Peripherally Acting Skeletal Muscle Relaxants

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Before surgery, we have to intubate the patient by inserting a tube through their mouth then down their trachea. To make this process effective, we use those peripherally acting relaxtants, also they will enable us to reach the surgical site. (it's easier to manipulate a relaxed muscle than to manipulate a constricted one)

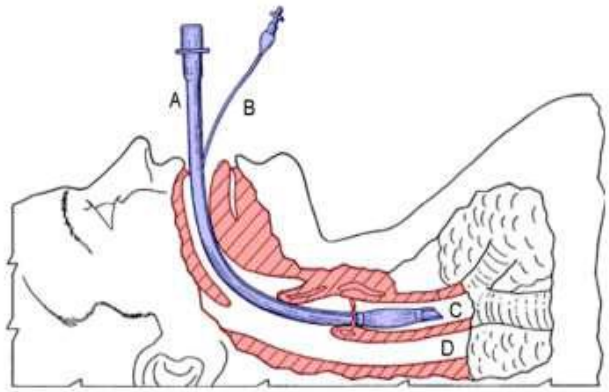
Peripherally Skeletal Muscle Relaxation Uses:

→ nicotinic receptors antagonist/blockers

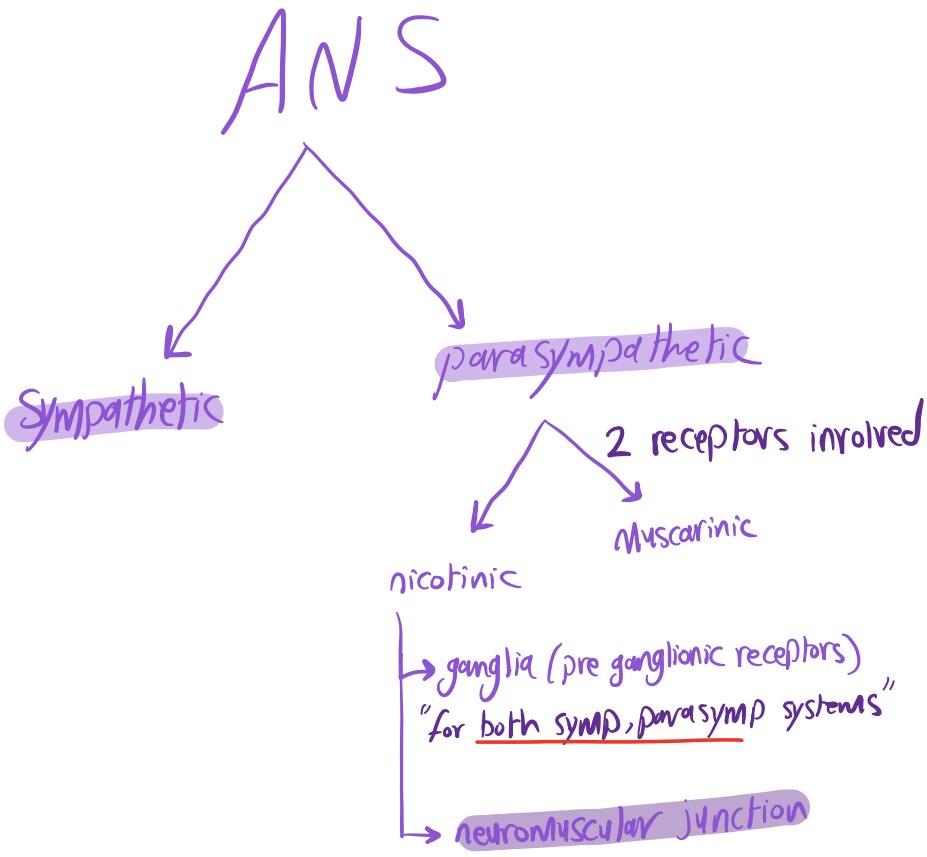
In conjugation with General Anesthetics: (NOT to cause anesthesia)

So they don't make the patient unconscious

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



* Quick rivision



As we know, Ach is the peripheral PSNS neurotransmitter, by acting on nicotinic receptors of NM junction

→ opens the channels for sodium ion influx

→ Causing end plate depolarization

→ Muscle Contraction

- So our peripherally acting drugs are supposed to block this action in order to relax the muscle, it can also block pre ganglionic receptors affecting sympathetic system.

