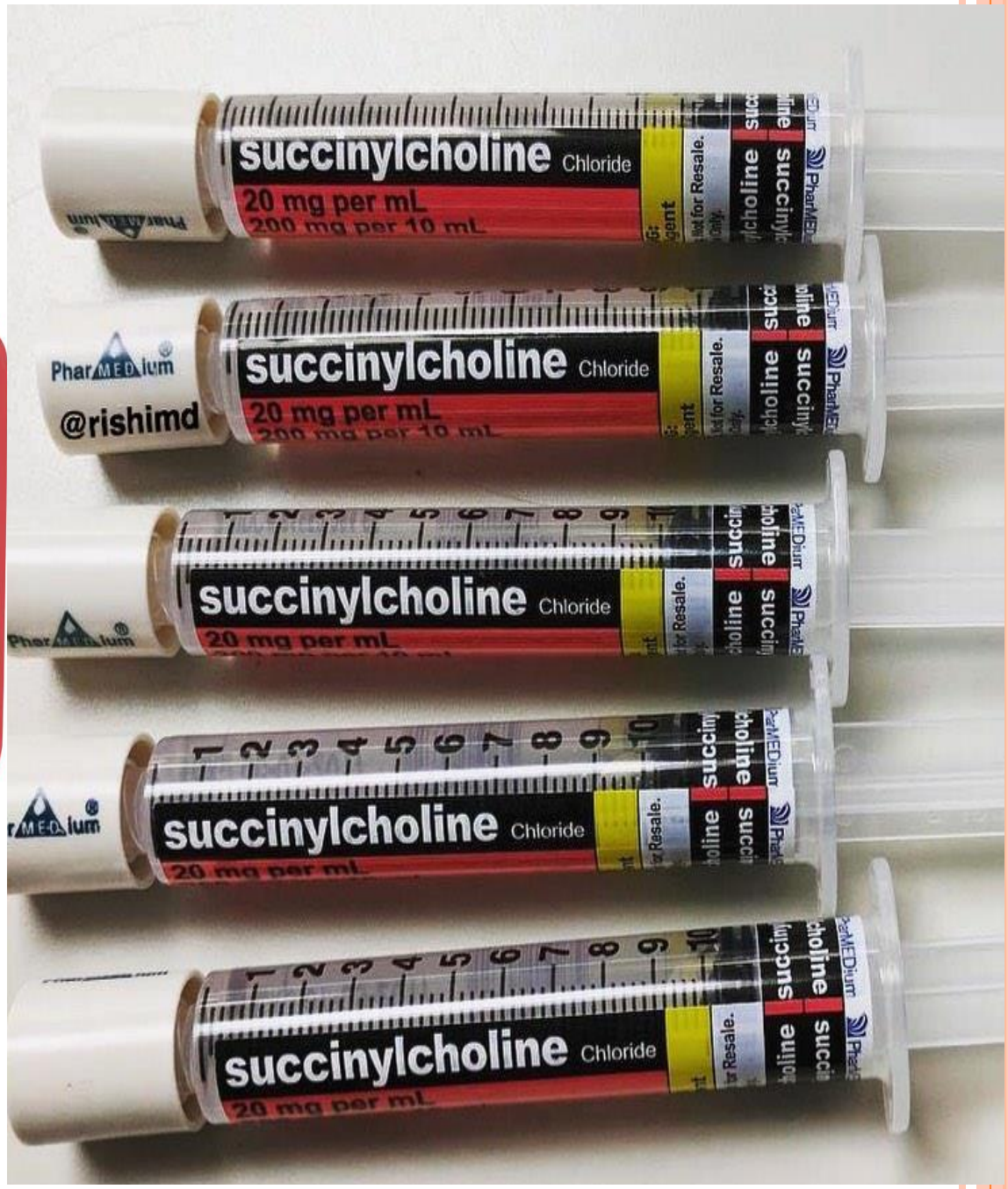
- Reduce spasticity in a variety of painful conditions e.g. backache etc.

# CONTRAINDICATIONS

- Myasthenia gravis
- Concomitant use of aminoglycosides
- Asthmatic patients
- Hypotensive states
- Succinylcholine in children
- Hyperkalemia (caution with other conditions/drugs)
- Severe liver/kidney disease
- Atypical pseudocholinesterase in patients

# SUCCINYL - CHOLINE


5 Ampoules of 2 ml
Succinylcholine Chloride Injection US
Succiflex* 100 mg/2 ml
For I.M/I.V./I.V. Infusion Use
A Synthetic muscle relaxant
Single dose Ampoule
Manufactured by :
SGPharma Pvt. Ltd.
Regd. Office : 542, 310, Bhuta Niwas,
Dr. Ambedkar Road, Matunga (E),
Mumbai 400 019. INDIA
Succiflex*


succinylcholine Chloride
20 mg per mL
200 mg per 10 mL
PharMEDium
@rishimd
Not for Resale.

# Pharmacokinetics

- *Succinylcholine* is injected intravenously.
- Its brief duration of action results from redistribution and rapid hydrolysis by plasma pseudocholinesterase.
- It is sometimes given by continuous infusion to maintain a longer duration of effect.
- Drug effects rapidly disappear upon discontinuation.

# Metabolism of succinylcholine

- $ED_{95}$ 0.51-0.63mg/kg.
- Onset of action-30-60sec.
- Duration of action-9-13 min.
- Shortest acting neuromuscular blocking agent.
- Metabolised by- butrycholinesterase or
  - plasma cholinesterase or
  - pseudocholinesterase

# Plasma cholinesterase

- Has  an enormous capacity to hydrolyze succinylcholine
- Only a small percentage of the IV dose of Succinylcholine reaches the NMJ
- The amount of plasma cholinesterase at the motor end plate == negligible
- So action of succinylcholine is terminated by its diffusion away from the end plate into ECF and  plasma

- Therefore, the circulating levels of plasma cholinesterase influence the duration of action of succinylcholine

# Qualitative analysis of
## Butrycholinesterase

- **Dibucain number-**
- it is a amide based local anesthetic that inhibits normal butrycholinesterase by 80%.

  Abnormal enzyme by 20%.

- **Flouride number**

# DURATION OF ACTION

- Extremely short (5–10 minutes)
- Rapid hydrolysis by:-
- Pseudocholinesterase and butyrylcholinesterase in plasma & liver
  - Primary metabolite = succinyl monocholine
  - Rapidly broken down to succinic acid and choline
- A non depolarizing blocker, Mivacurium is also eliminated by these enzymes

# Metabolism of succinylcholine

- Scuccinycholine on breakdown by butrycholinesterase produces

  1- succinylmonocholine - succinic acid & choline

  2-choline.

- At neuromuscular junction effect of succinylcholine terminated by diffusion.

