Peripherally Acting Skeletal Muscle Relaxants

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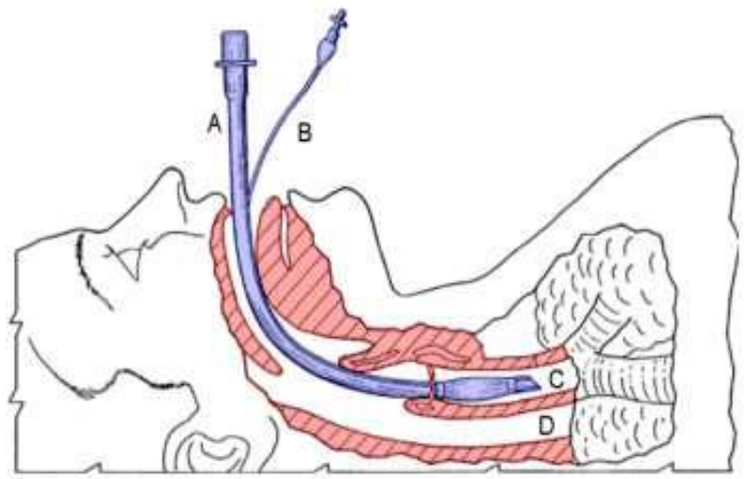
Peripherally Skeletal Muscle Relaxation Uses:

In conjugation with General Anesthetics:

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



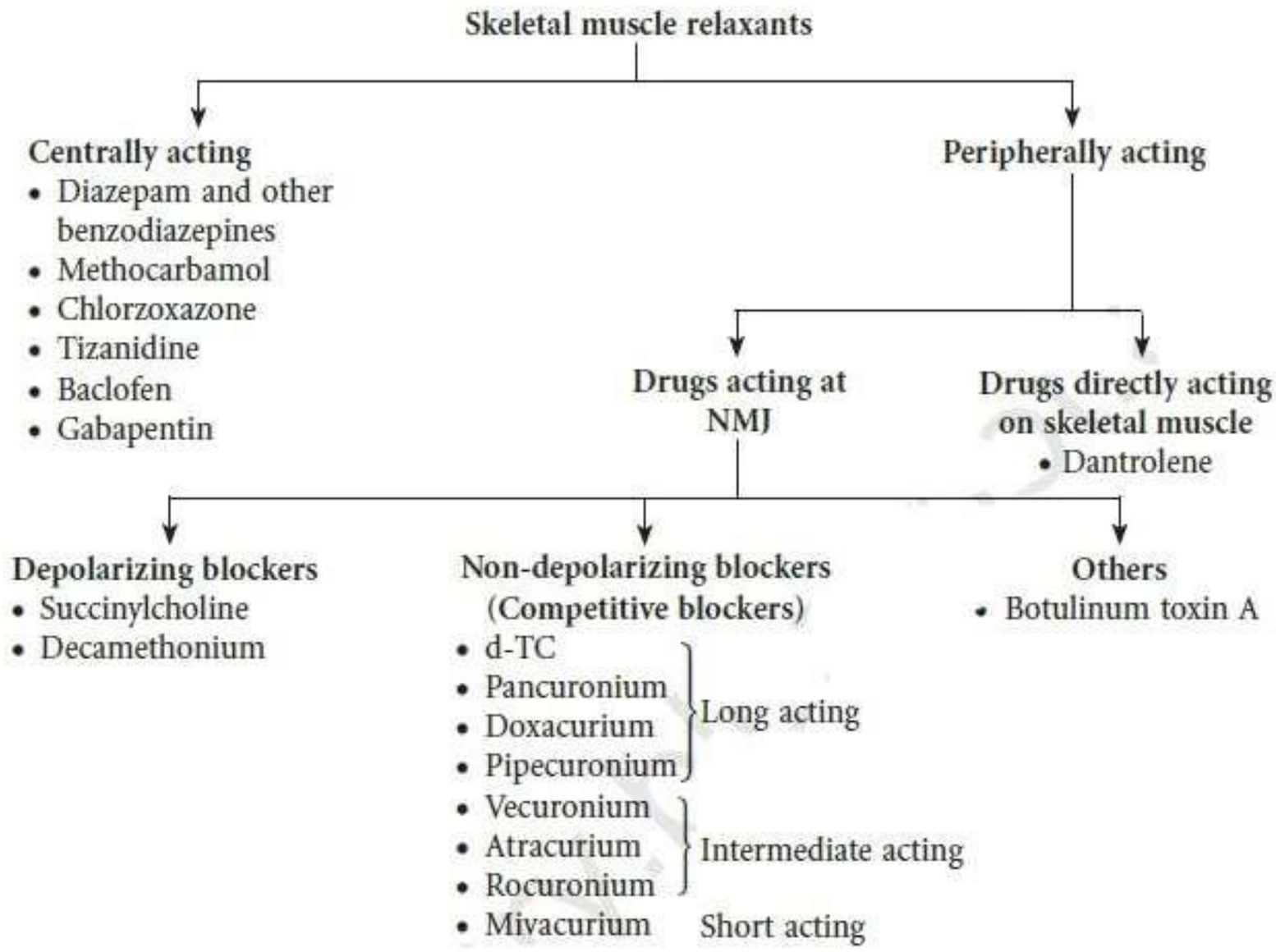
History of Skeletal Muscle Relaxants

•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

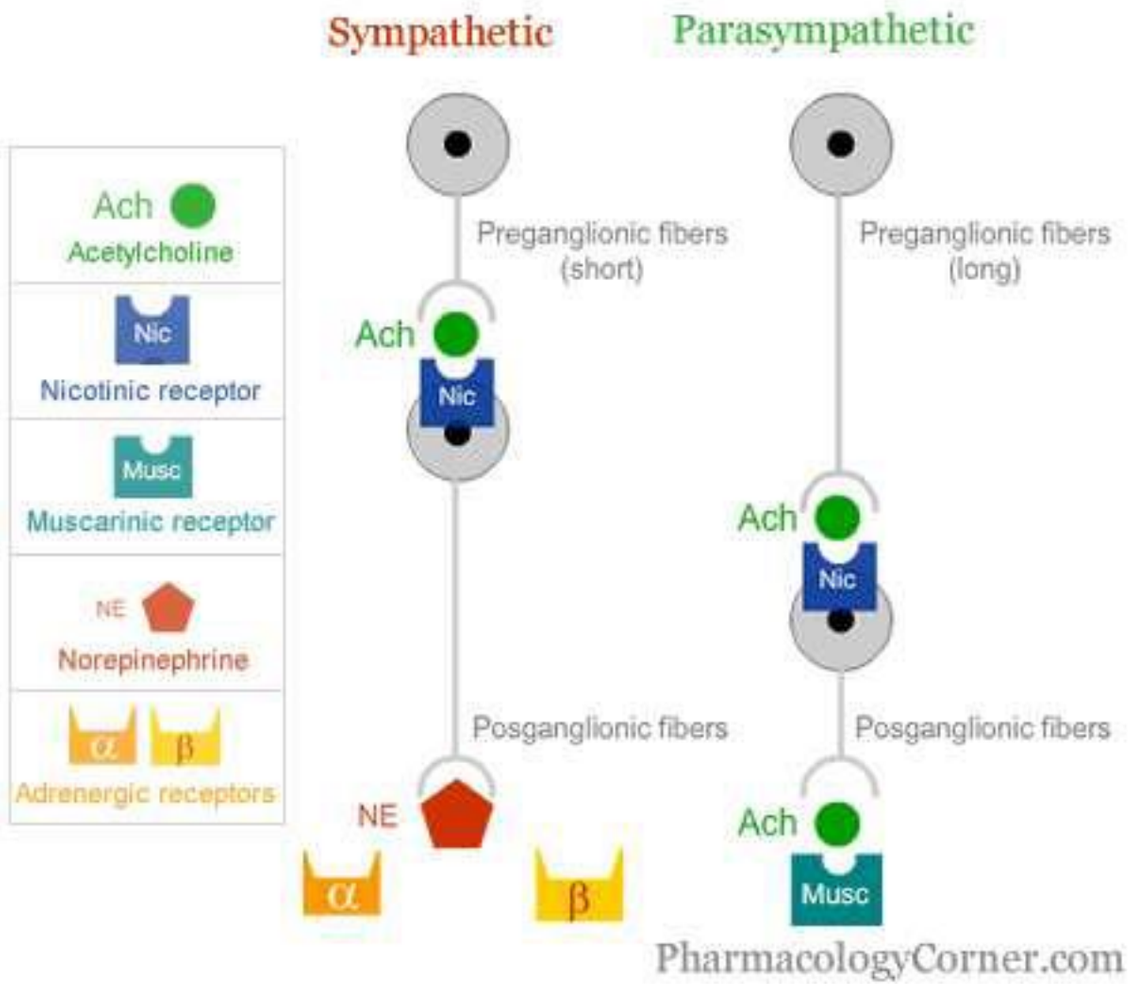
Acetylcholine is a major neurohumoral transmitter at autonomic, somatic and central nervous system:

.1All preganglionic sites (Both Parasympathetic and sympathetic(

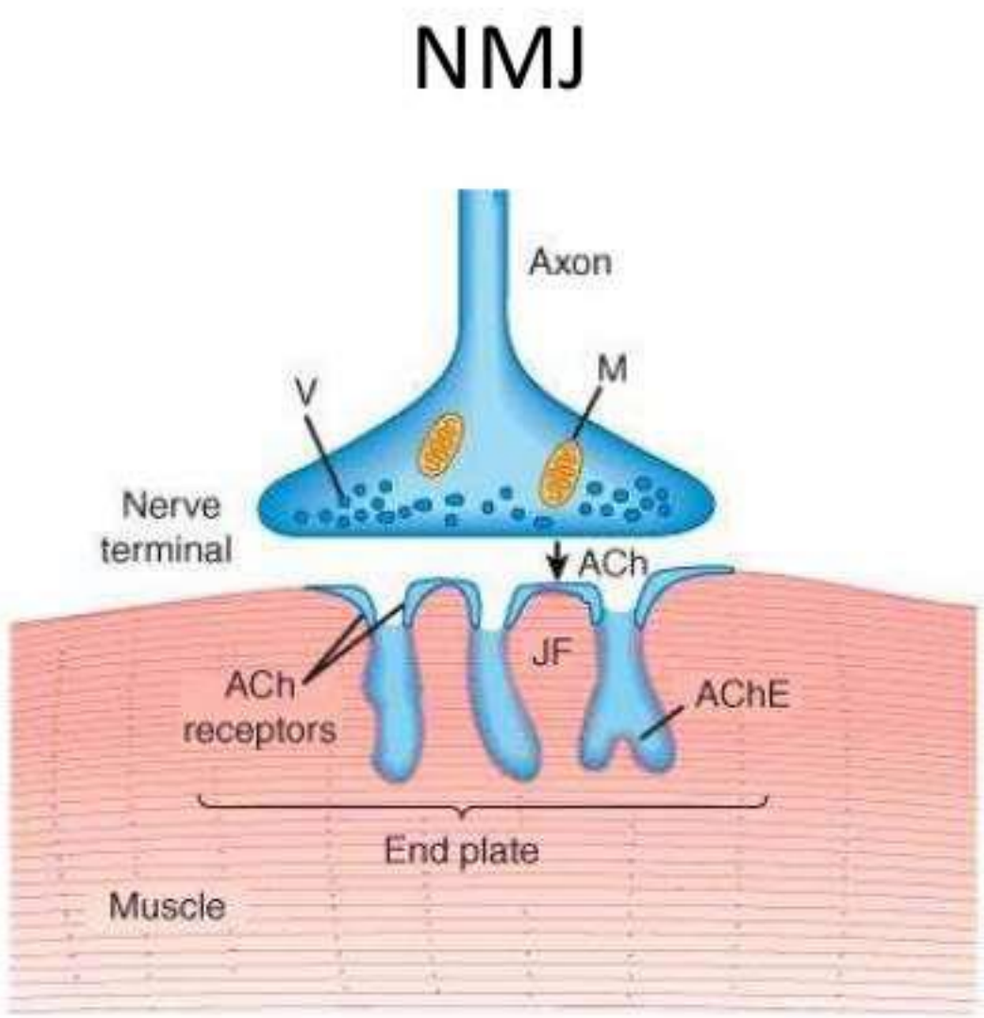
.2Skeletal Muscles

.3CNS: Cortex Basal ganglia, spinal cord and others

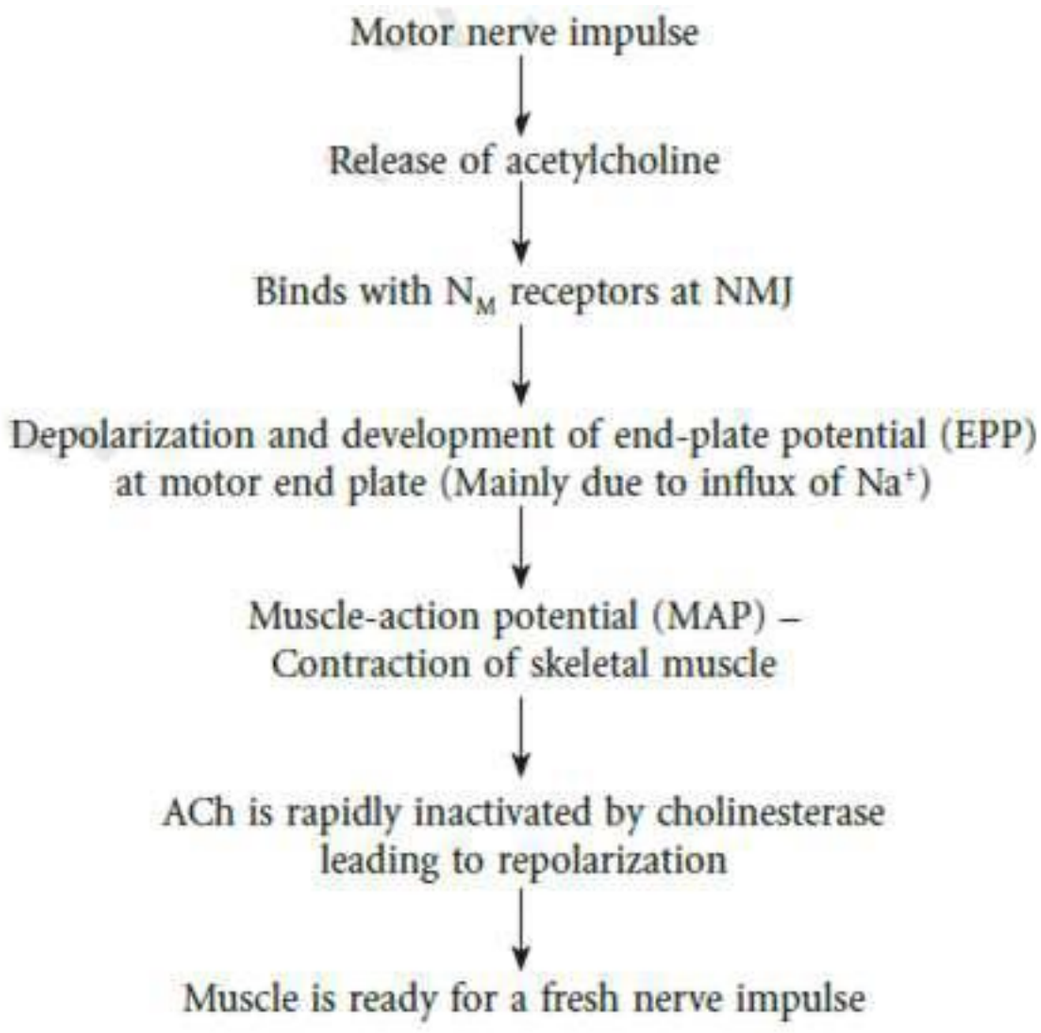
Parasympathetic Stimulation – Acetylcholine (ACh) release at neuroeffector junction – biological effects Sympathetic stimulation – Nonadrenaline (NA) at neuroeffector junction – biological effects


Sympathetic
Parasympathetic
Ach
Acetylcholine
Nic
Nicotinic receptor
Musc
Muscarinic receptor
NE
Norepinephrine
α
β
Adrenergic receptors
Preganglionic fibers (short)
Preganglionic fibers (long)
Ach
Nic
Posganglionic fibers
Posganglionic fibers
NE
α
β
Ach
Nic
Ach
Musc
PharmacologyCorner.com

