Skeletal Muscle Relaxants

Types of skeletal muscle relaxants: 2 groups

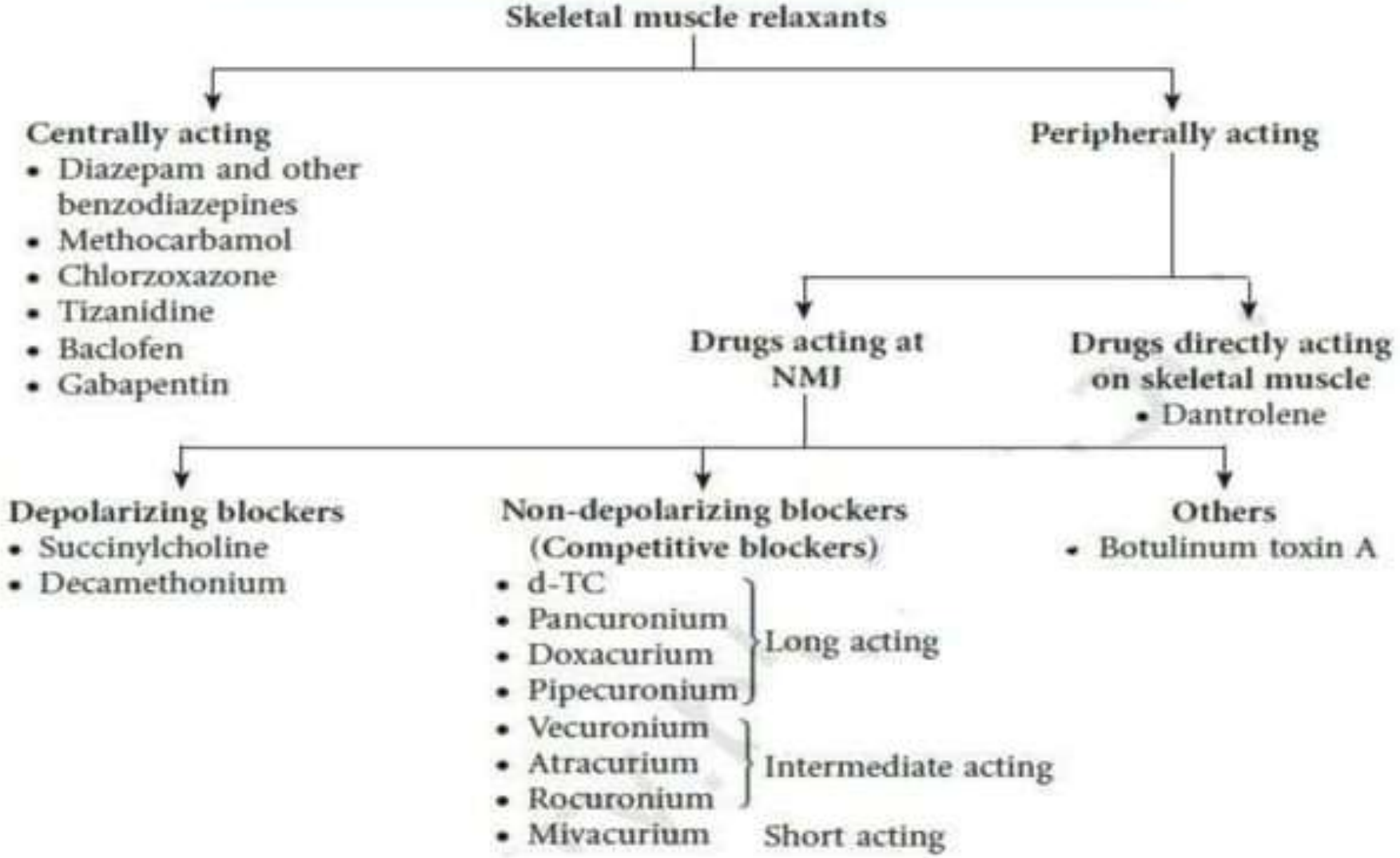
- Neuromuscular blockers

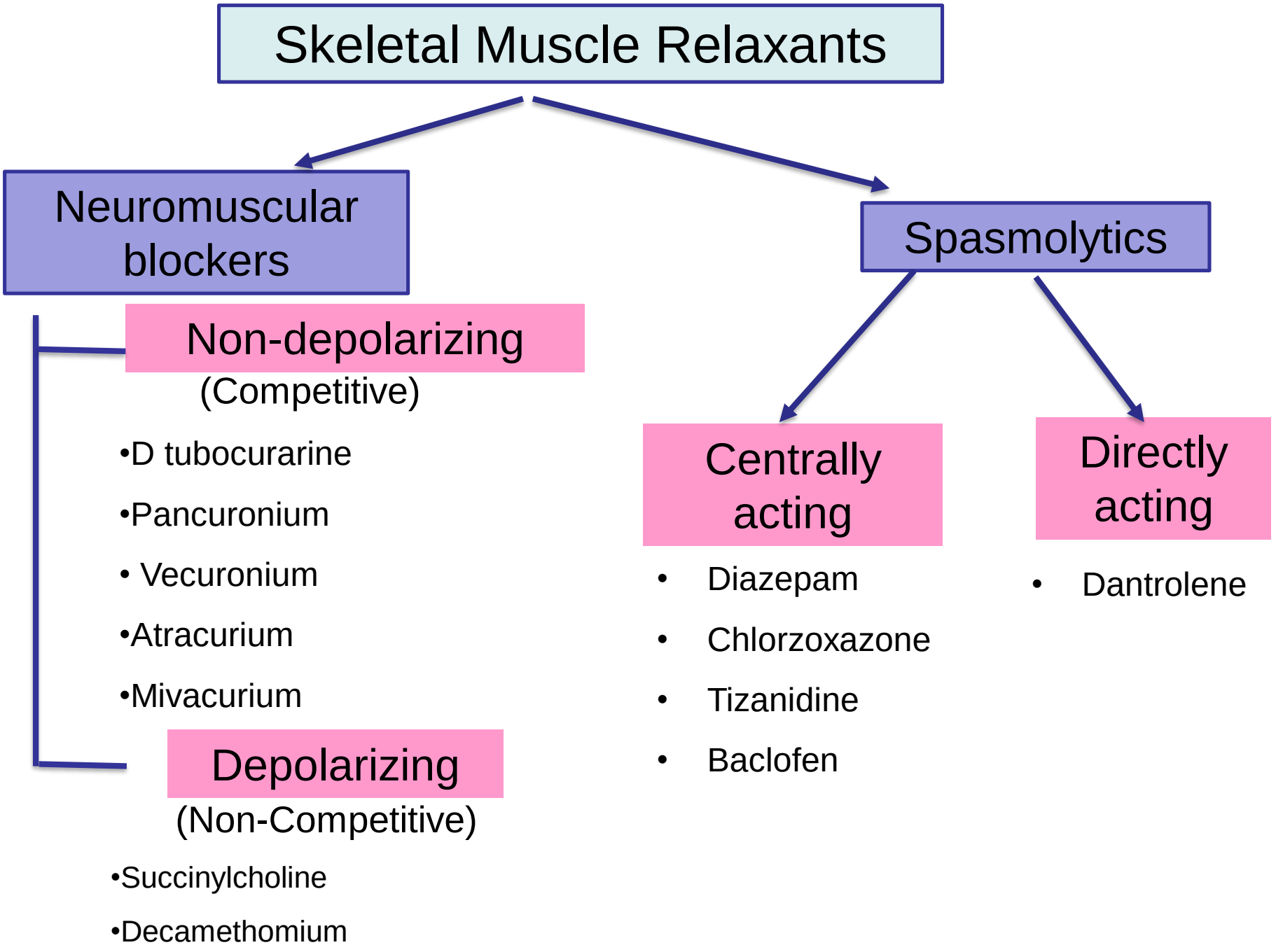
- Relax normal muscles (surgery and assistance of ventilation)
- No central nervous system activity.
- Used primarily as a part of general anesthesia

