Peripherally Acting Skeletal Muscle Relaxants

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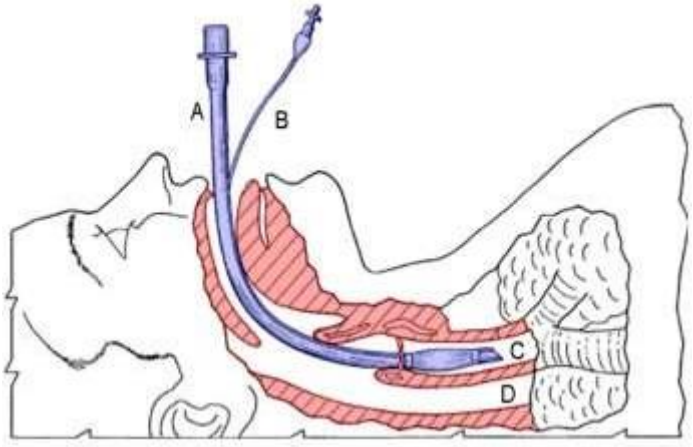
Skeletal Muscle Relaxation, Why Clinically ?

In conjugation with General Anesthetics:

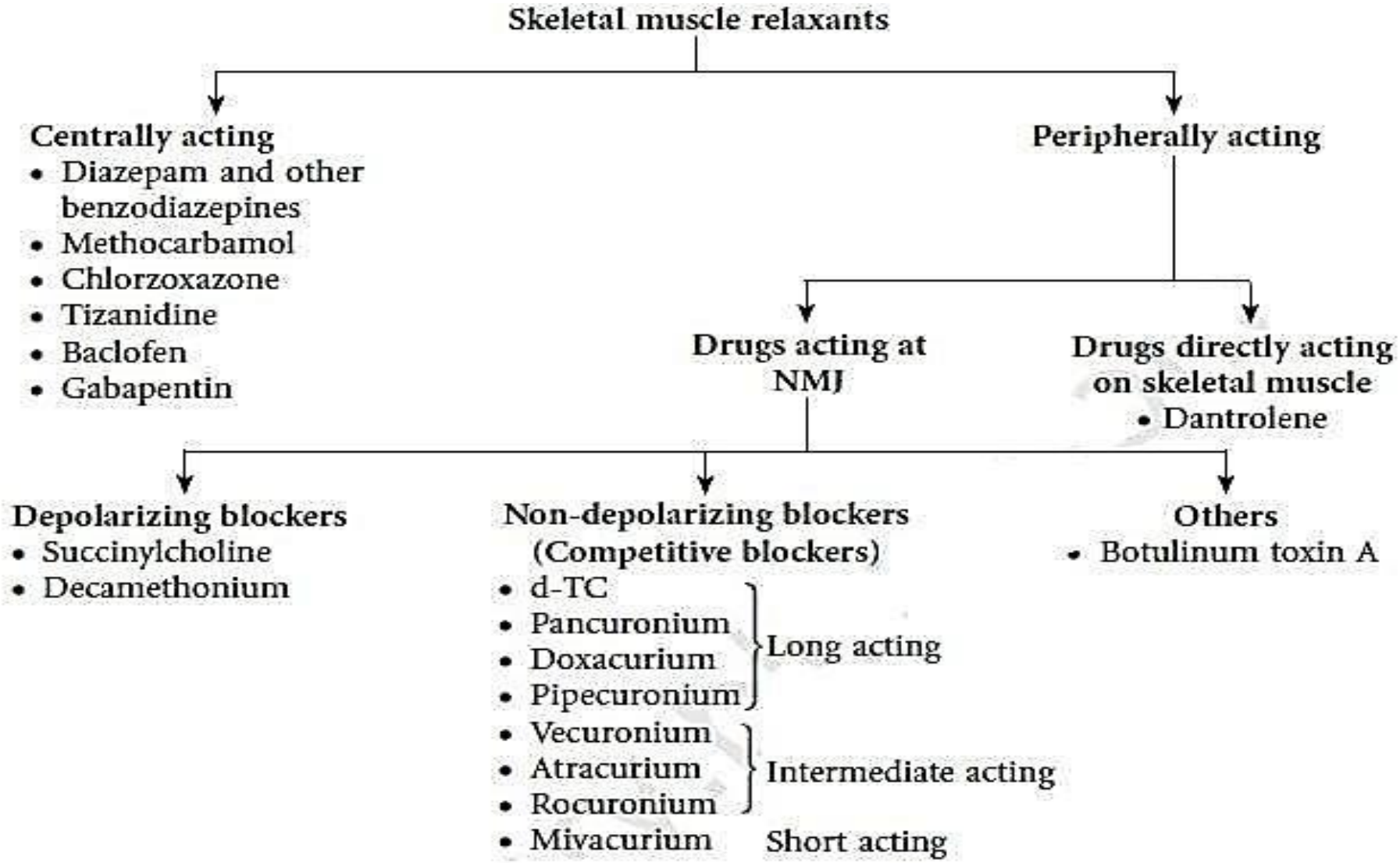
- Facilitate intubation of the trachea
- Facilitate mechanical ventilation
- Optimized surgrical working conditions



History of Skeletal Muscle Relaxants

- Curare is a common name for various plant extract alkaloid arrow poisons originating from Central and South America.
- Source: *Chondrodendrone tomentosum* and *Strychnos toxifera*
- Tubocurarine name because of packing in “hollow bamboo tubes”