# Depolarizing Neuromuscular Blocker

- Succinylcholine (also called Suxamethonium)
- Succinylcholine is two acetylcholine molecules linked end-to-end

- Phase I - Depolarizing block
- Phase II – Desensitizing block

# 1. Depolarizing Muscle Relaxant

- **Succinylcholine**

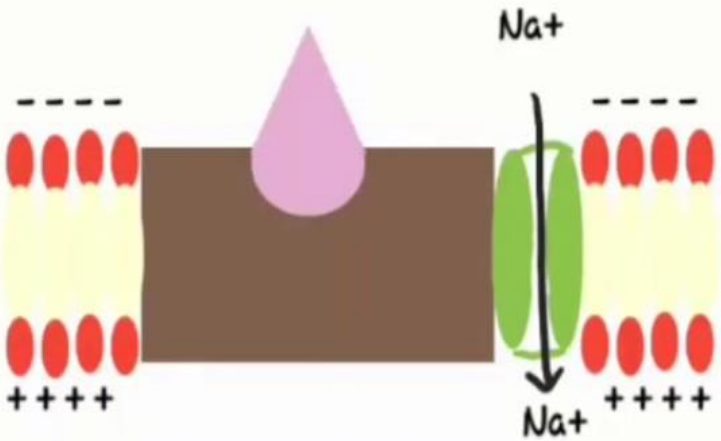
**Mechanism of action:**

- Physically resemble Acetylcholine
- Act as acetylcholine receptor agonist
- Not metabolized locally at NMJ
- Metabolized by pseudocholinesterase in plasma
- Depolarizing action persists > Acetylcholine
- Continuous end-plate depolarization causes muscle relaxation

# *Succinylcholine-Mechanism of Action(Summary)*

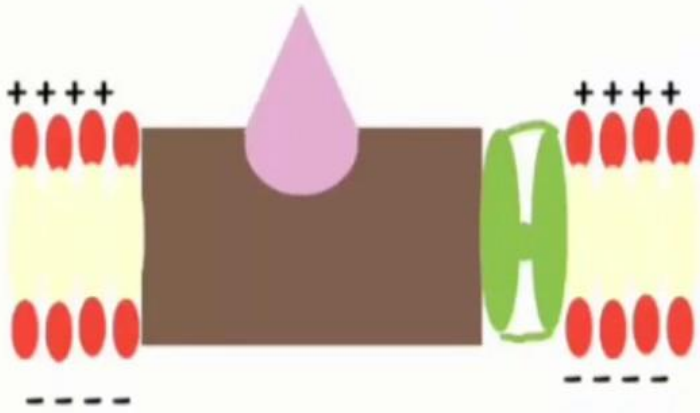
- Phase 1 block: acts as an agonist of ACh to bind with $N_M$ receptor at NMJ - membrane depolarization-transient fasciculations followed by paralysis
- Phase 2 block: desensitization-membrane repolarizes, hyposensitive to ACh

# SUCCINYLCHOLINE: M.O.A




Phase I

Depolarising phase



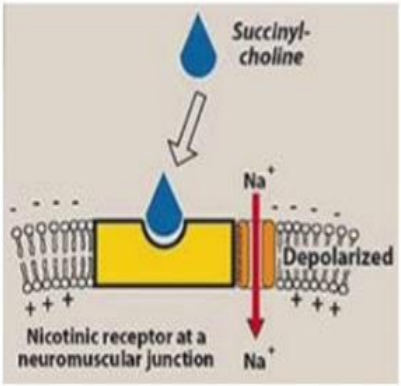
Phase II

Desensitising phase

# Two Phases:

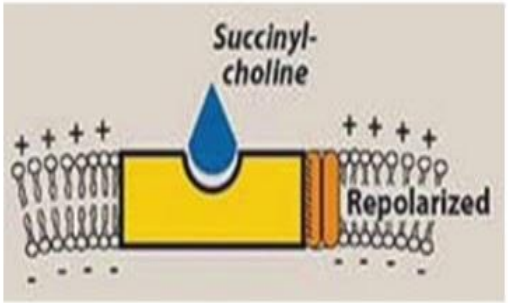
## Phase I

- Membrane depolarization
- Refractory period extends as long as succinylcholine is present
- Initial contraction, then flaccid paralysis



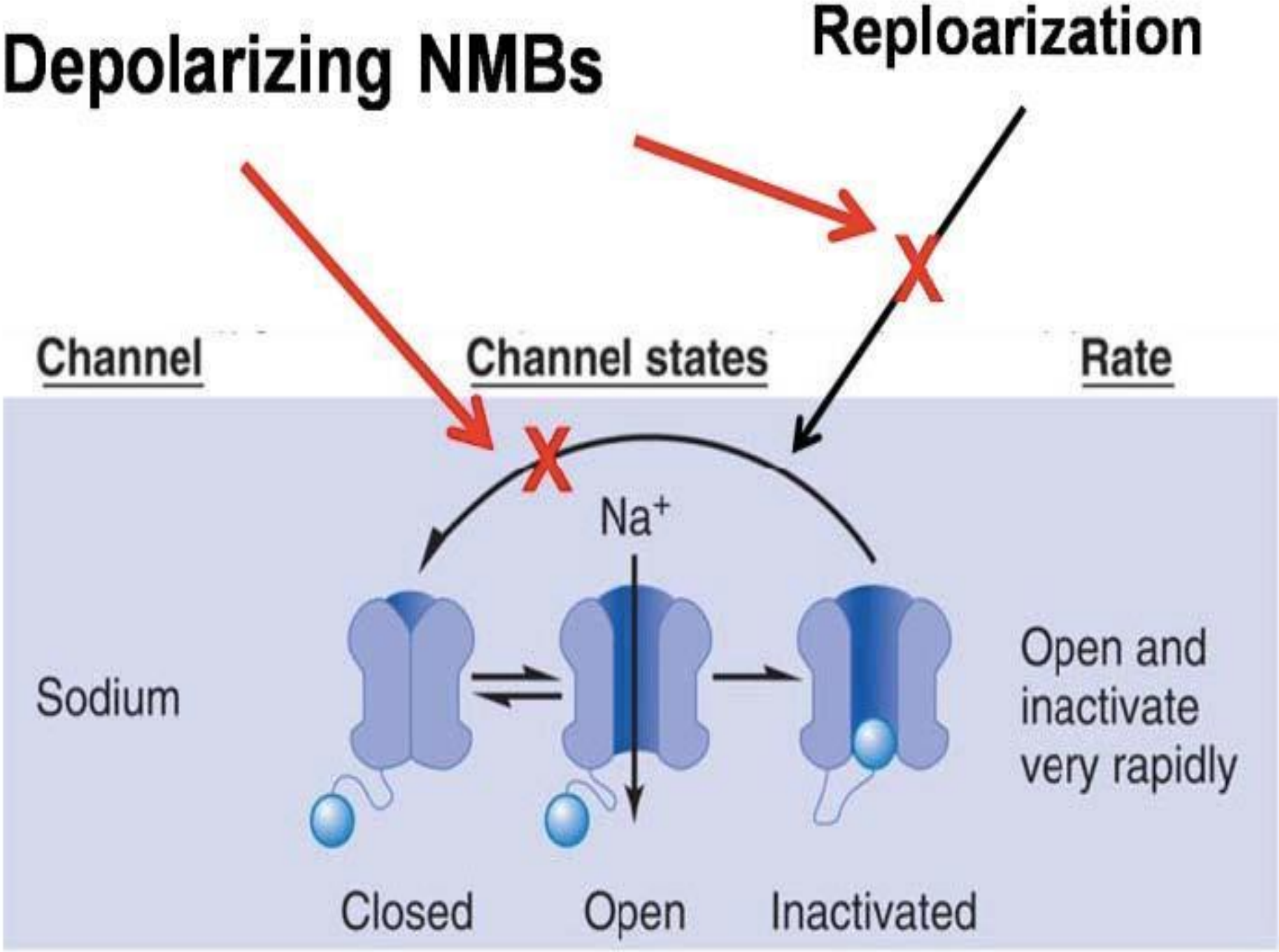

## Phase II

- Membrane repolarization
- Desensitization of the nACh receptor



# Phase I – Depolarizing Block

- Acts as acetylcholine with a longer effect at NMJ
- Opens Na channels causing depolarization of the motor end plate
- Causes contractions of muscle motor units
- **Because of the lack of pseudo cholinesterase at NMJ, the depolarized membranes remain depolarized and unresponsive to subsequent impulses with no end plate repolarization ("repriming")**
- Resulting in a state of depolarizing blockade