History of Skeletal Muscle Relaxants

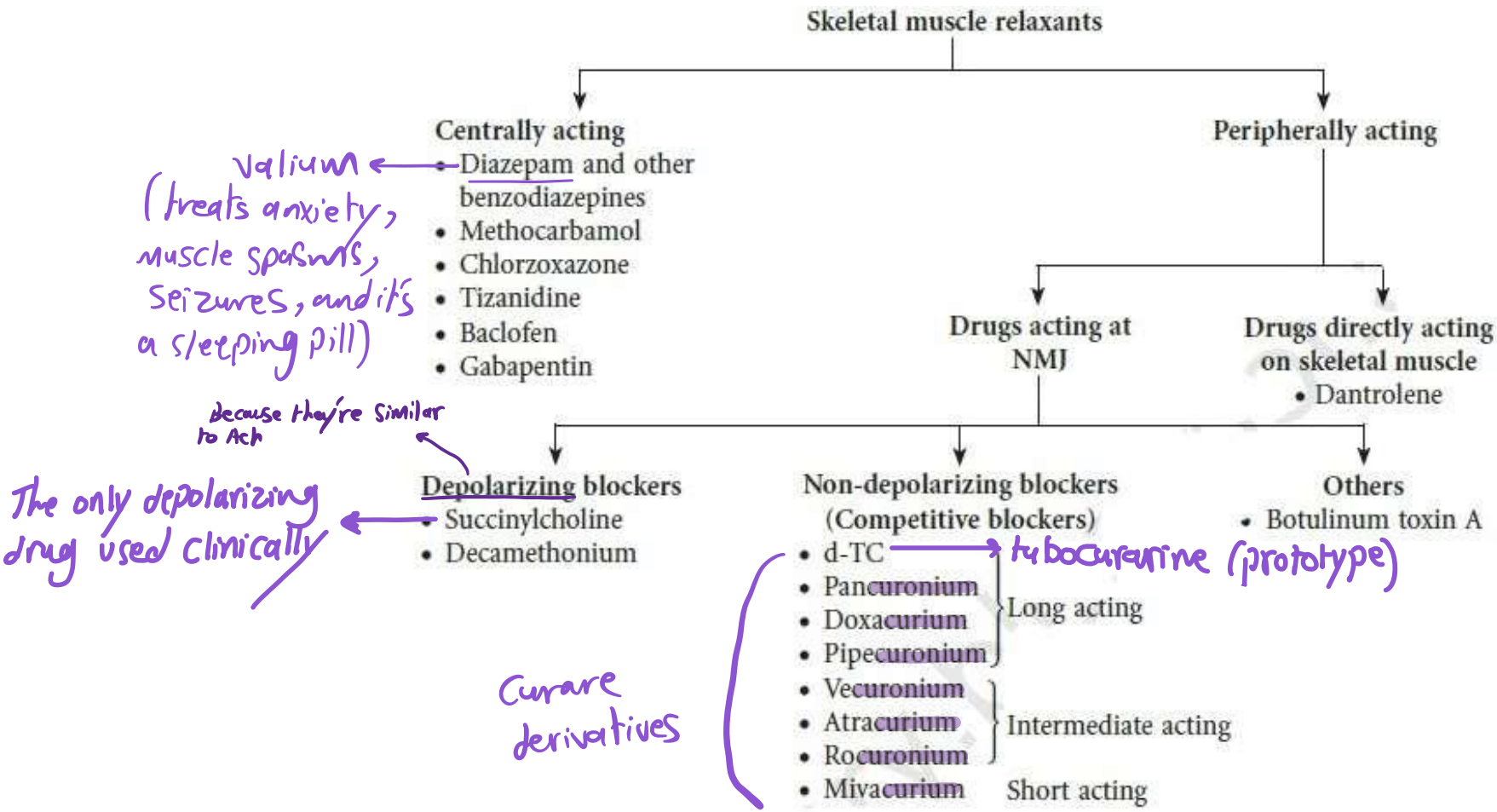
antagonist of the nicotinic receptors at NM junction

- 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"

it was used as a poison arrow for hunting by causing paralysis of the animal

*why this paralytic poison didn't affect the person who ate it ? It can't be absorbed due to its structure and that's why those drugs are given IV.