Classification



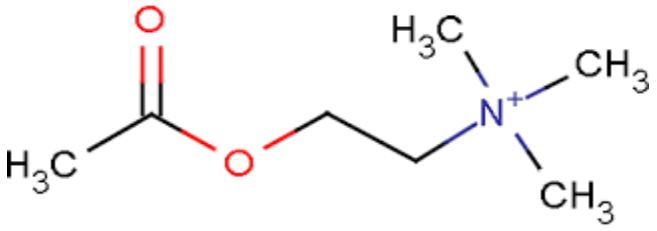
Acetylcholine

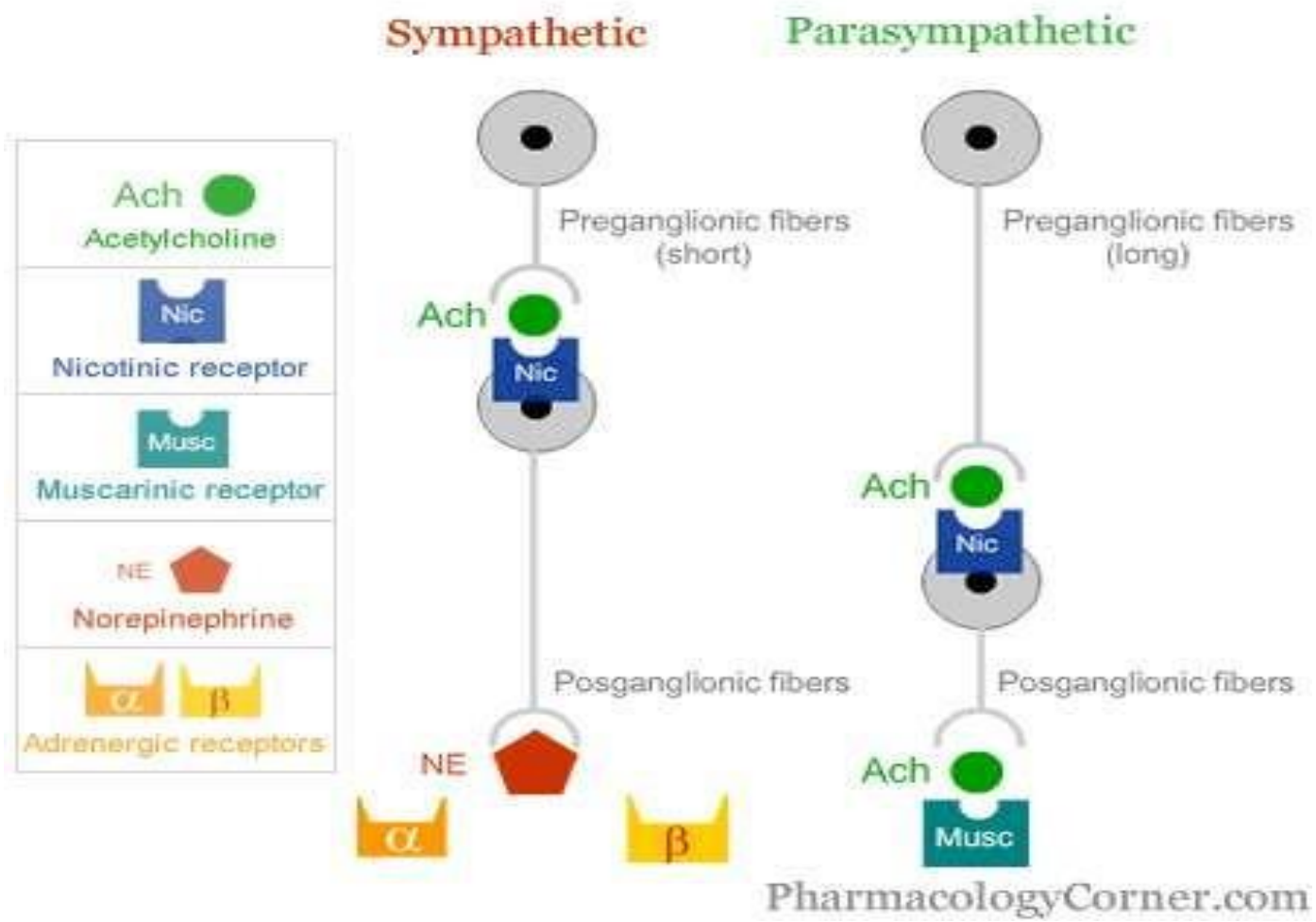
- Acetylcholine is a major neurohumoral transmitter at autonomic, somatic and central nervous system:
  1. All preganglionic sites (Both Parasympathetic and sympathetic)
  2. Skeletal Muscles
  3. CNS: Cortex Basal ganglia, spinal cord and others

Parasympathetic Stimulation – Acetylcholine (ACh) release at neuroeffector junction – biological effects