Depolarizing NMBs
Reploarization
Channel
Channel states
Rate
Na+
Sodium
Open and inactivate very rapidly
Closed
Open
Inactivated

# Phase I – Depolarizing Block

- With no end plate repolarization, a flaccid paralysis results

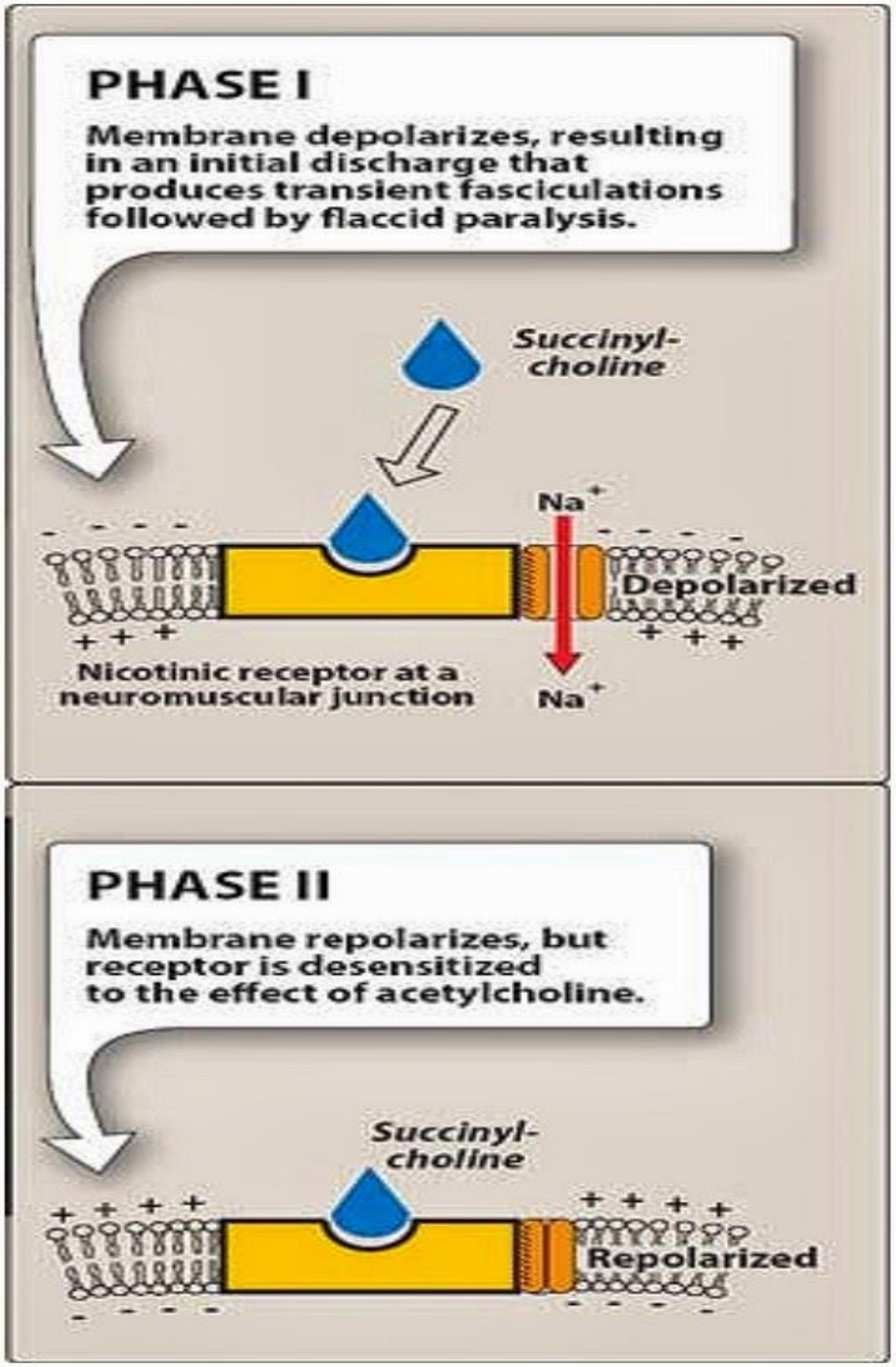
- **The initial depolarization is often accompanied by twitching and fasciculations**

- This Phase I (depolarizing) block is **AUGMENTED**, not reversed, by cholinesterase inhibitors

# Phase II – Desensitizing block

- Depolarization decreases and the membrane becomes repolarized
- Despite this the membrane cannot easily be depolarized again because it is **Desensitized**
- The mechanism is unclear
- It  is postulated:

***succinylcholine enters the channel and block the channel from inside causing desensitization***


PHASE I
Membrane depolarizes, resulting in an initial discharge that produces transient fasciculations followed by flaccid paralysis.
Succinyl-choline
Na+
Depolarized
Nicotinic receptor at a neuromuscular junction
Na+
PHASE II
Membrane repolarizes, but receptor is desensitized to the effect of acetylcholine.
Succinyl-choline
Repolarized