Classification



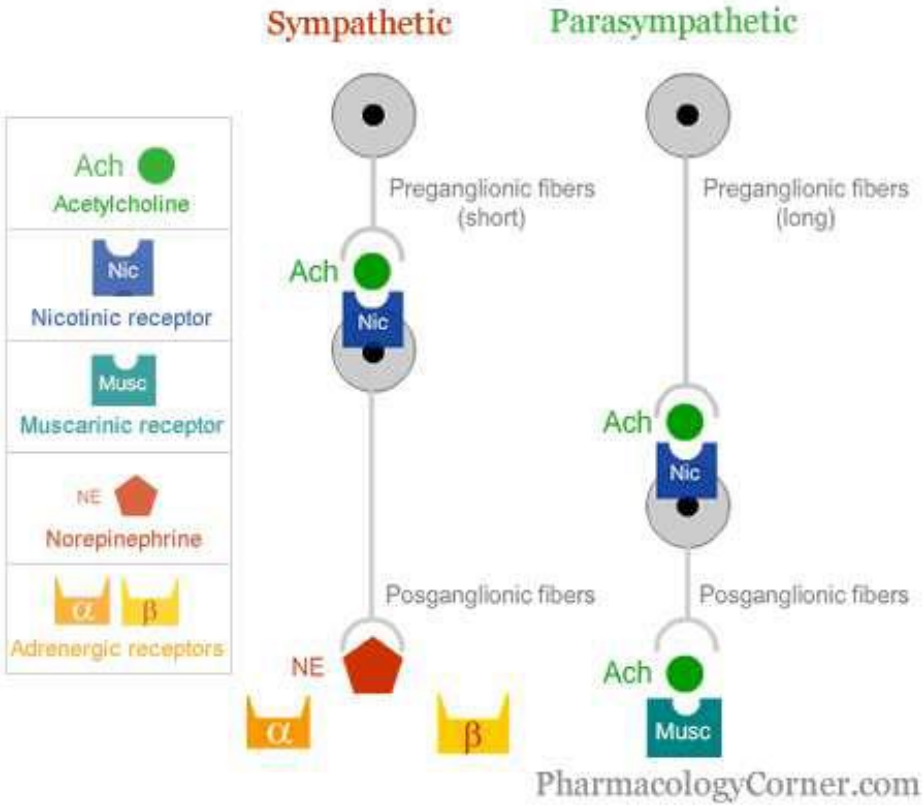
Acetylcholine

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

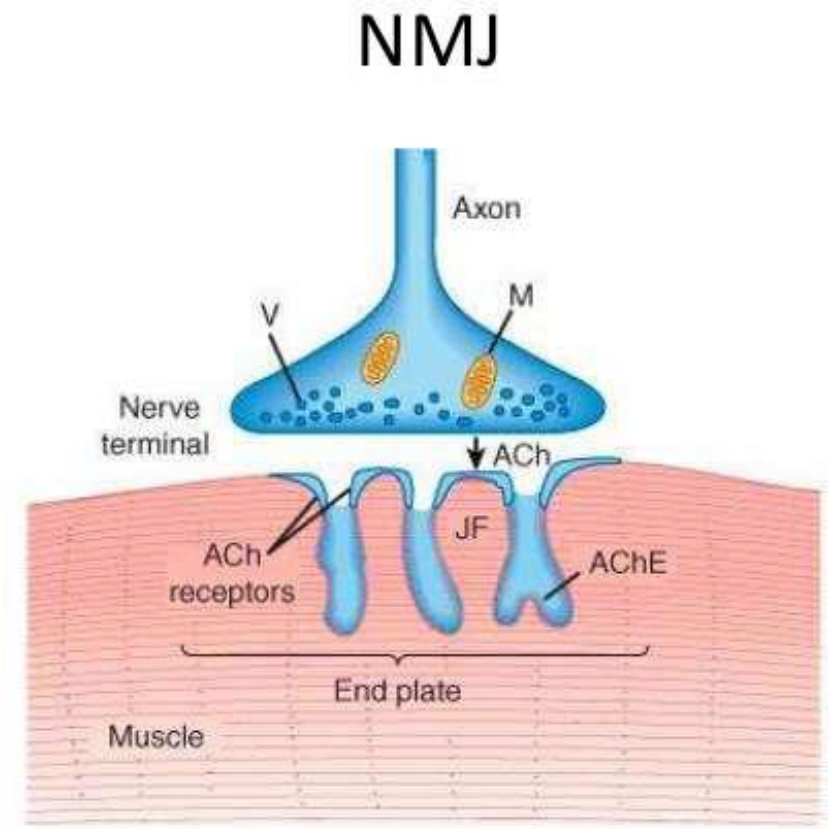
.1All preganglionic sites (Both Parasympathetic and sympathetic(
.2Skeletal Muscles
.3CNS: Cortex Basal ganglia, spinal cord and others