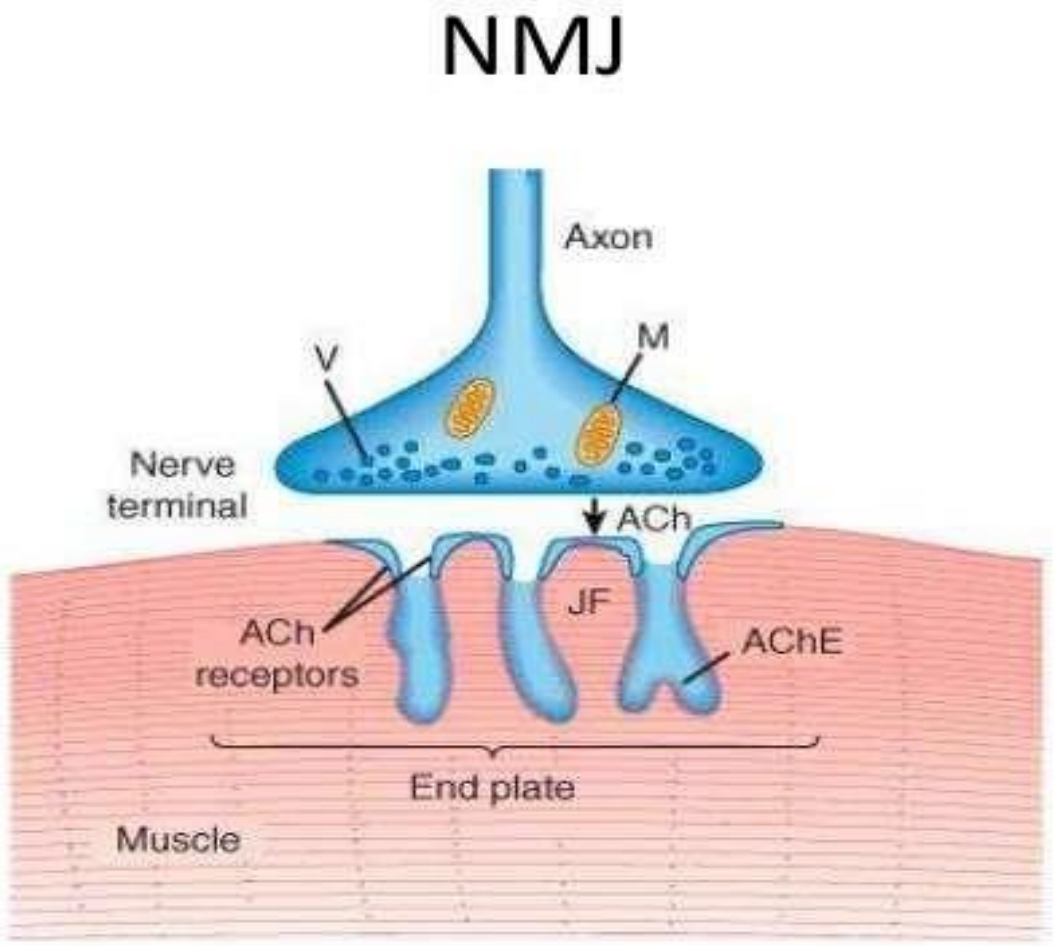
Sympathetic stimulation – Nonadrenaline (NA) at neuroeffector junction – biological effects