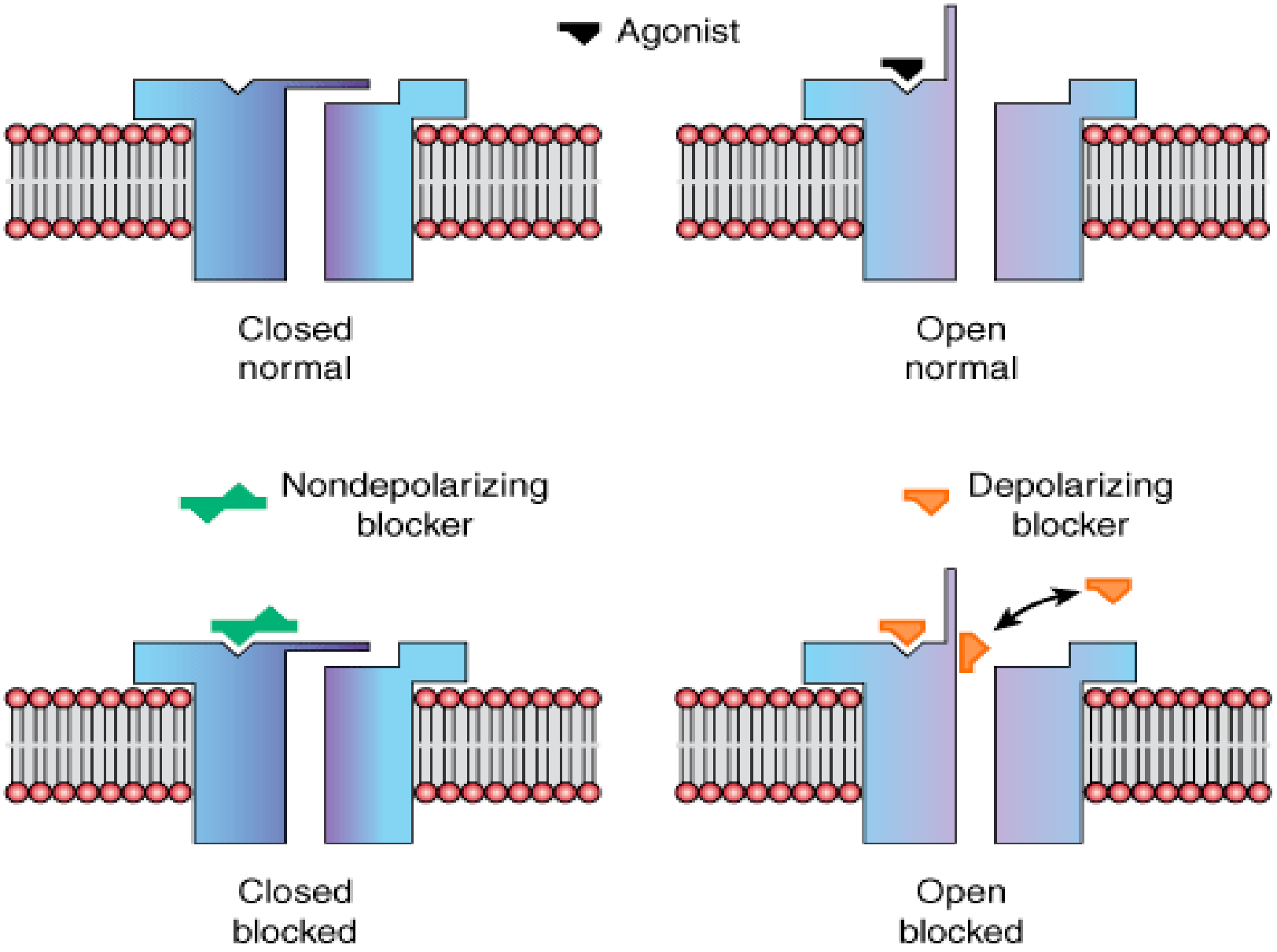
# Phase II – Desensitizing block

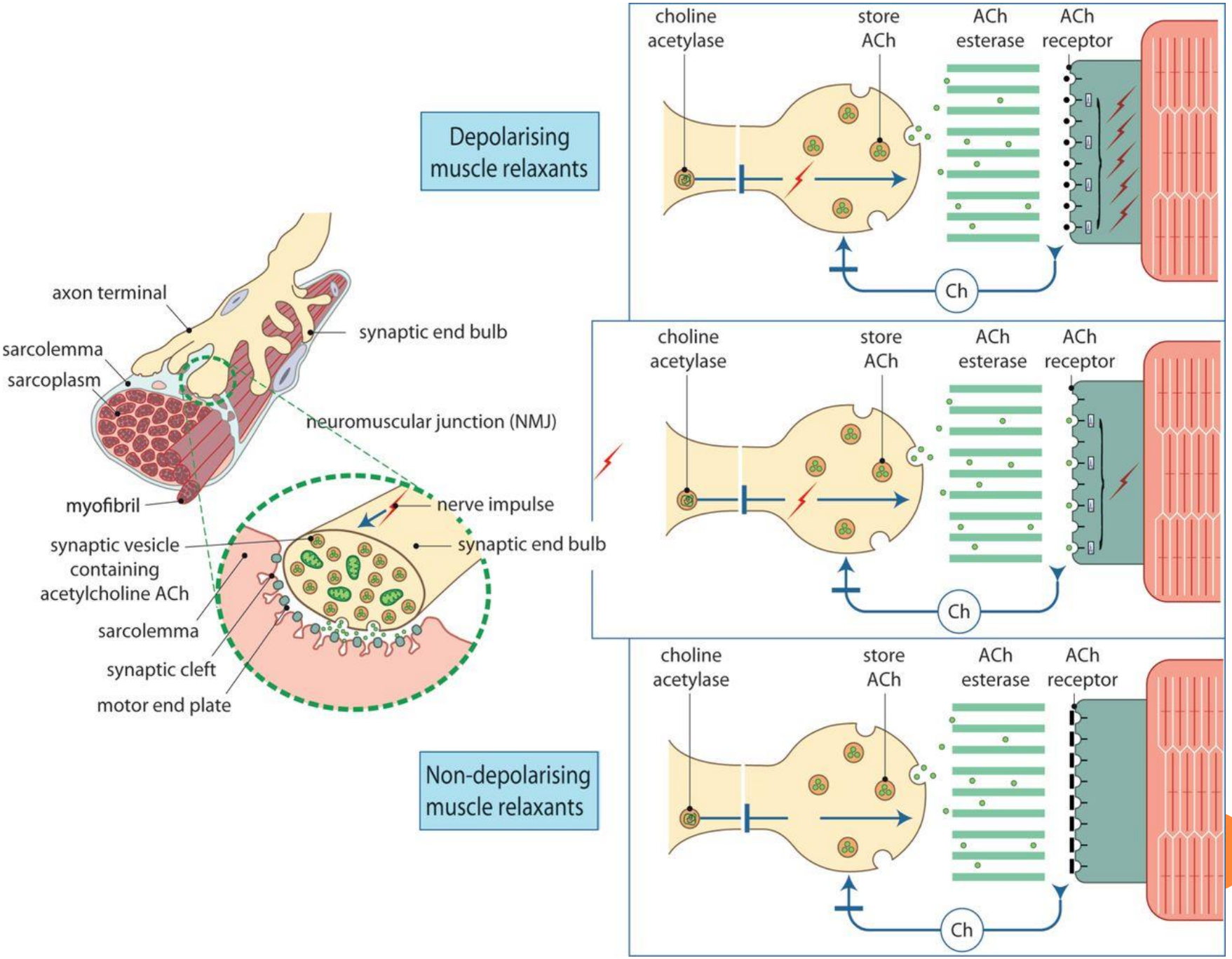
- The channels behave as if they are in a prolonged closed state
- Phase II block of Succinylcholine is identical to that of Nondepolarizing block