- Spasmolytics

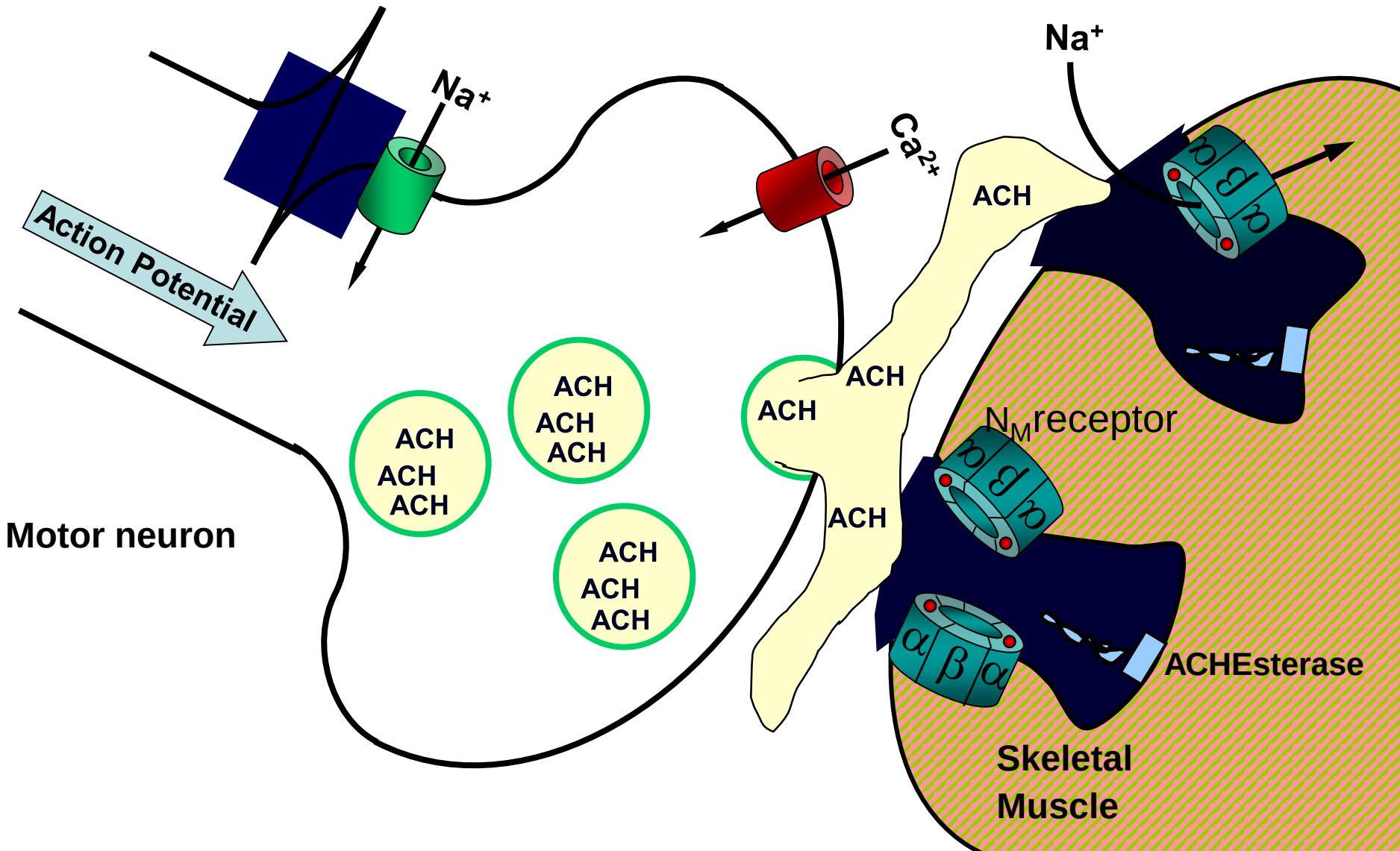
- Reduce spasticity
- Centrally acting (except dantrolene which act on the skeletal muscle)
- Used in a variety of neurologic conditions

Classification




Skeletal Muscle Relaxants
Neuromuscular blockers
Spasmolytics
Non-depolarizing
(Competitive)
•D tubocurarine
•Pancuronium
• Vecuronium
•Atracurium
•Mivacurium
Depolarizing
(Non-Competitive)
•Succinylcholine
•Decamethomium
Centrally acting
• Diazepam
• Chlorzoxazone
• Tizanidine
• Baclofen
Directly acting
• Dantrolene

Skeletal Muscle contraction



Physiology of Skeletal Muscle Contraction

Motor nerve impulse

↓

Release of acetylcholine

↓

Binds with N_M receptors at NMJ

↓

Depolarization and development of end-plate potential (EPP) at motor end plate (Mainly due to influx of Na^+)