Acetylcholine

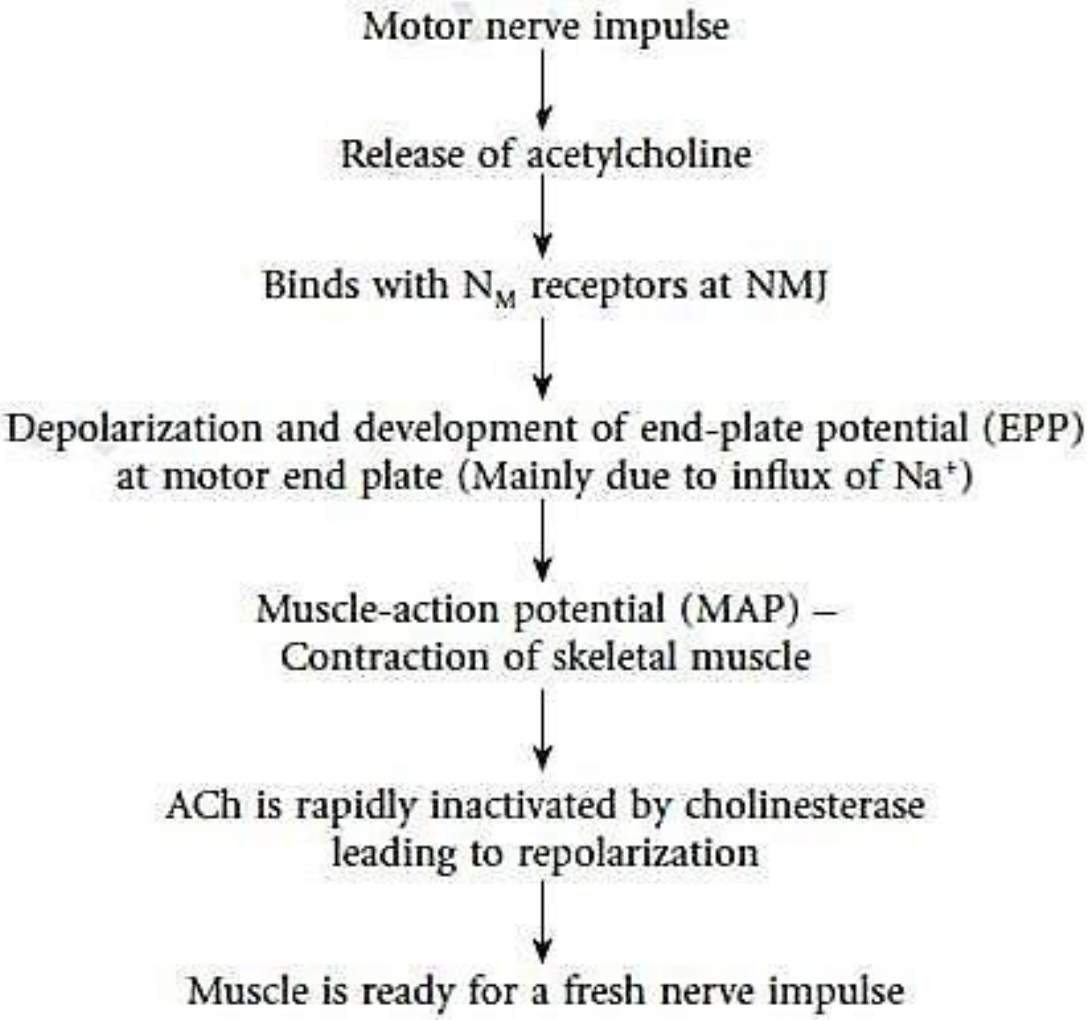




Neuromuscular Junction (NMJ(



Physiology of Skeletal Muscle Contraction



Peripherally acting: Neuromuscular Blockers

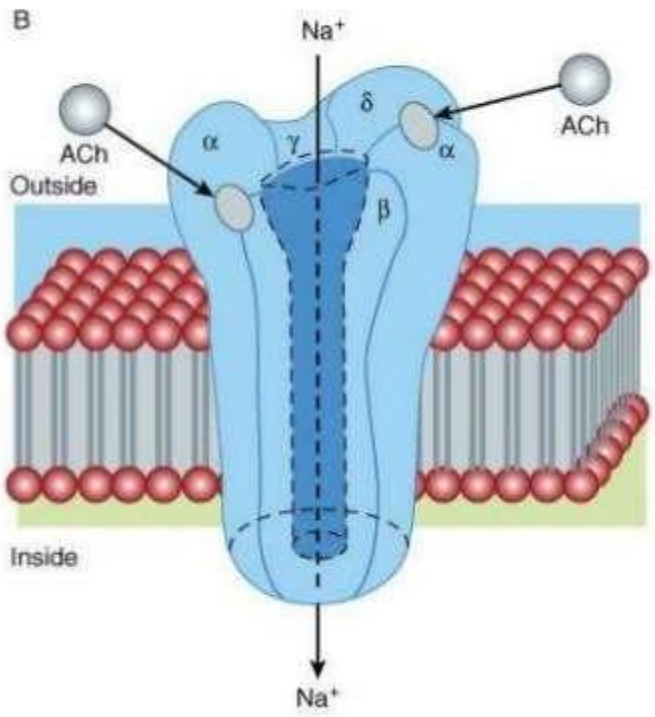
- **Depolarizing Blockers** – mimic the action of acetylcholine (Ach)
  - Agonists
  - Succinylcholine (SCh) is the only drug used clinically
- **Non-Depolarizing** – interferes with the action of ACh
  - Competitive Blockers (Antagonist)
  - Further divided into short, intermediate and long acting non-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