***(i.e. a non-sustained twitch response to a tetanic stimulus)***

***with possible reversal by acetylcholinesterase inhibitors***

# PHARMACODYNAMICS



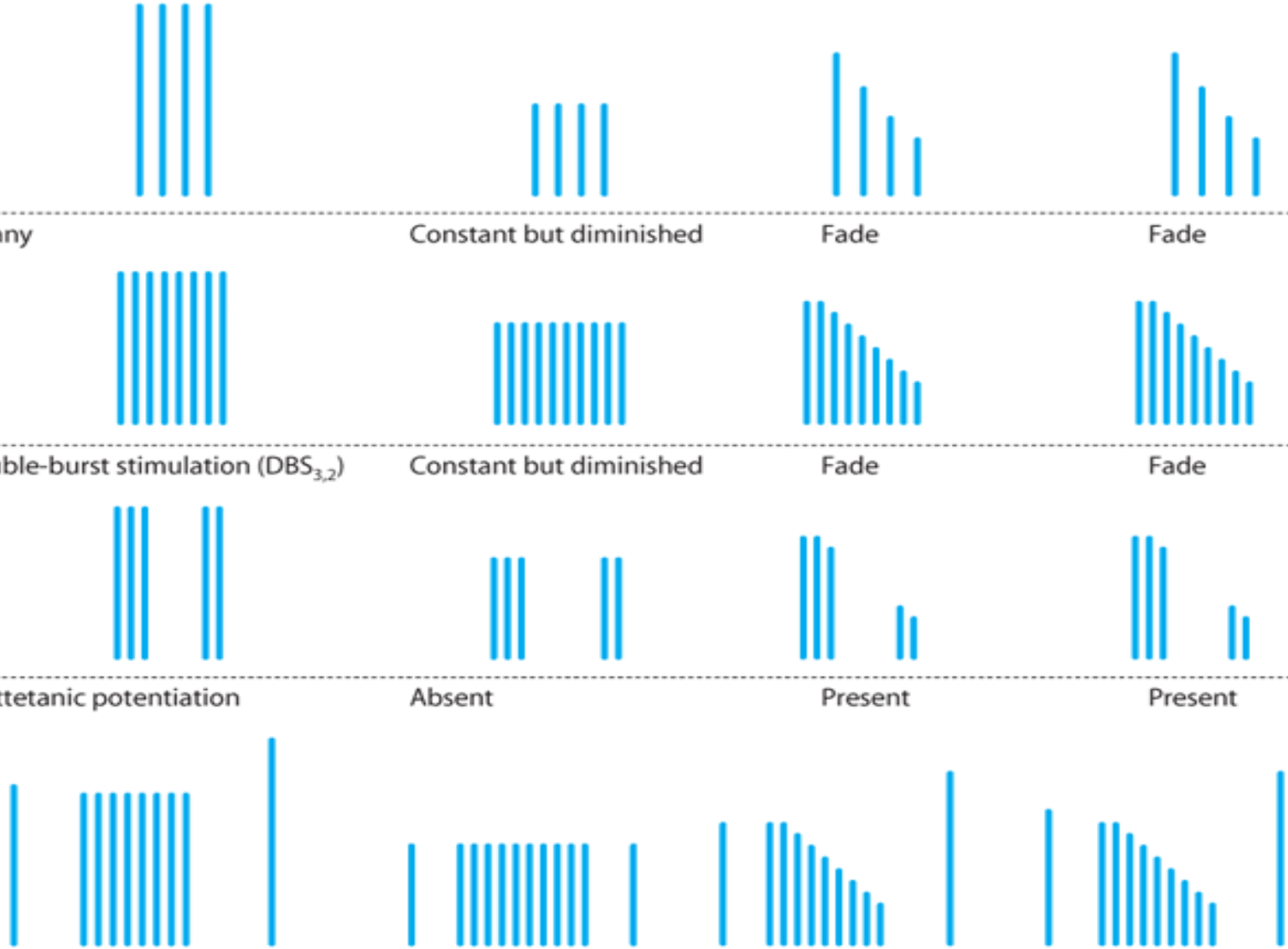

Depolarising muscle relaxants
choline acetylase
store ACh
ACh esterase
ACh receptor
Ch
axon terminal
synaptic end bulb
sarcolemma
sarcoplasm
neuromuscular junction (NMJ)
myofibril
nerve impulse
synaptic vesicle containing acetylcholine ACh
synaptic end bulb
sarcolemma
synaptic cleft
motor end plate
Non-depolarising muscle relaxants

# MONITORING OF NEUROMUSCULAR TRANSMISSION

- Response of a peripheral nerve to transdermal electrical stimulation

1. Single twitch stimulation
2. Train of four (TOF) stimulation
3. Tetanic stimulation
4. Double burst
5. Post tetanic potentiation

| Normal Evoked Stimulus | Depolarizing Block | | Nondepolarizing Block |
|---|---|---|---|
| | Phase I | Phase II | |
| Train-of-four | Constant but diminished | Fade | Fade |
| Tetany | Constant but diminished | Fade | Fade |
| Double-burst stimulation ($DBS_{3,2}$) | Constant but diminished | Fade | Fade |
| Posttetanic potentiation | Absent | Present | Present |



# PHARMACOLOGICAL ACTIONS

- **Cardiovascular Effects:-**
  - Low dose
    - Direct myocardial depressant effects
    - Muscarinic (Vagal) stimulation and parasympathetic ganglionic stimulation
    - Bradycardia
  - High dose
    - Positive inotropic and chronotropic effects

# PHARMACOLOGICAL ACTIONS

- **Effects on Electrolytes:-**

- Hyperkalemia
  - During prolonged depolarization
  - In patients with
    - extensive injury to soft tissues
    - Burns
    - Trauma

- Can cause cardiac arrest

# PHARMACOLOGICAL ACTIONS

- **Effects on Eye:-**

- Increased Intraocular Pressure
  - Peaking at 2–4 minutes, and declining after 5 minutes
  - Tonic contraction of myofibrils and/or transient dilation of ocular Choroidal blood vessels

- Contraindicated in trauma to  anterior chamber ("open globe")

# PHARMACOLOGICAL ACTIONS

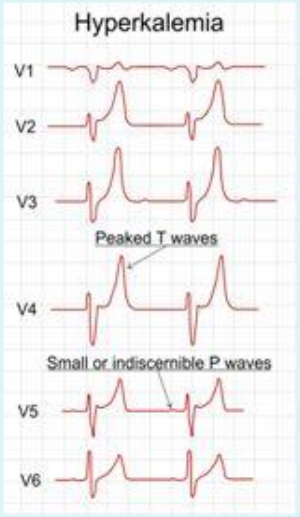
- **Effects on GIT:-**
- Increased Intragastric Pressure
  - In heavily muscled patients related to fasciculation
  - Increases the risk for regurgitation and aspiration of gastric contents
  - More in patients with delayed gastric emptying
    - Diabetes mellitus
    - Traumatic injury
    - Esophageal dysfunction
    - Morbid obesity

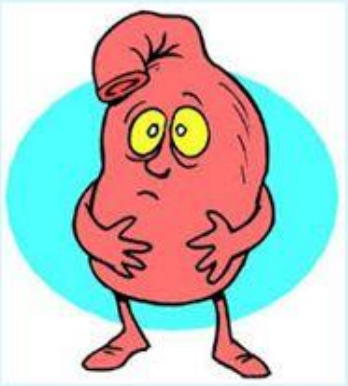
# Reversal of depolarizing Blockade

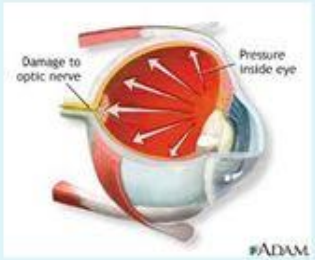
- Short duration of action
- Action terminates itself in 5 – 10 min
- Give ventilatory support