↓

Muscle-action potential (MAP) – Contraction of skeletal muscle

↓

ACh is rapidly inactivated by cholinesterase leading to repolarization

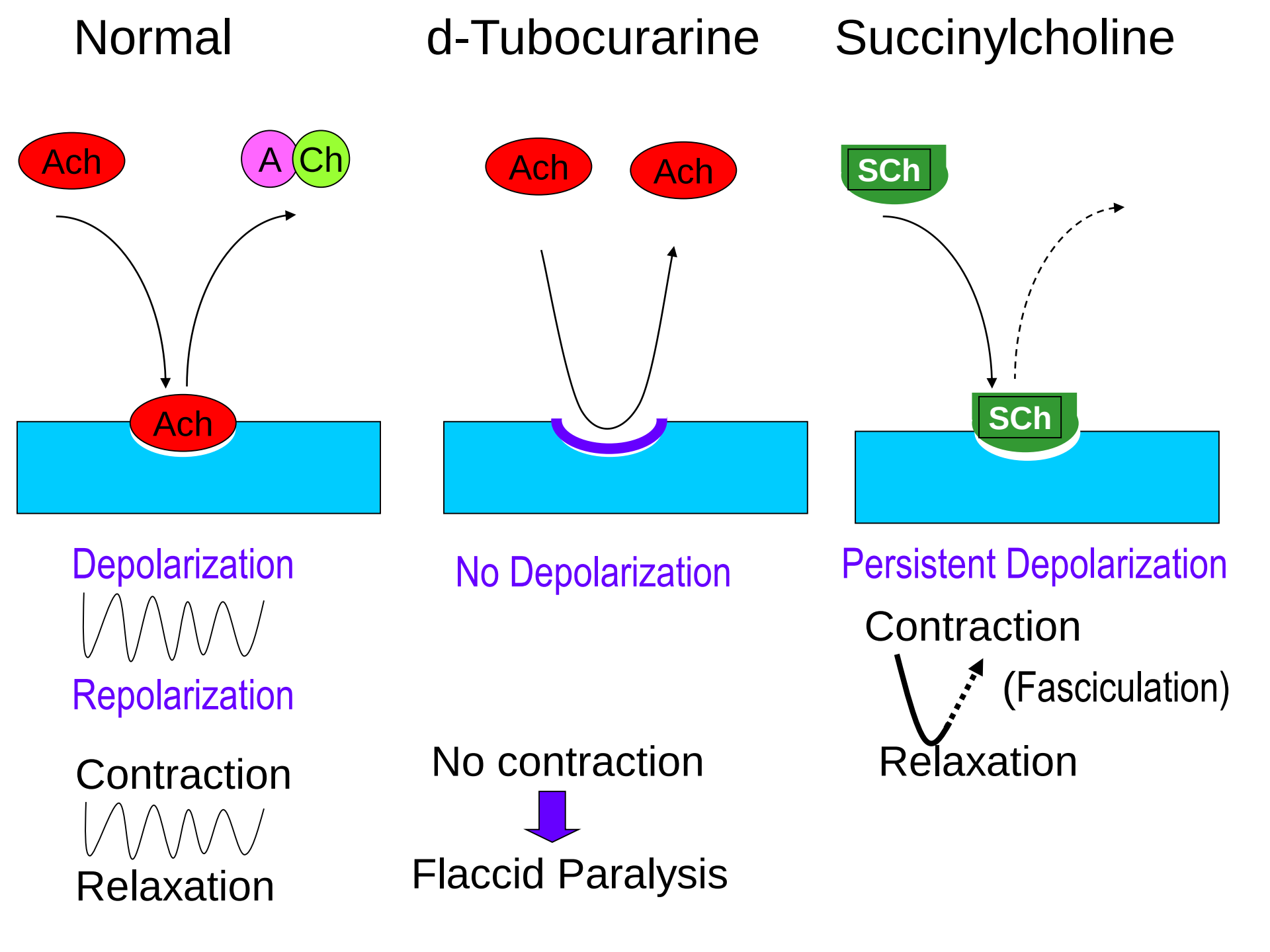
↓

Muscle is ready for a fresh nerve impulse

Peripherally acting: Neuromuscular Blockers

- **Depolarizing Blockers** – mimic the action of acetylcholine (ACh)
  - Agonists
  - Succinylcholine (SCh) is the only drug used clinically
- **Non-Depolarizing** – interferes with the action of ACh
  - Competitive Blockers (Antagonist)
  - Further divided into short, intermediate and long acting non- depolarizing drugs

Mechanism of action of Neuromuscular Blockers


Normal
d-Tubocurarine
Succinylcholine
Ach
A
Ch
Ach
Ach
Ach
SCh
SCh
Depolarization
Repolarization
Contraction
Relaxation
No Depolarization
No contraction
Flaccid Paralysis
Persistent Depolarization
Contraction
(Fasciculation)
Relaxation

Competitive Antagonists
(Non-depolarizing Blockers)