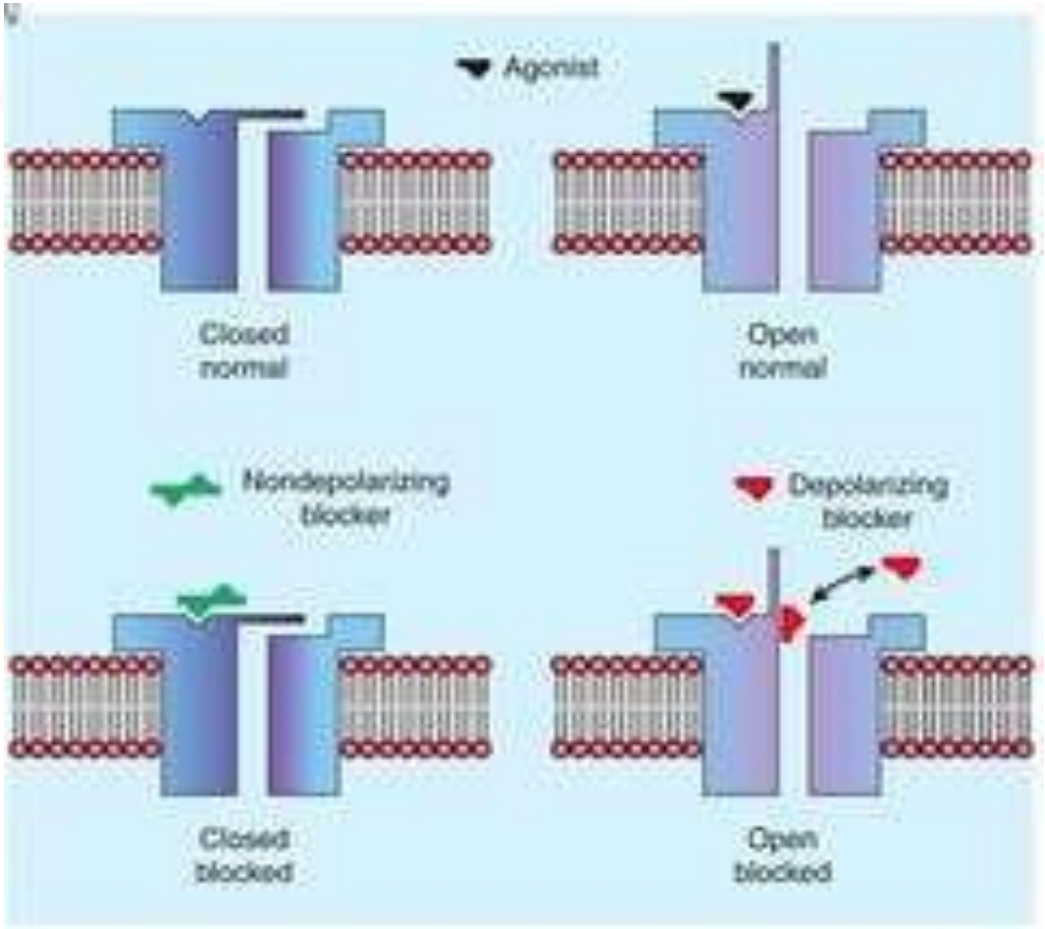
Depolarizing Block - Succinylcholine

- Succinylcholine have affinity and **sub-maximal intrinsic** activity at Nm receptor.
- It acts on sodium channels, open them and causes initial twitching and fasciculation.
- It does not dissociate rapidly from the receptors resulting in prolonged depolarisation and inactivation of Na+ channels.

Mechanism of Action: Succinylcholine

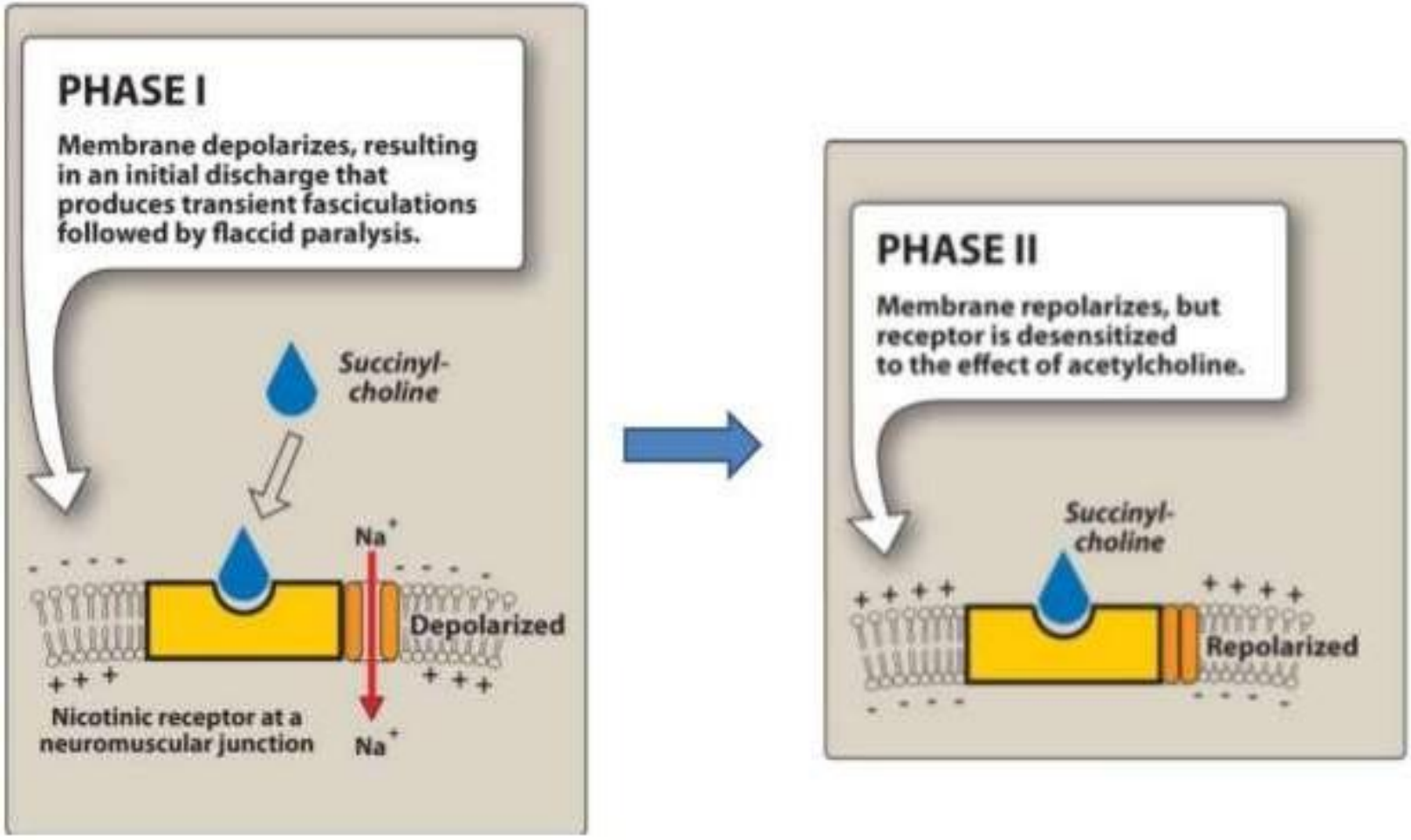
Nicotinic ACh Receptor





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.