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

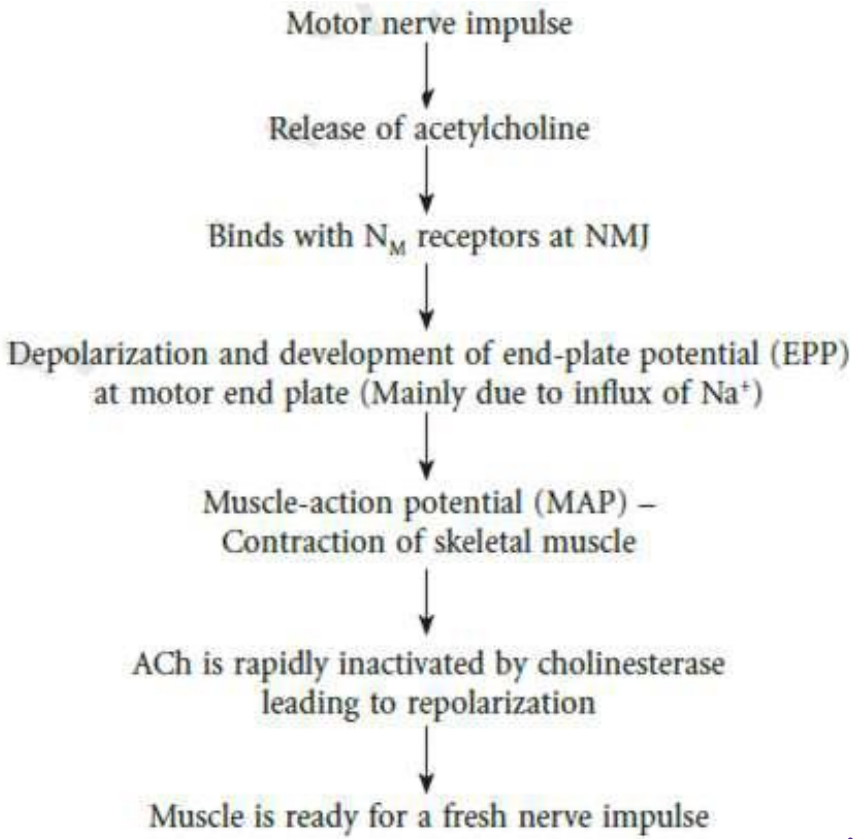
preganglionic binding of Ach stimulates the postganglionic release of NE (sympathetic stimulation)


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

– it's subjected to the action of cholinesterases so it has a short half life.

•**Non-Depolarizing** – interferes with the action of ACh

–Competitive Blockers (Antagonist(it binds to nicotinic receptors preventing ACh from binding

–Further divided into short, intermediate and long acting non- depolarizing drugs

Depolarizing Block - Succinylcholine (Agonist)

- Succinylcholine have affinity and **sub-maximal/ intrinsic** activity at Nm receptor. → less than Ach activity

- It acts on sodium channels, open them and causes initial twitching and fasciculation. → fast muscle contraction

So How it's gonna block the receptor?