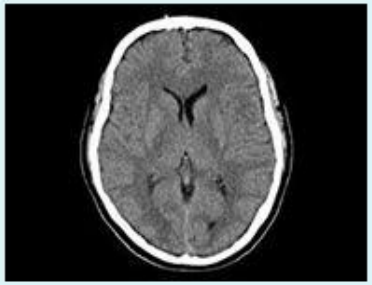
# Succinylcholine-Adverse Side Effects

- Cardiac Dysrhythmia
- Fasciculations
- Hyperkalemia
- Myalgias
- Myoglobinuria
- Increased Intraocular Pressure
- Increased Intracranial Pressure
- Increased Intragastric Pressure
- Trismus
- Malignant Hyperthermia Trigger





# Succinylcholine

## Advantages:

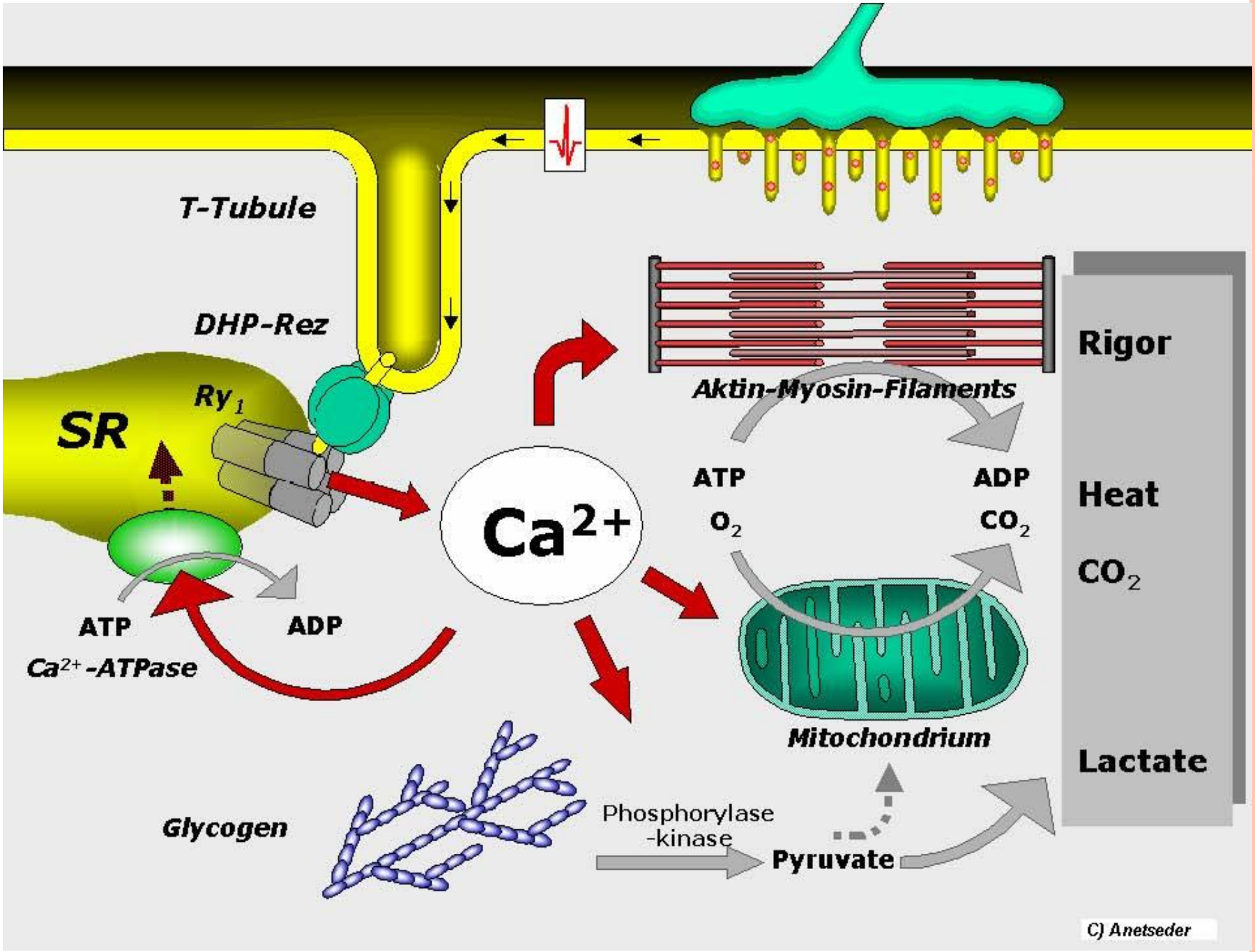
- Most commonly used for Tracheal intubation
- Rapid onset (1-2 min)
- Good intubation conditions – relax jaw, separated vocal chords with immobility, no diaphargmatic movements
- Short duration of action (5-10 minutes)
- Dose 1-1.5mg/kg
- Used as continous infusion occasionally

## Disadvantages:

- Cardiovascular: unpredictable BP, heart rate and arrhythmias
- Fasciculation
- Muscle pain
- Increased intraocular pressure
- Increased intracranial pressure
- Hyperkelemia: k+ efflux from muscles, life threatening in Cardiac Heart Failure, patient with diuretics etc

# Succinylcholine
# Adverse Effects – Malignant Hyperthermia (MH)

- **Malignant Hyperthermia**
  - Very rare condition – 1:15,000
  - Patient experiences a rapid increase of temperature, metabolic acidosis, rhabdomyolysis, and DIC
  - Treatment includes administration of Dantrolene and external means of temp. reduction