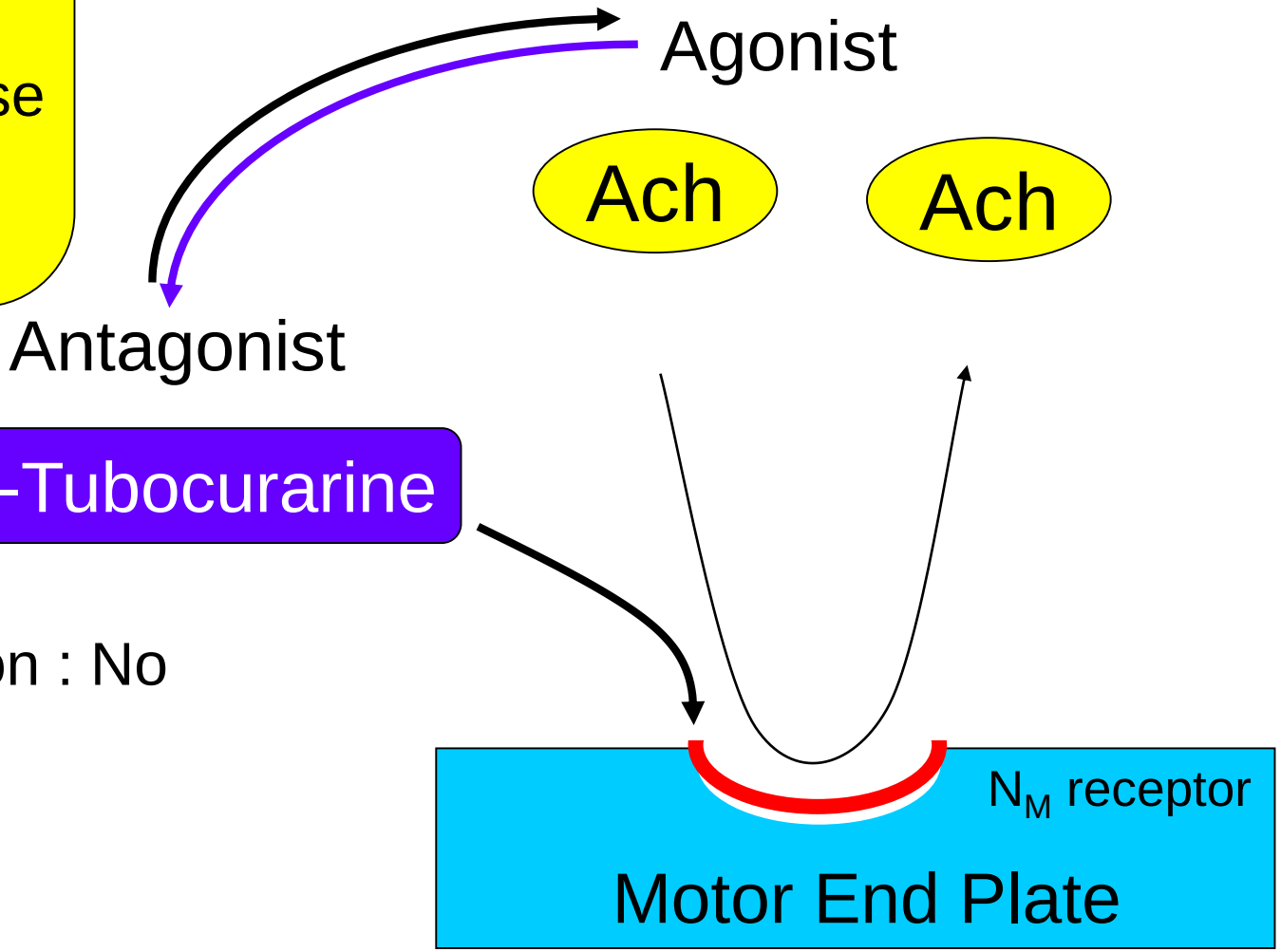
(Non-depolarizing blockers)

- Long-acting: d tubocurarine, pancuronium
- Intermediate: Atracurium , vecuronium , rocuronium ,
- Short-acting: Mivacurium

Anti-cholinestrases (neostigmine, edrophonium) which preserve acetylcholine are used to reverse the effect of d-tubocurarine