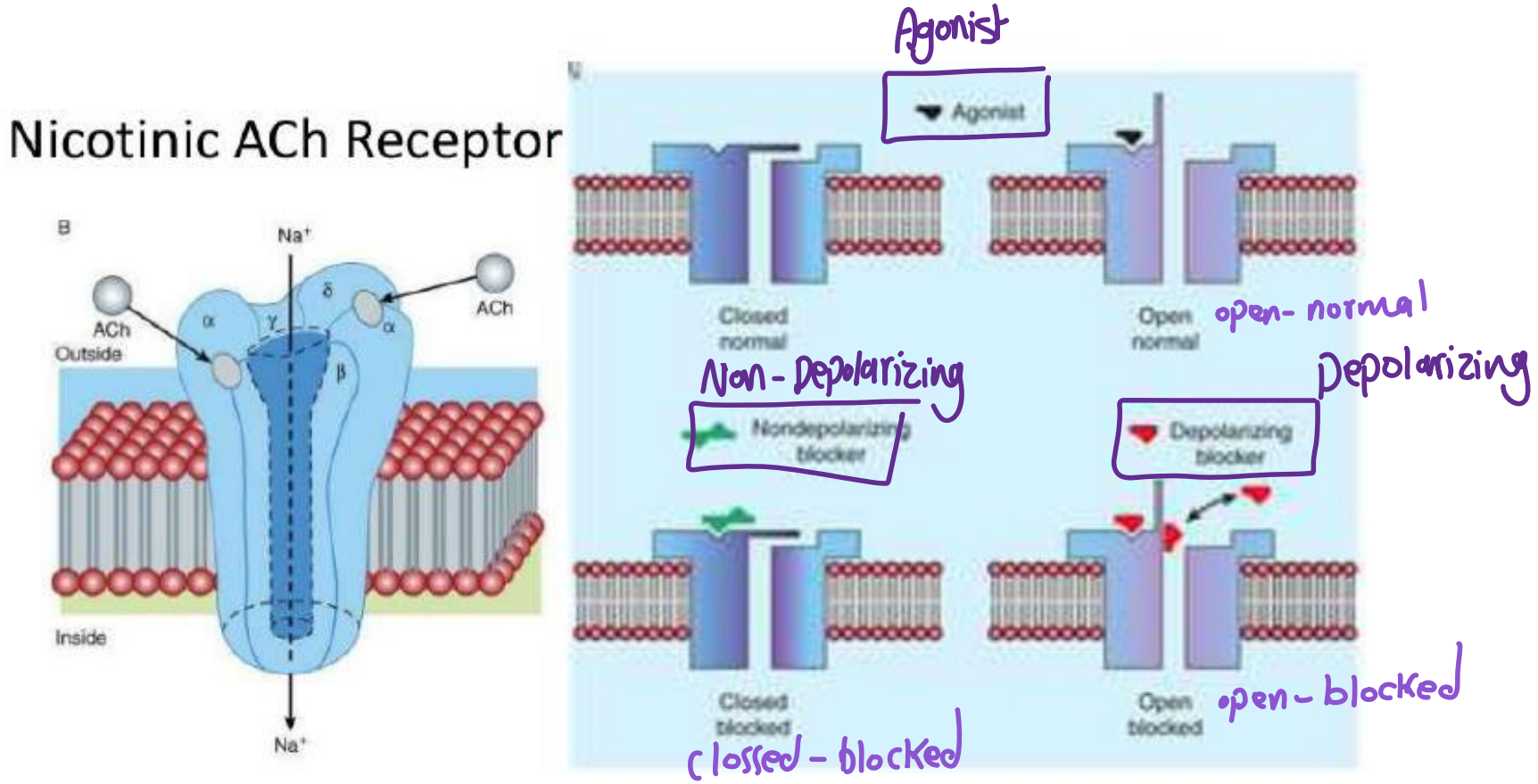
- It does not dissociate rapidly from the receptors resulting in prolonged depolarisation and inactivation of Na+ channels.

Remember the normal physiology of Ach:

it binds – causes deplorization – gets degraded – repolarization – new nerve impulse (new contraction)

While this drug doesn't dissociate preventing repolarization and generation of new action potential, so when the membrane finally repolarizes it's no longer responsive (So we're only gonna see an initial fasiculation that will progress into flaccid paralysis)

Mechanism of Action: Succinylcholine



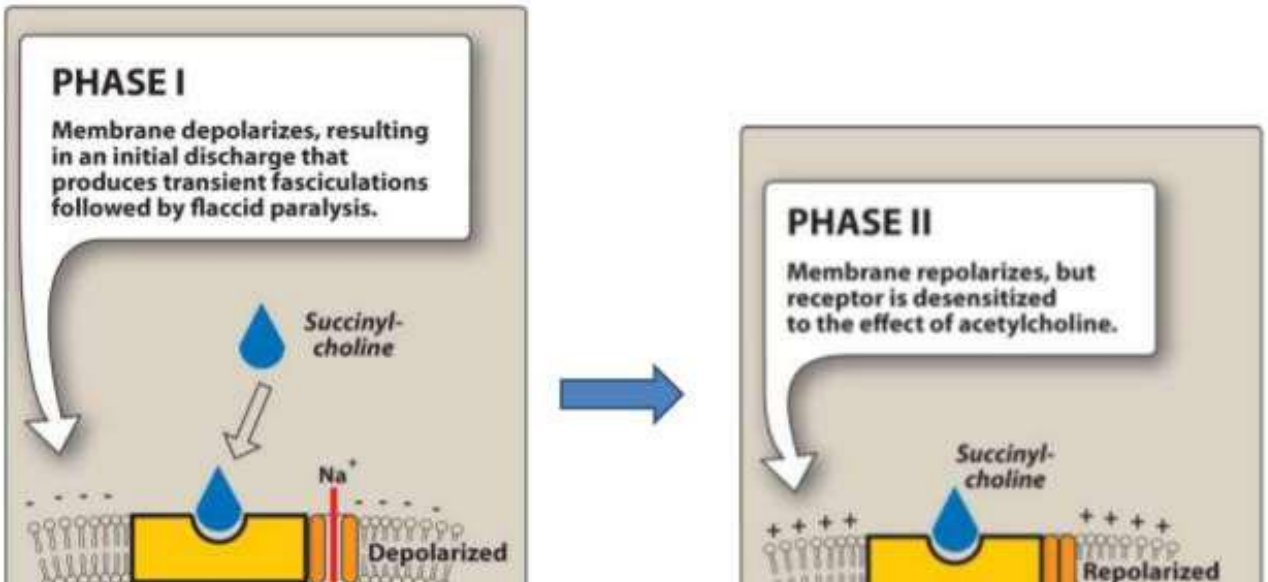
Succinylcholine acts on the Nicotinic receptors of the muscles, stimulates them and ultimately cause their relaxation.