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

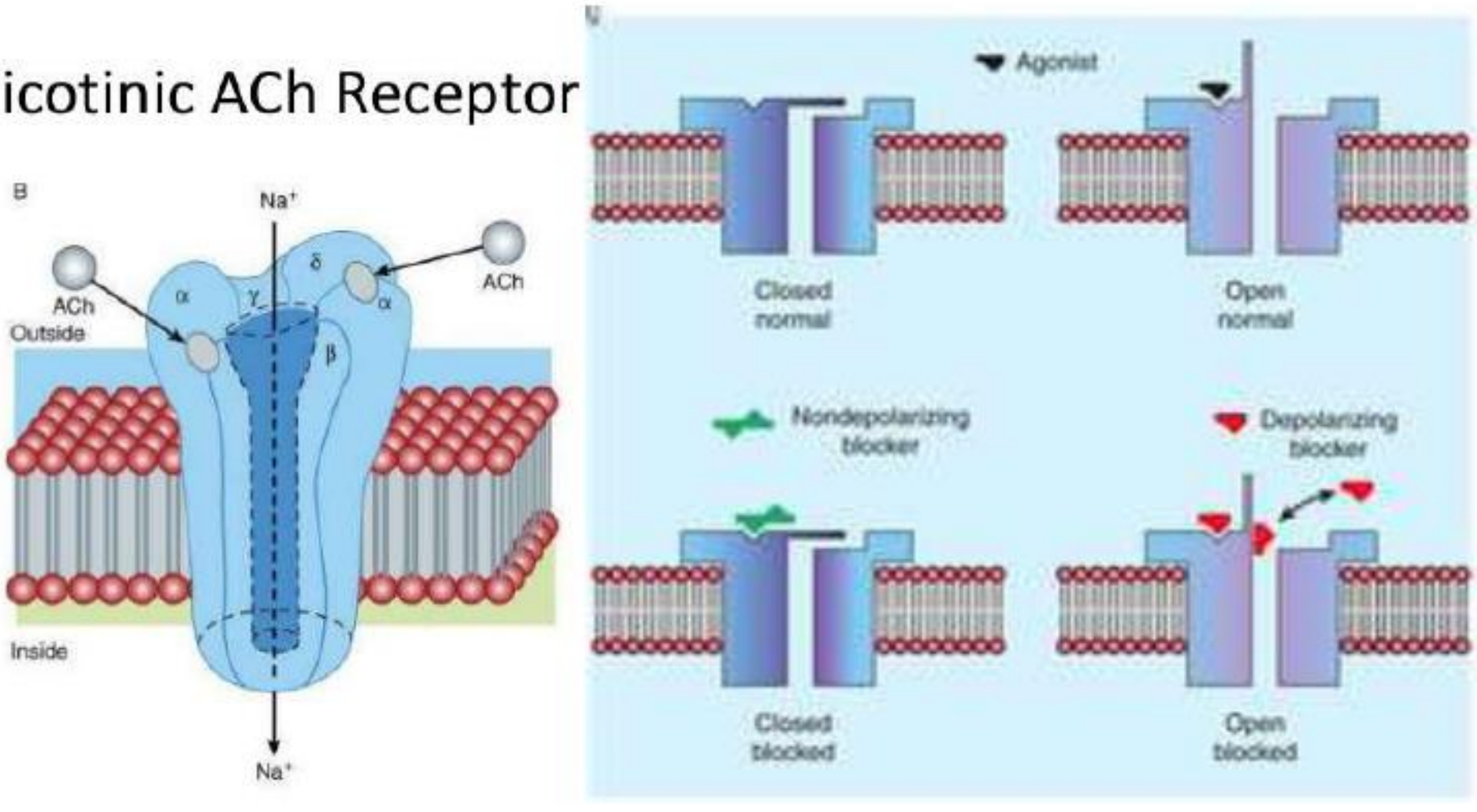
•Succinylcholine have affinity and **sub-maximal/ intrinsic** activity at Nm receptor.