Mechanism of Action

Competitive Antagonism



Affinity : Yes

Intrinsic action : No

Actions

- Muscle weakness → Flaccid paralysis
- Order of muscle affected:
  - Extrinsic eye muscles, muscles of finger
  - Neck muscles (muscles of phonation and swallowing)
  - Face
  - Hands,
  - Feet
  - Trunk
  - Respiratory muscles (intercostal and diaphragm)
- Recovery in the reverse order
- Consciousness, appreciation of pain not affected

Actions

- Autonomic ganglion blocking property
- Histamine release (by d-tubocurarine)
- CVS
  - Significant fall in BP
  - Increase in Heart rate
  - Vagal gangionic blockade (also ‘ve’ and ‘pan’)
- Newer competitive blockers:
  - Negligible effect on BP and HR

Adverse effects

- Hypotension
- Tachycardia
- Respiratory paralysis
- Bronchospasm
- Aspiration of gastric contents

Non-depolarizing Drug: d-Tubocurarine

- 1st agent to undergo clinical investigation
- purified curare – *Chondodendrom tomentosum*
- ED_{95}= 0.5mg/kg
- undergoes minimal metabolism- is excreted
  - 10% in urine
  - 45% in bile
- excretion impaired in Renal Failure

Non-depolarizing Drugs

- Gallamine
  - Less potent than curare
  - Tachycardia
- D-Tubocurarine
  - 1-2 hr duration of action
  - Histamine releaser (Brochospasm, hypotension)
  - Blocks autonomic ganglia (Hypotension)
- Atracurium
  - Rapid recovery
  - Safe in hepatic & renal impairment
  - Spontaneous inactivation to laudanosine (seizures)

Non-depolarizing Drugs

- Mivacurium
  - Metabolized by pseudocholinesterase
  - Fast onset and short duration
- Pencuronium
  - Long duration of action
  - Tachycardia
- Vecuronium
  - Intermediate duration of action
  - Fewer side effects (no histamine release, no ganglion blockade, no antimuscarinic action)

Advantages of synthetic (Newer) competitive blockers

- Less histamine release
- Do not block autonomic ganglia
- Spontaneous recovery with most of drugs
- Rapacuronium & rocuronium have rapid onset
- Atracuronium: Hoffmans elimination
- Mivacurium short acting

Uses

- As an adjunct to general anaesthesia
  - For producing satisfactory skeletal muscle relaxation
- For facilitating endotracheal intubation
  - Rocuronium preferred due to rapid onset of action
  - Succinylcholine is better due to short lasting duration

Depolarizing Blocker

(Non-competitive Antagonist)

Succinylcholine

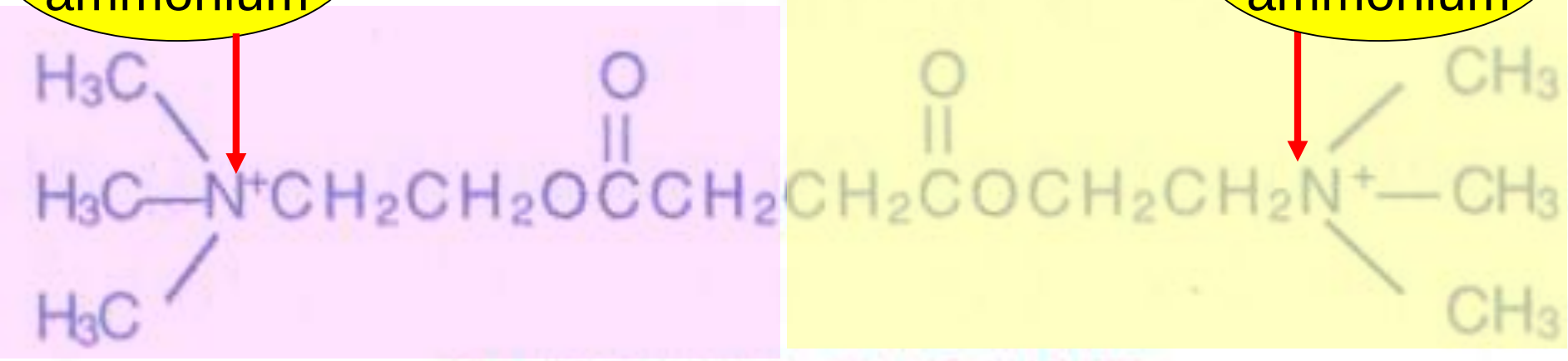
One Drug, Two blocks,
Brief and quick,
Genetic variability in metabolism,
Malignant hyperthermia