This process occur in two phases:

•Phase I: During Phase I (depolarizing phase), they cause muscular fasciculations while they are depolarizing the muscle fibers.

from the prolonged depolarization

•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

*Succinylcholine is contraindicated for patients with
- Spinal cord injury
- burn victim patient

Why? because in both cases there will be upregulation of Ach receptors that will result in further paralysis, hyperkalemia caused by denervation hypersensitivity

Advantages:

- Most commonly used for Tracheal intubation (Because)
- Rapid onset (1-2 min(
- Good intubation conditions – relax jaw, separated vocal chords with immobility, no diaphragmatic movements
- Short duration of action (5-10 minutes(
- Dose 1-1.5mg/kg (depending on the patient's weight)
- Used as continous infusion occasionally (since it has a short half life)

Disadvantages:

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

intrinsic activity: a proportionately constant ability of the agonist to activate the receptor to produce a maximum functional response.

Non-Depolarising Drugs

Most of them are used clinically

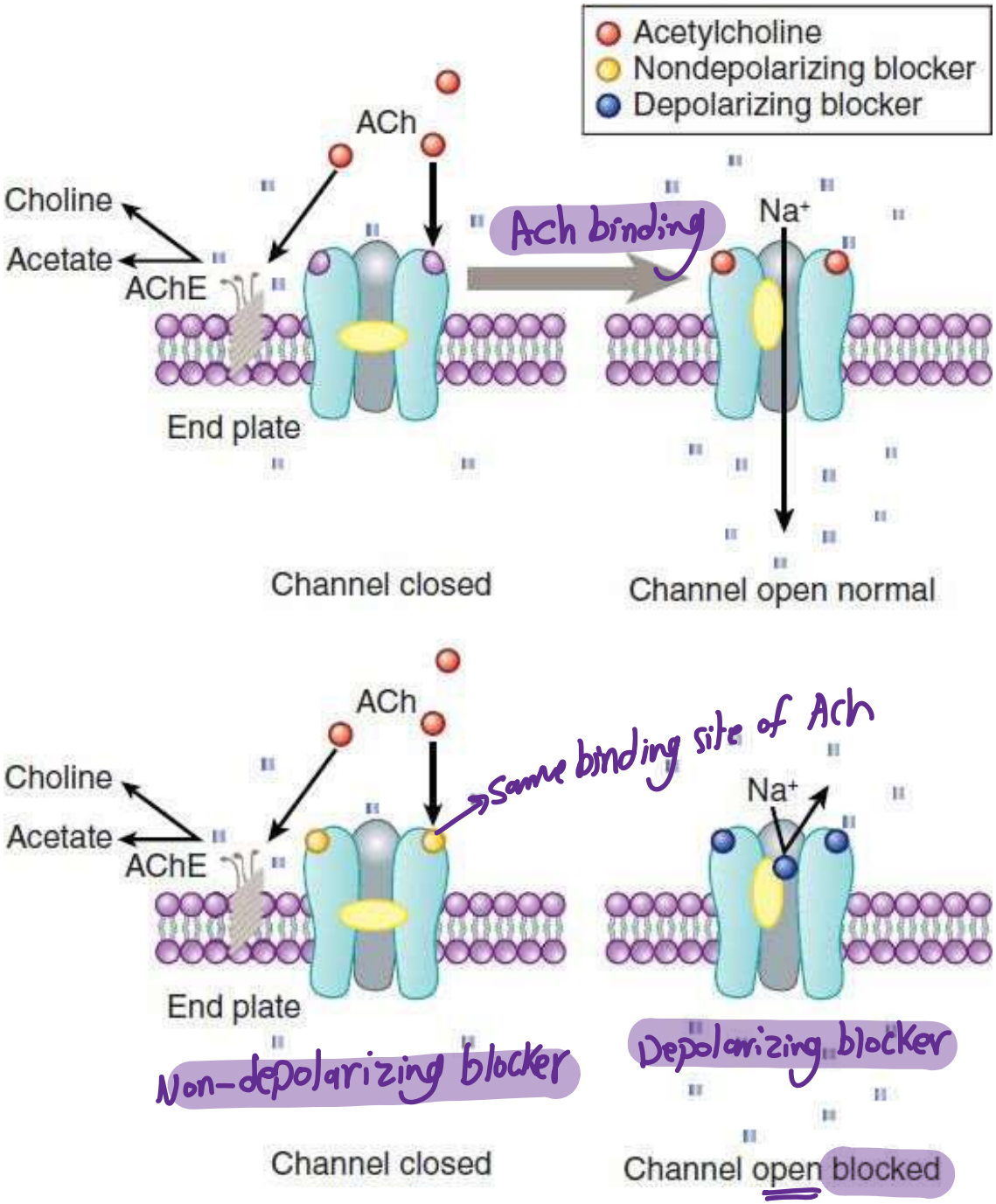
- Competitive Blockers having no intrinsic activity (they can't activate a receptor or channel)