•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

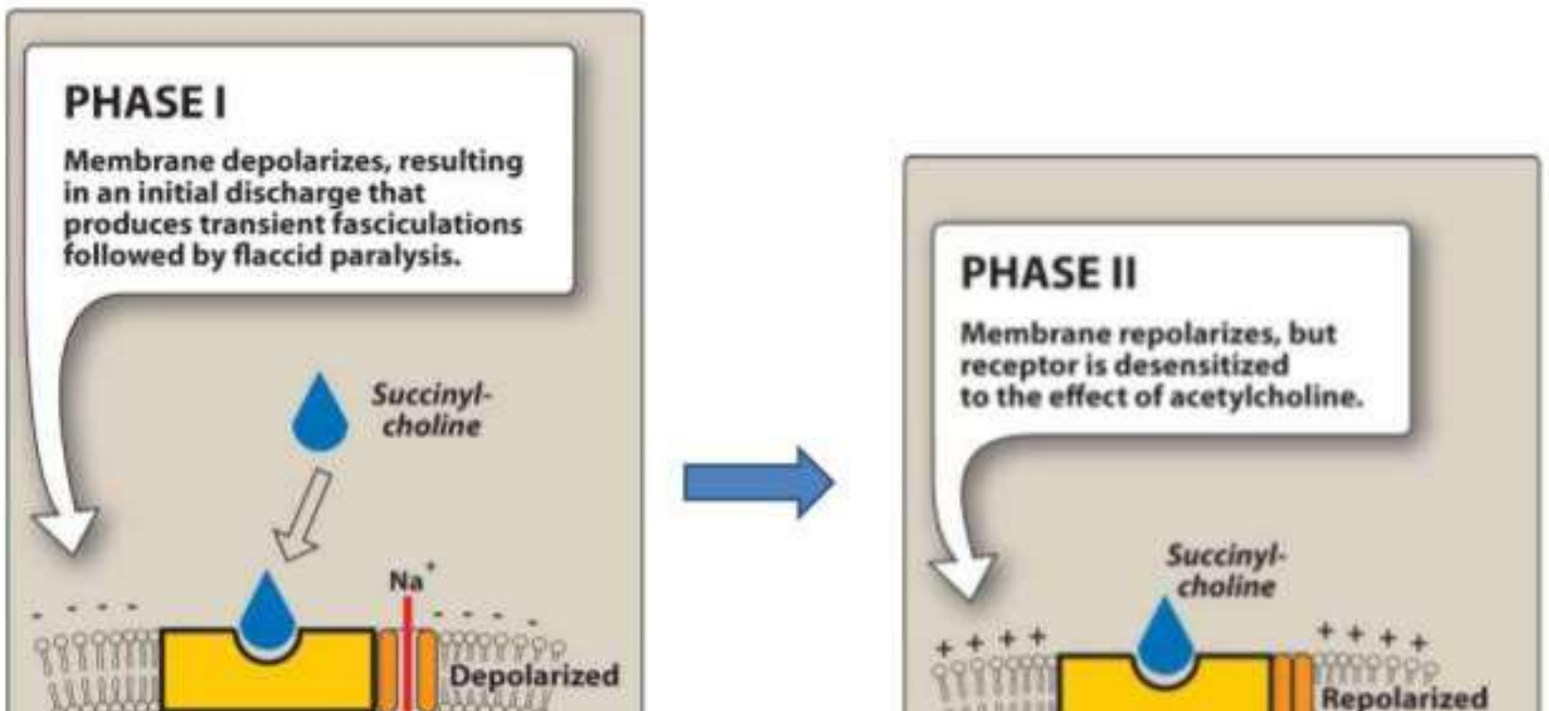
Nicotinic ACh Receptor



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.