Succinyl Choline

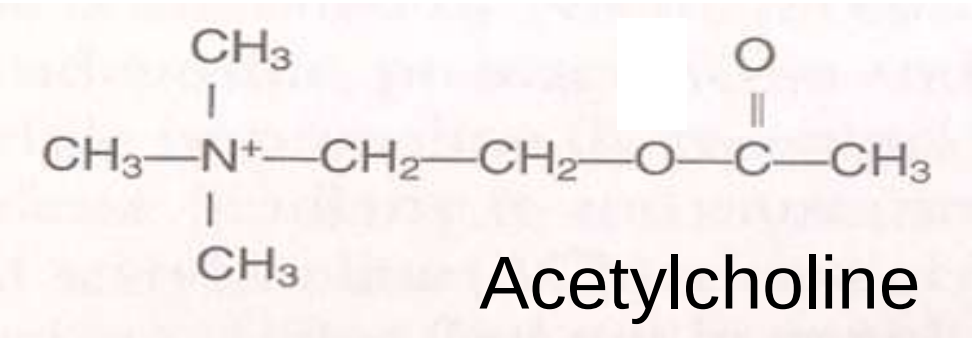
Depolarising muscle relaxants

Quaternary ammonium

Quaternary ammonium



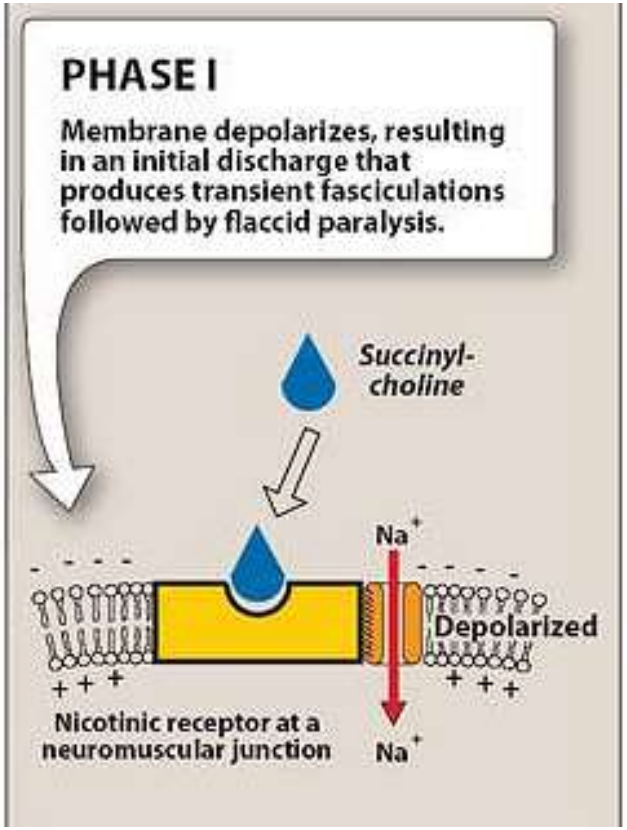
Two molecules of Acetylcholine)

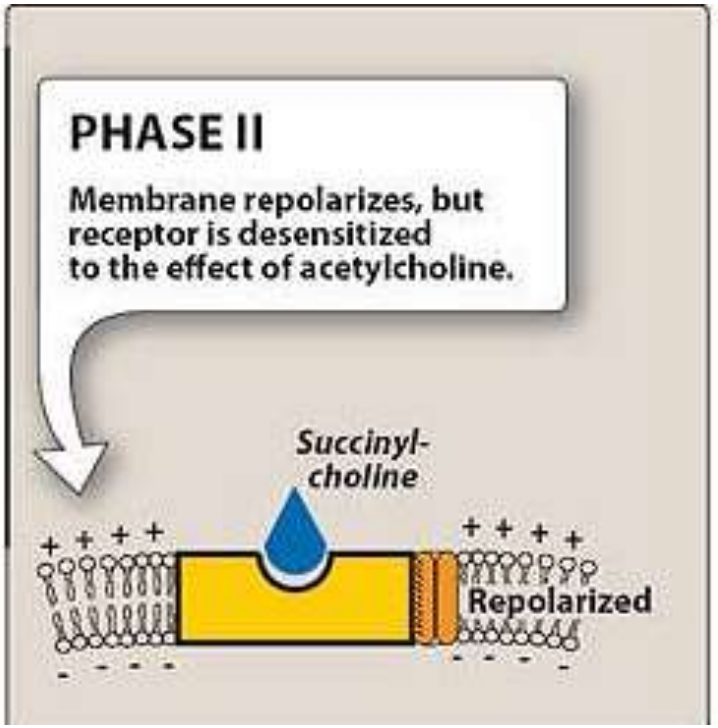


Succinylcholine acts on the Nicotinic receptors of the muscles, stimulates them and ultimately cause their relaxation.