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

Succinylcholine

Uses:

- 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

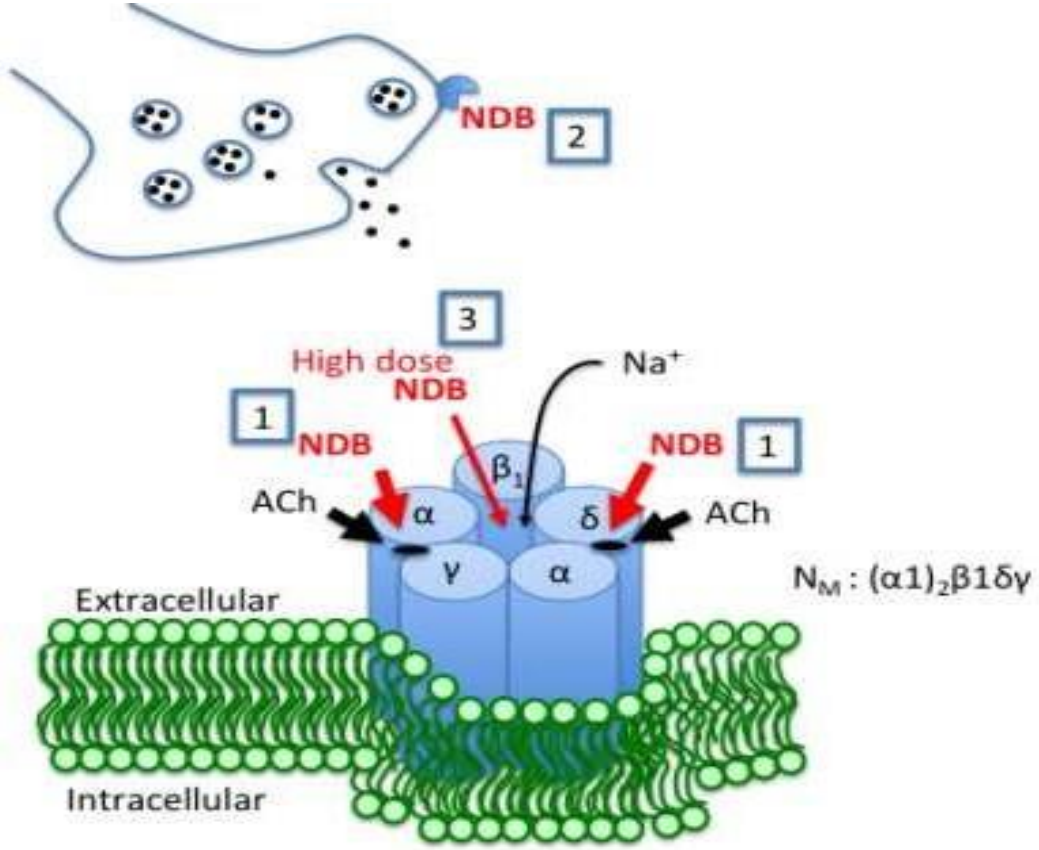
Side effects:

- 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

Non-Depolarising Drugs

- Competitive Blockers having no intrinsic activity (antagonist(
- These are of 3 types based on their activity:
  - *Long Acting :* d-TC, Pancuronium, Pipecuronium, Gallamine (Kidney Excretion(
  - *Intermediate :* Vecuronium, Rocuronium, Atracuronium (eliminated by liver(
  - *Short Acting :* Mivacuronium, Ropcacuronium (inactivated by plasma cholinesterase(