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

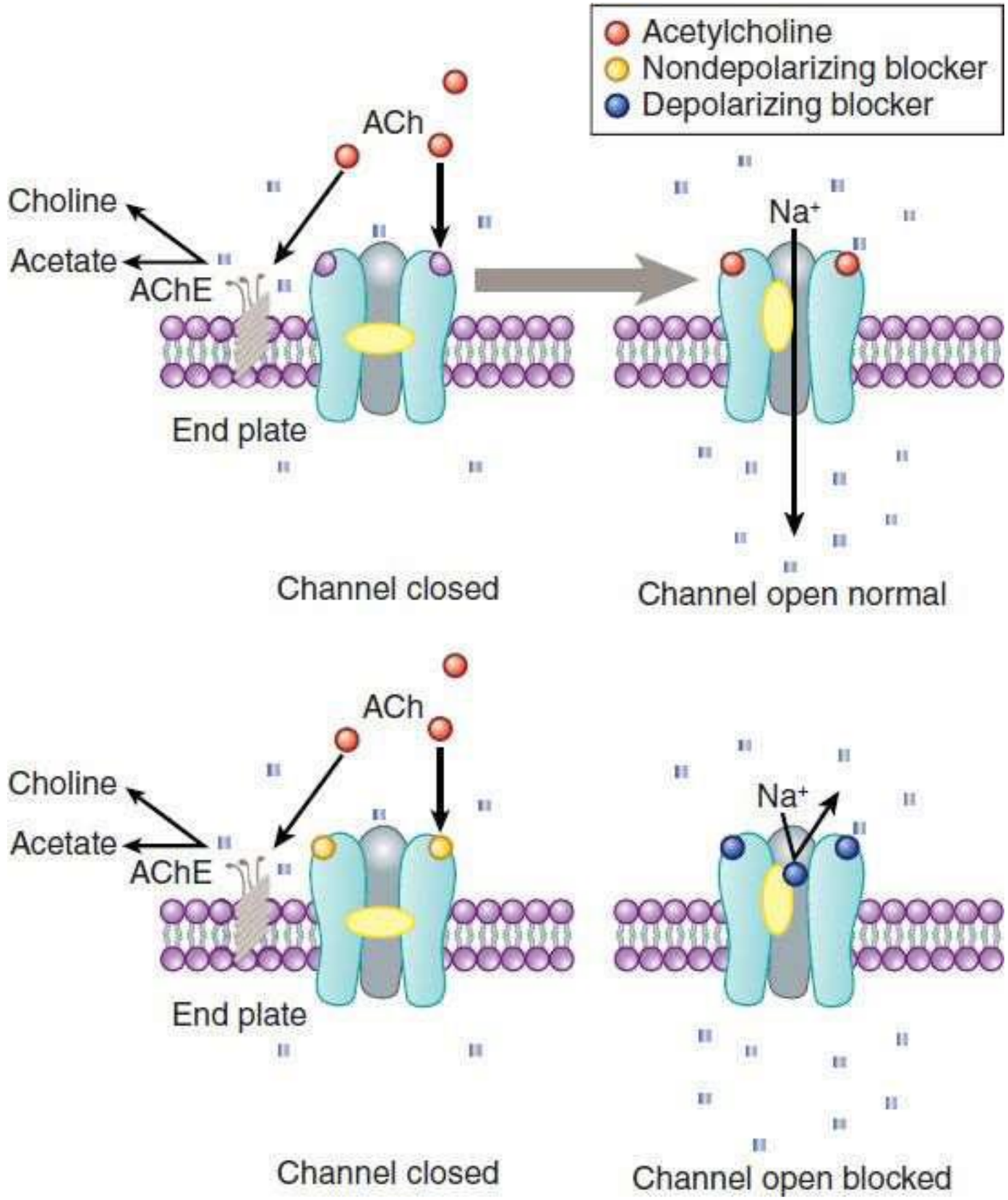
Non-Depolarising Drugs

- Competitive Blockers having no intrinsic activity
- 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(


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

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 on motor nerve endings

Non-depolarizing Drug: d-Tubocurarine

1 •st 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