- These are of 3 types based on their activity:

– *Long Acting :* d-TC (the father), Pancuronium, Pipecuronium, Gallamine (Kidney Excretion((in general, long acting drugs are usually excreted by kidneys)

– *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
Ach binding
Na+
Channel closed
Channel open normal
ACh
Choline
Acetate
AChE
End plate
same binding site of Ach
Na+
Non-depolarizing blocker
Depolarizing blocker
Channel closed
Channel open blocked

Effects of Non-depolarizing blockers

Since it's a competitive antagonism, binding depends on conc of both the agonist and antagonist. So we can reverse the action of NDB by increasing conc of Ach by

- **Low Doses:**
  - –Competitive antagonists of ACh
  - –Action reversed by ACh ecterase inhibitors like neostigmine, physostigmine
- **Large Doses**:
  - –Ion Channel is blocked (No antagonistic effect, even if we increased conc of Ach the channel itself 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

Remember the presynaptic receptors that controls the release of neurotransmitters from that neuron they're located on (binding to these receptors prevent further release)
So here those drugs can bind to them preventing the release of Ach
This process is called fade of Ach

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

highly polar ⟹ that's why it's administered IV, Not absorbed orally

so we still have action potential

it's a competitive antagonism, so Ach can still bind to some receptor

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

CVS Effects:

- hypotension frequently even at doses < ED95
- histamine released (skin flushing frequently(Anti-histamines are given along with this drug
- autonomic ganglionic blockade- manifests as hypotension
  - by blocking the vasoconstriction effect of sympathetic system

Clinical Use:

- long duration of action(60 to 120 mins) and CVS effects restricted its use
- used as “precurarization”
  - it's used to reduce side effects of succinylcholine

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 (advantage)
  - Safe in hepatic & renal impairment (because it can be degraded very fast)
  - Spontaneous inactivation to laudanosine (seizures(

Atracurium is metabolized to laudanosine, this toxic product can cross BBB and can cause seizures if acummulated