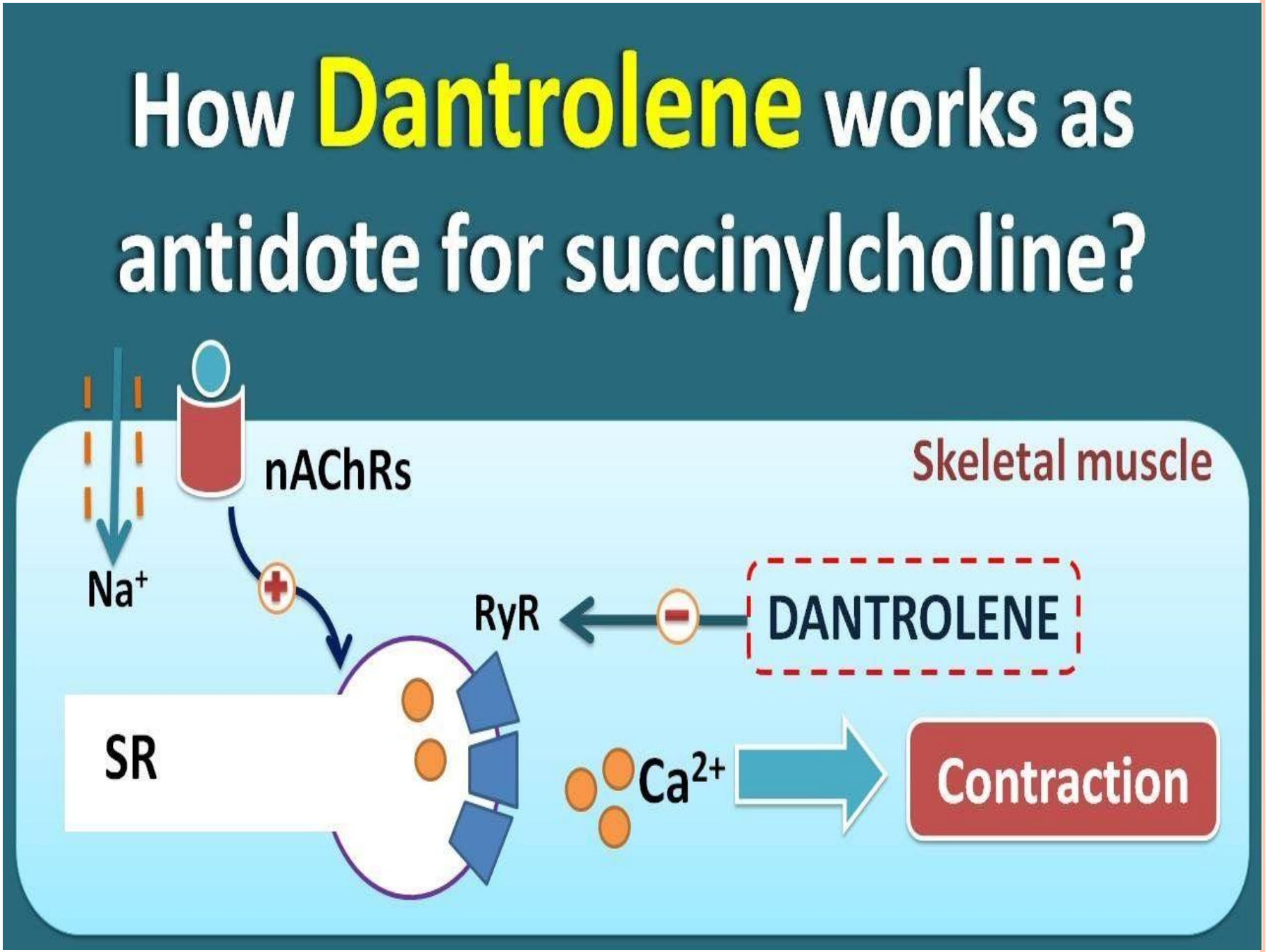

T-Tubule
DHP-Rez
SR
Ry 1
Ca2+
ATP
Ca2+ -ATPase
ADP
Aktin-Myosin-Filaments
ATP
O2
ADP
CO2
Mitochondrium
Rigor
Heat
CO2
Lactate
Glycogen
Phosphorylase
-kinase
Pyruvate
C) Anetseder

# MALIGNANT HYPERTHERMIA,

- Idiosyncratic condition :Genetic condition
- Triggered by  general anesthesia involving halothane protocols
- That  include succinylcholine or tubocurarine

# MALIGNANT HYPERTHERMIA

- Succinylcholine, halothane
- Life threatening condition
- Contracture, rigidity & heat production from skeletal muscle - hyperthermia, metabolic acidosis, tachycardia
- Uncontrolled release of $Ca^{+2}$ from SR (Ryanodine receptor)
- Genetic predisposition
- Dantrolene, rapid cooling 100% oxygen, control of acidosis


How Dantrolene works as antidote for succinylcholine?
nAChRs
Skeletal muscle
Na+
RyR
DANTROLENE
SR
Ca2+
Contraction

# DANTROLENE: MOA
## (HYDANTOIN DERIVATIVE)

- Acts on the Ryanodine receptor (RyR1) channels of the ssarcoplasmic reticulum of skeletal muscle.
- These channels also release Ca++
- It interferes with the release of the $Ca^{++}$
- Resulting in decreased contraction of skeletal muscle
- Thus decreasing the body temperature
- Given IV

✓ ***Cardiac &smooth muscles are depressed slightly***

# DANTROLENE (CONTD.)

**ADVERSE EFFECTS**

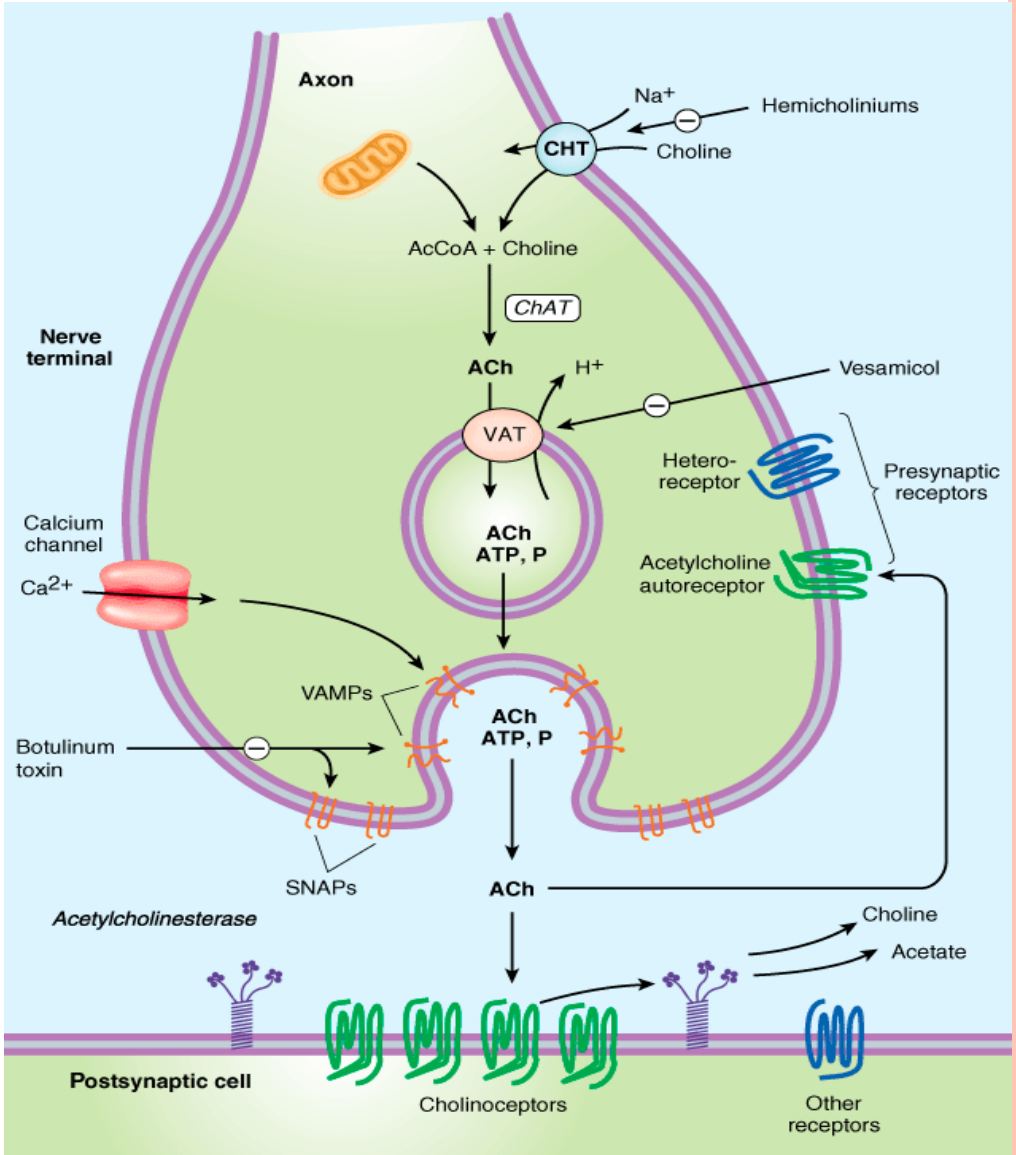
- Sedation
- Muscular weakness
- Fatigue
- Rashes
- Jaundice/hepatitis
- Diarrhea
- Should be used with caution in concomitant hepatic, renal ,cardiac and pulmonary disorders.