CVS Effects:

- hypotension frequently even at doses < ED95
- 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
2-1 –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(

•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(120-60 –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

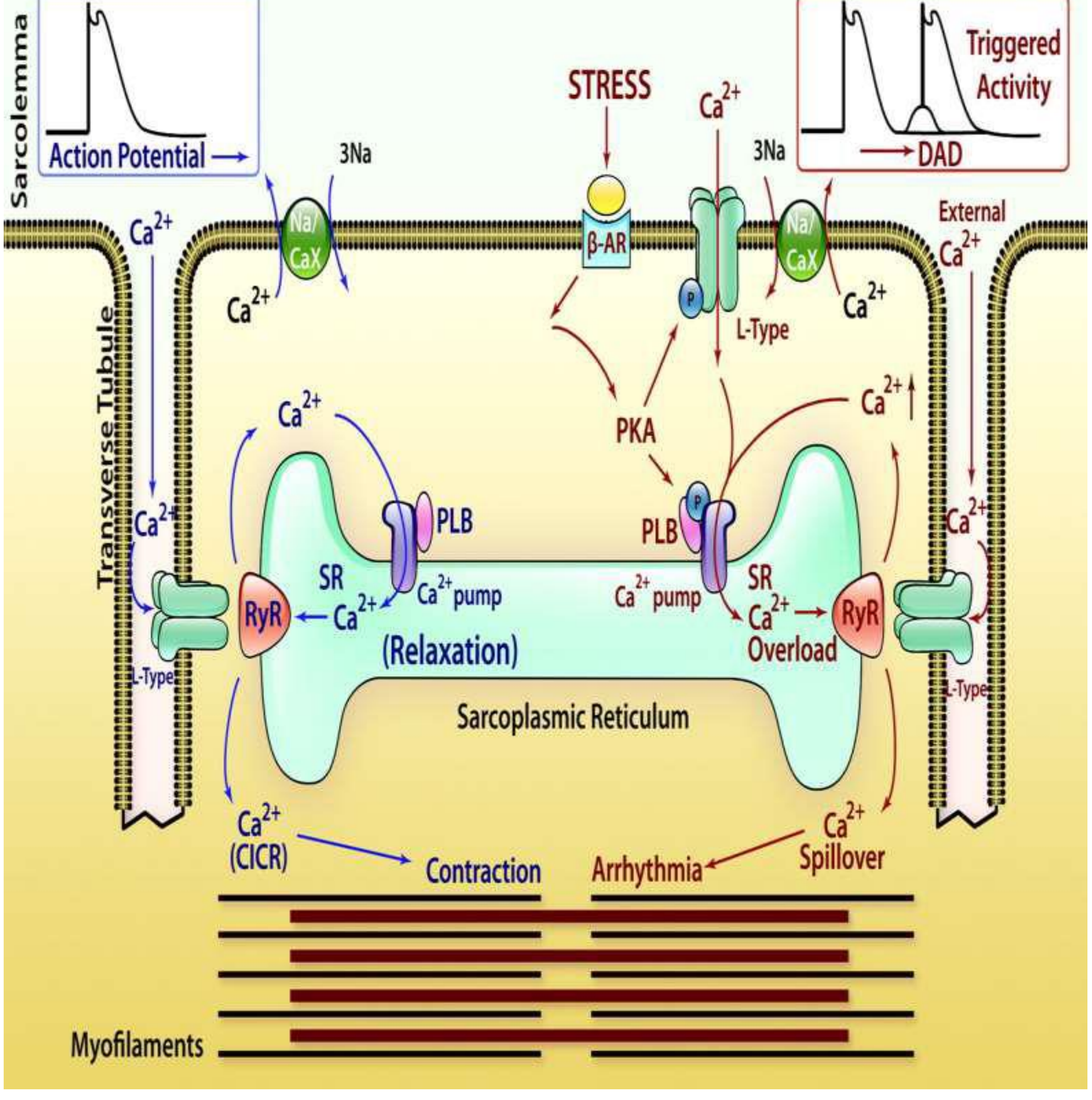
•Mechanism of Action: Ryanodine receptors (RyR) calcium channels – prevents depolarization – no intracellular release of Ca^{++}