- This process occur in two phases :
  - Phase I: During Phase I (depolarizing phase), they cause muscular fasciculations while they are depolarizing the muscle fibers.
  - Phase II: After sufficient depolarization has occurred, phase II (desensitized phase) sets and the muscle is no longer responsive to Ach released by the nerve endings.

Mechanism of action





Agonist at Nicotinic (N_M) receptor

Produces neuromuscular block by overstimulation, end plate is unable to respond to further stimulation.

Longer lasting or persistent depolarization

Actions

- Small rapidly moving muscles (eye, jaw, larynx) relax before those of limbs and trunks
- Ultimately intercostals and finally diaphragm paralysis occur $\rightarrow$ respiratory paralysis
- Recovery in the reverse order
- Muscle relaxation: Onset: within 1 min; peak: 2 min, duration: 5 min; longer duration relaxation requires continued IV infusion

Uses

Suitable for short-term procedures

- Rapid endotracheal intubation during induction of anaesthesia
- During Electro-Convulsive shock Therapy (ECT)
  - To prevent injury

Adverse Effects

- Transient ↑Intraocular Tension
- Hyperkalemia : Fasciculations release potassium in blood
- Succinylcholine apnoea
- Malignant hyperthermia: when used alng with halothane in general anaesthesia
  - Treatment is by rapid cooling of patient & dantrolene i.v
- Muscle pain

Treatment of succinylcholine apnoea

- No antidote is available
- Fresh frozen plasma should be infused
- Patient should be ventilated artificially untill full recovery

Comparison of Competitive and Depolarizing Blocking Agents

Sr.no	Competitive	Succinyl choline
1	Competitive blockade	Persistant depolarization
2	Non depolarizing	Depolarizing
3	Single block	Dual block
4	Anticholinesterases reverse blockade	Do not reverse
5	Initial fasciculations not present	Present
6	Slow onset long duration	Rapid onset short duration
7	Release histamine	Doesn’t release

Difference between the competitive and depolarisinng muscle blocker

parameter	D tubocurarine	Succinylcholine
Blockade type	Competitive blockade	Depolarising blockade
Type of relaxation	Flaccid paralysis	Fasciculation followed by paralysis
Neostigmine addition +	antagonism	Potentiation
Effect of other neuromuscular blocking drug	Decreased effect	Increases effect
Histamine release	++ release	negligible
Serum k+ level	No change	Hyperkalemia
Pharmocogenetic variation	nil	pesudocholinesterase
Cardiac M2 receptor	No effect	stimulate (bradycardia)

Dantrolene

- Directly acting skeletal Muscle relaxant
- Inhibits depolarization induced calcium release from sarcoplasmic reticulum by acting on ryanodine receptors
- Drug of choice in malignant hyperthermia

Drug interactions

- Non depolarizing blockers
  - Anticholine-esterases (Neostigmine)
    - Reverse the action of only non depolarizing blockers
  - Halothane, Aminoglycoside antibiotic like gentamicin & calcium channel blockers like nifedipine
    - Enhances the neuromuscular blockade
- Depolarizing blockers
  - Halothane can cause malignant hyperthermia

Ganglion blockers

- Competitive blockers
  - Hexamethonium
  - Trimethaphan
  - Mecamylamine
- Persistant depolarizing
  - Nicotine large dose

Actions & Adverse effects of ganglion blockers

S.No	Organ	Dominant ANS	Effect/(side effect)of ganglionic blockade
1.	Heart	Parasympathetic	Tachycardia (Palpitations)
2.	Blood vessels	Sympathetic	Vasodilation (Hypotension)
3.	Iris	Parasympathetic	Mydriasis (Photophobia)
4.	Ciliary Muscle	Parasympathetic	Cycloplegia (Blurring of vision)
5.	Intestines	Parasympathetic	↓ motility (Constipation)
6.	Bladder	Parasympathetic	↓ tone (difficulty in micturation)
7.	Male sexual function	Parasympathetic	Inhibition of erection & ejaculation (Impotence)
8.	Salivary Glands	Parasympathetic	Inhibition of salivation (dry mouth, difficulty in swallowing)
9.	Sweat Glands	Sympathetic	Inhibition of sweating