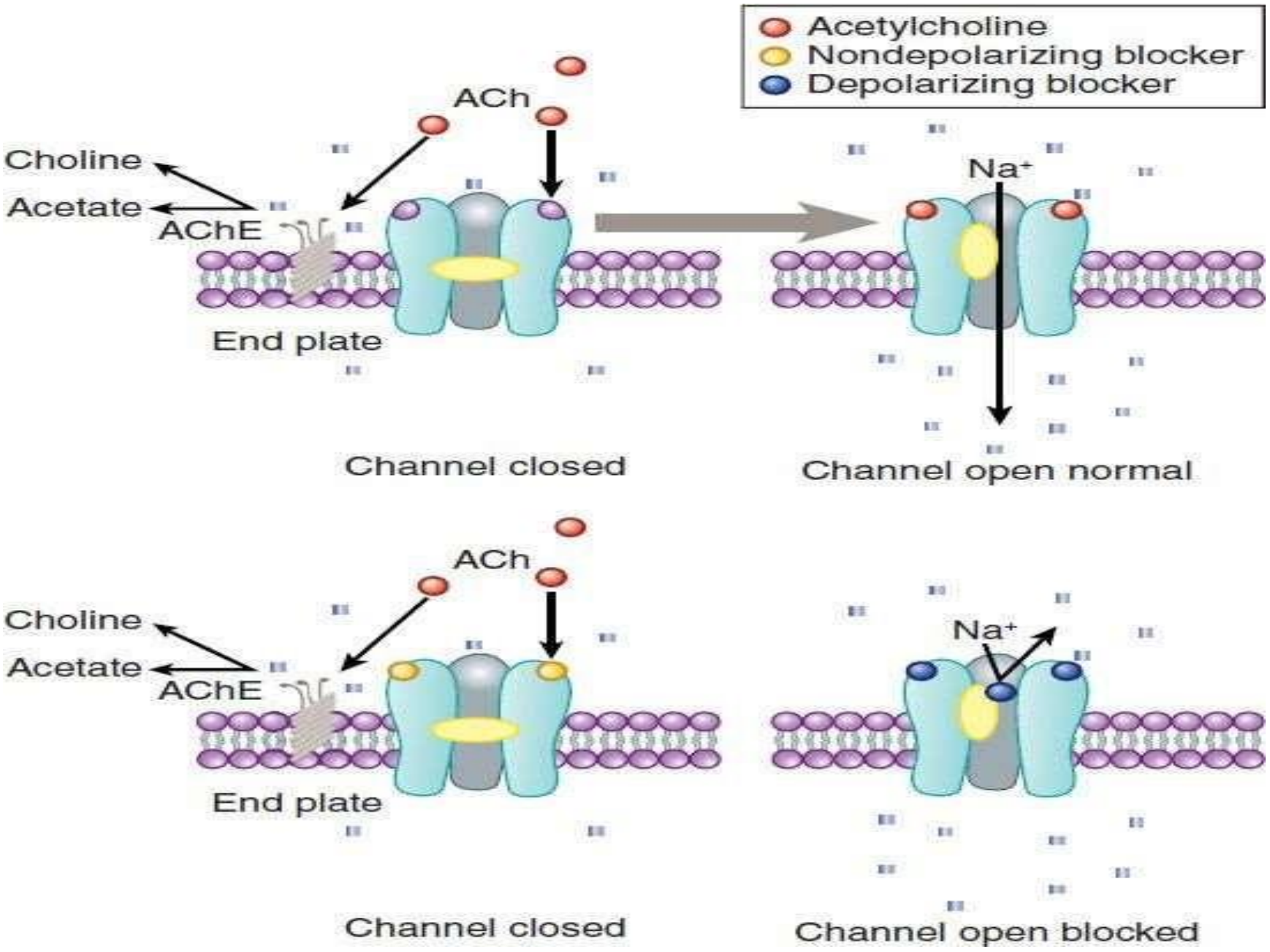
Mechanism of Action: Non-depolarizing Block in Muscles



Drawing Adapted from: *Karlin A: Nature Reviews Neuroscience 3, 102-114 (February 2002)*
Pentameric data from: *Millar NS: Assembly and subunit diversity of nicotinic acetylcholine receptors. Biochem Soc Trans 31:869, 2003.*

Mechanism of Action

- They have affinity but no intrinsic activity for Nicotinic receptors (Antagonist)
- They are quaternary N+ compounds that contain cationic head that act only on closed Na_+ channels – No action on already opened Na_+ channels
- The cationic head binds to the anionic ACh binding site at the α – subunit of the N_m receptor but cannot bring conformational change & Na+ channels remians closed
- No End Plate Potential generation in nerve endings
- Muscle Action Potential decreases
- Action can be overcome by increased ACh concentration or blocking of acetylcholinesterase
- They also block prejunctional ACh receptors on motor nerve endings – FADE PHENOMENON


Acetylcholine
Nondepolarizing blocker
Depolarizing blocker
ACh
Choline
Acetate
AChE
End plate
Channel closed
Na+
Channel open normal
ACh
Choline
Acetate
AChE
End plate
Channel closed
Na+
Channel open blocked

Effects of Non-depolarizing blockers

- **Low Doses:**
  - Competitive antagonists of ACh
  - Action reversed by ACh ecterase inhibitors
- **Large Doses:**
  - Ion Channel is blocked
  - More weakness of neuromuscular transmission
  - Action could not be reversed by ACh esterase inhibitors
- **Other actions:**
  - Can block pre-junctional Na^+ channels and interfere with mobilization of ACh at nerve endings

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
  - %10in urine
  - %45in bile
- excretion impaired in Renal Failure

CVS Effects:

- hypotension frequently even at doses < ED_{95}
- histamine released (skin flushing frequently)
- autonomic ganglionic blockade- manifests as hypotension

Clinical Use:

- long duration of action(60 to 120 mins) and CVS effects restricted its use
- used as “precurarization”

Non-depolarizing Drugs

- Gallamine
  - Less potent than curare
  - Tachycardia
- D-Tubocurarine
  - 2-1hr 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(

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)