# BOTULINUM TOXIN (BoNT)

- Chemodenervation & local paralysis in muscle

**USES**

- Cosmetic
- Cerebral palsy
- Dystonia
- Overactive bladder incontinence
- Chronic



# Succinylcholine Apnea

- Typical example of Idiosyncrasy
- Seen in patients with
  - Atypical/absent pseudo cholinesterase due to genetic defect
  - Liver diseases
- Metabolism of succinylcholine is slow
- Results in:-
  - Severe neuromuscular blockade
  - Respiratory paralysis with prolonged apnoea

# Treatment of Succinylcholine Apnea

- No antidote
- Fresh frozen plasma/ fresh whole blood
- Anesthesia should be continued till recovery from neuromuscular blockade
- Artificial ventilation till the recovery of active respiration

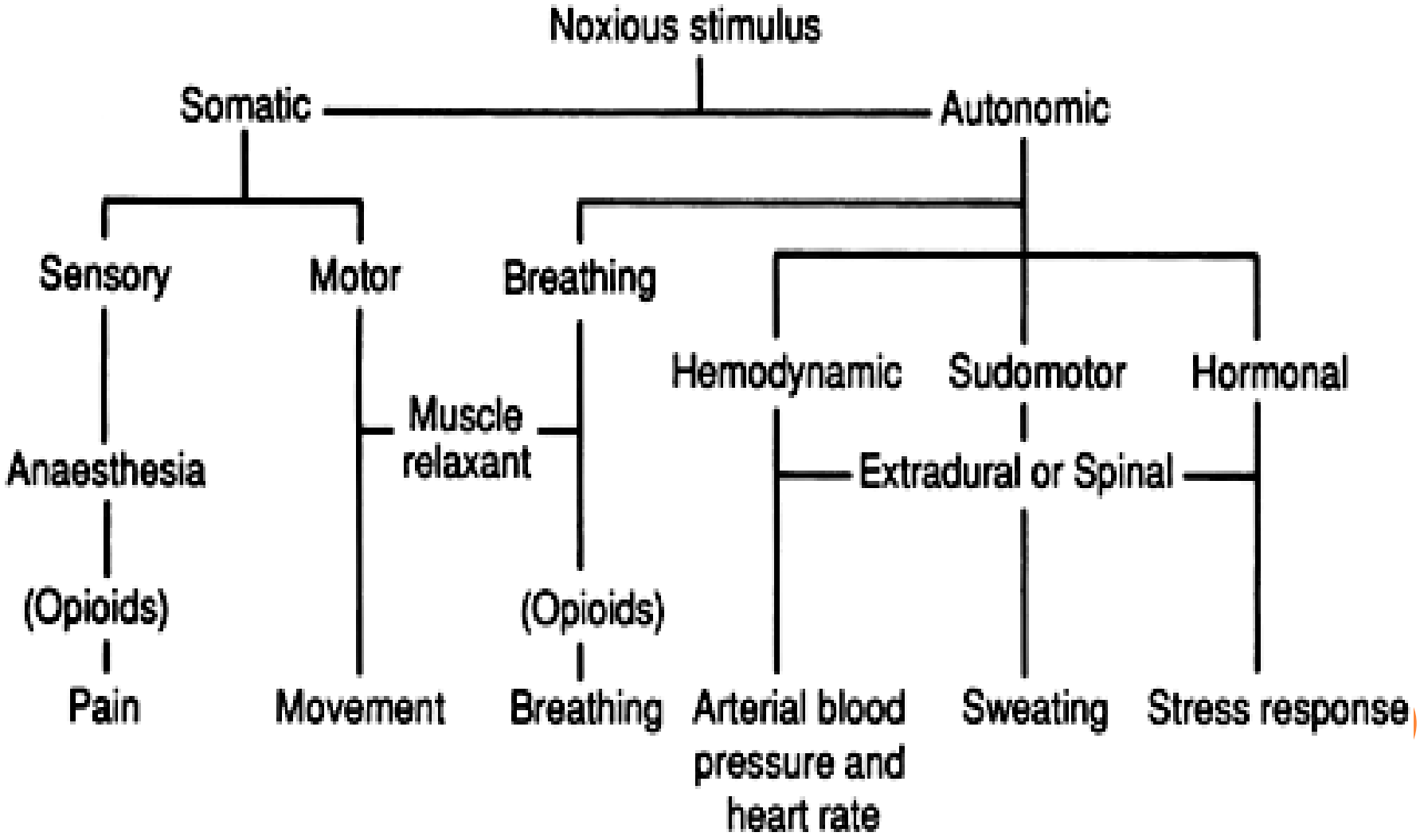
# CLINICAL PHARMACOLOGY: SUCCINYLCHOLINE

- The negative inotropic and chronotropic responses
- With large doses of succinylcholine, positive inotropic and chronotropic effects
- Stimulates
  - Autonomic cholinoceptors at both sympathetic and parasympathetic ganglia
  - Muscarinic receptors in the heart (eg, sinus node)
- Cardiac arrhythmias, especially when administered during halothane anesthesia
- Treatment:-
  - Glycopyrrolate/ Atropine : for negative inotropic and chronotropic effects

# CLINICAL PHARMACOLOGY: SUCCINYLCHOLINE

- Bradycardia - observed when a second dose of succinylcholine is given less than 5 minutes after the initial dose
- Direct myocardial effects, increased muscarinic stimulation, and ganglionic stimulation contribute to this bradycardia
- This transient bradycardia prevented by
  - Thiopental
  - Atropine
  - Ganglionic -blocking drugs
  - Pretreating  with a small dose of a nondepolarizing muscle relaxant (eg, rocuronium)
- .

# DON'T FORGET GENERAL ANESTHESIA



# Quiz

- Succinylcholine is a:- select true answer
  a) Pharmacological antagonist at Muscarinic receptors with lesser antagonism at nicotinic receptors
  b) Pharmacological antagonist at nicotinic receptors with lesser agonism at muscarinic receptors
  c) Pharmacological agonist at nicotinic receptors with lesser agonism at muscarinic receptors
  d) Pharmacological agonist at muscarinic receptors with lesser antagonism at nicotinic receptors

# REFERENCES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