•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

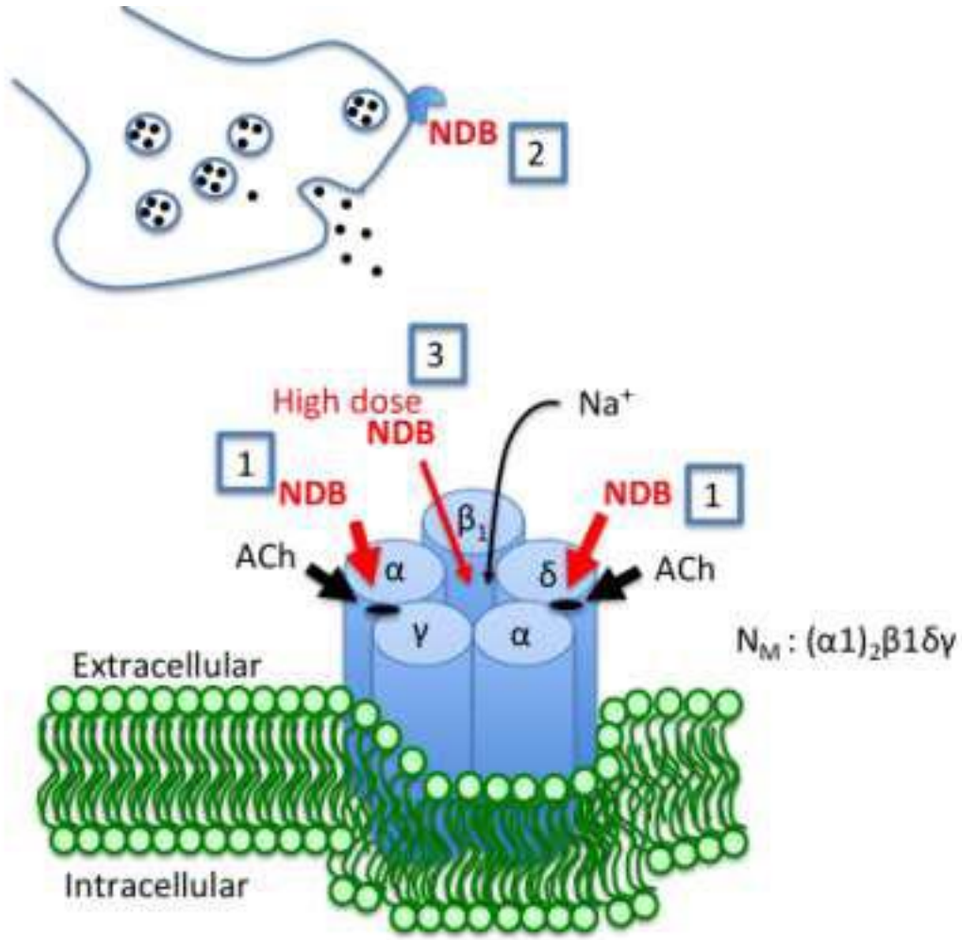
•Uses: Upper Motor Neuron disorders – paraplegia, hemiplegia, cerebral palsy and malignant hyperthermia)drug of choice 2.5-4 mg/kg(

- Adverse effects – Sedation, malaise, light headedness, muscular weakness, diarrhoea and hepatotoxicity


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

Malignant Hyperthermia

are heritable disorder triggered by a variety of stimuli, including general anest
atieents have a hereditary impairment of the sarcoplasmic reticulum to seques
he trigger can causes sudden and prolonged release of calcium, with massive
eatment is by cooling, correcting acidosis, and dantrolene to reduce calcium



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.*