Other Actions of N_m Blockers

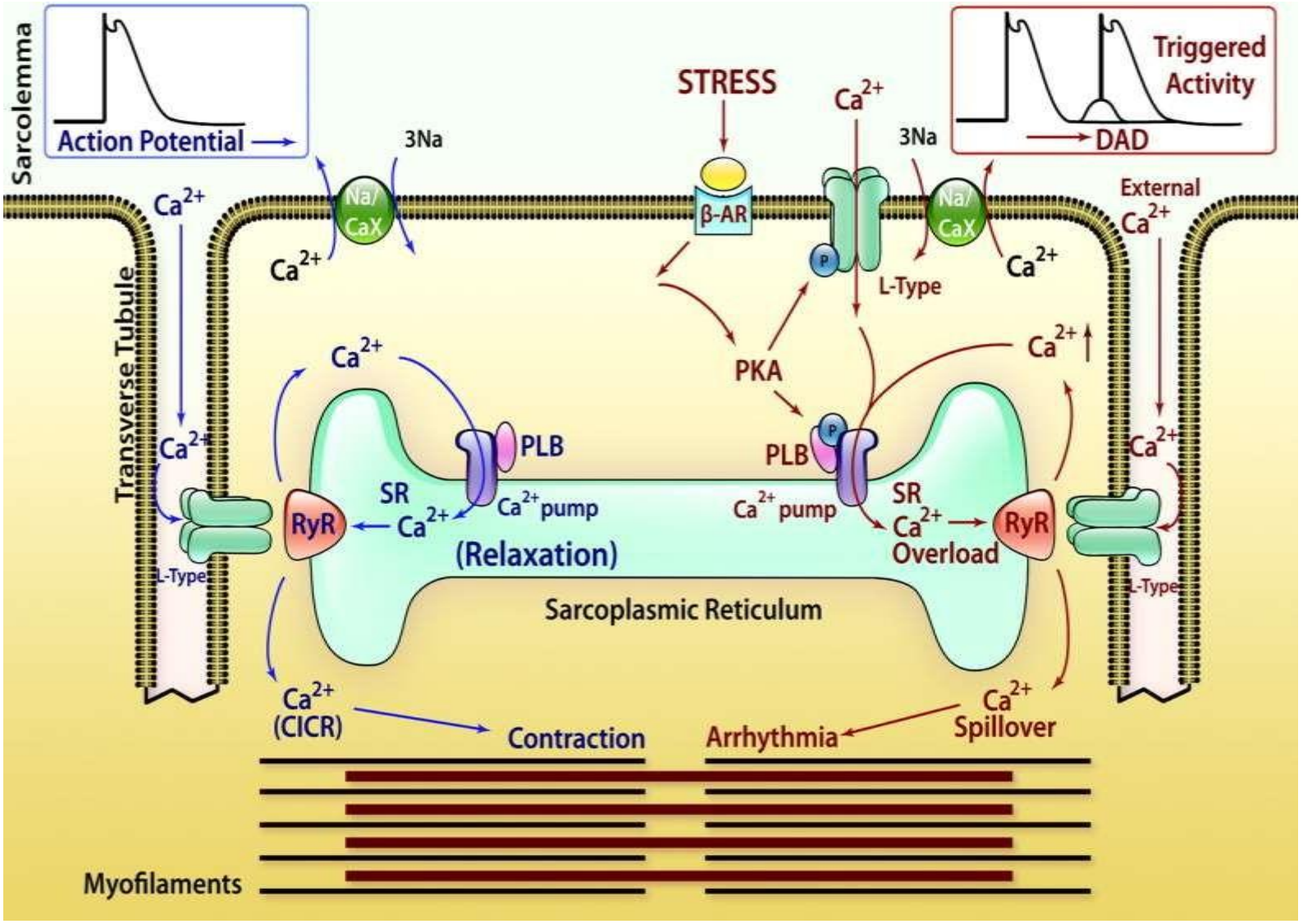
- Automic ganglia:
  - Partial blockage of ganglia (Nm type of receptor)
  - Results in fall in BP and tachycardia
- Histamine release:
  - Hypotension
  - Bronchospasm, excess bronchial and salivary secretion
- Cardiovascular: Fall in BP due to
  - Ganglion blockage, histamine release and reduced venous return
  - Succinylcholine may cause cardiac arrhythmias
- GIT: Paralytic ileus

Pharmacokinetics of N_m blockers

- Polar quaternary compound - Not absorbed orally, do not cross cell membranes, Blood Brain Barrier or placental barrier, low Volume of distribution – always given intravenously or rarely intramuscular
- Muscles with high blood flow affect earlier
- Redistribution to non muscular tissues occur and action may persist longer than half life
- Drugs metabolised in plasma/liver (d-TC and pancuronium) – 60-120 min
- Succinylcholine ⟶ Succinylmonocholine ⟶ Succinc acid + choline (plasma cholinesterase): 3-5 min
- In some – generally determined abnormality and deficient pseudocholinesterase ⟶ Paralysis & apnoea

Directly acting relaxants - Dantrolene

- Different from neuromuscular blockers, no action on neuromuscular transmission
- Mechanism of Action: Ryanodine receptors (RyR) calcium channels – prevents depolarization – no intracellular release of Ca^{++}
- Absorbed orally, penetrate brain and produces sedation, metabolized in liver, excreted in kidney. $T_{1/2}$ 8-12 hrs
- Dose: 25-100mg - 4 times daily
- Uses: Upper Motor Neuron disorders – paraplegia, hemiplegia, cerebral palsy and malignant hyperthermia (drug of choice 2.5-4 mg/kg)
- Adverse effects – Sedation, malaise, light headedness, muscular weakness, diarrhoea and hepatotoxicity


Sarcolemma
Action Potential
3Na
Na/
CaX
Ca2+
STRESS
β-AR
P
L-Type
Triggered
Activity
DAD
External
Transverse Tubule
PKA
PLB
SR
Ca2+ pump
RyR
(Relaxation)
Sarcoplasmic Reticulum
Ca2+ Overload
Ca2+ Spillover
Ca2+ (CICR)
Contraction
Arrhythmia
Myofilaments

ThankYou!!!