- 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(

Summary

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

only highlighted things are required

•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

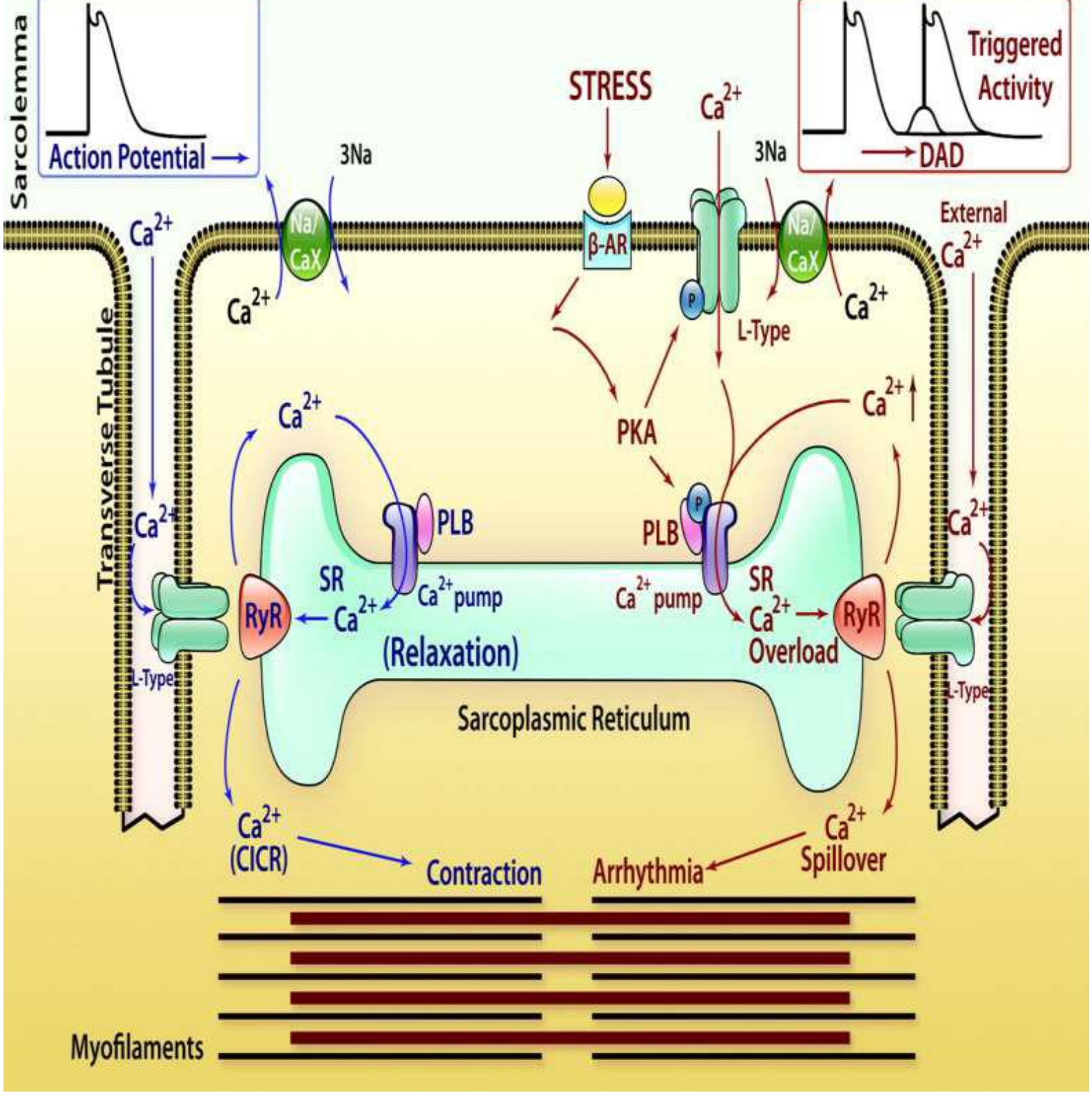
Directly acting relaxants - Dantrolene

Ryanodine receptors
ANTAGONIST

- present on sarcoplasmic reticulum membranes
- mediate the release of Ca^{++} (an important step in contraction)

decreasing intracellular Calcium levels

- 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
Ca^{2+}
3Na
3Na
β-AR
Na/CaX
Na/CaX
External Ca^{2+}
Ca^{2+}
Ca^{2+}
Ca^{2+}
P
L-Type
Transverse Tubule
PKA
Ca^{2+}
Ca^{2+}
Ca^{2+}
PLB
PLB
P
SR Ca^{2+}
Ca^{2+} pump
Ca^{2+} pump
SR Ca^{2+} Overload
RyR
RyR
(Relaxation)
L-Type
L-Type
Sarcoplasmic Reticulum
Ca^{2+} (CICR)
Contraction
Arrhythmia
Ca^{2+} Spillover
Myofilaments

Malignant Hyperthermia

Rare

~~a~~re heritable disorder triggered by a variety of stimuli, including general ~~anest~~

~~patients~~ ~~a~~tieents have a hereditary impairment of the sarcoplasmic reticulum to ~~seques~~

~~which~~ ~~t~~he ~~trigger~~ can causes sudden and prolonged release of calcium, with massive

Treatment eatment is by cooling, correcting acidosis, and dantrolene to reduce calcium

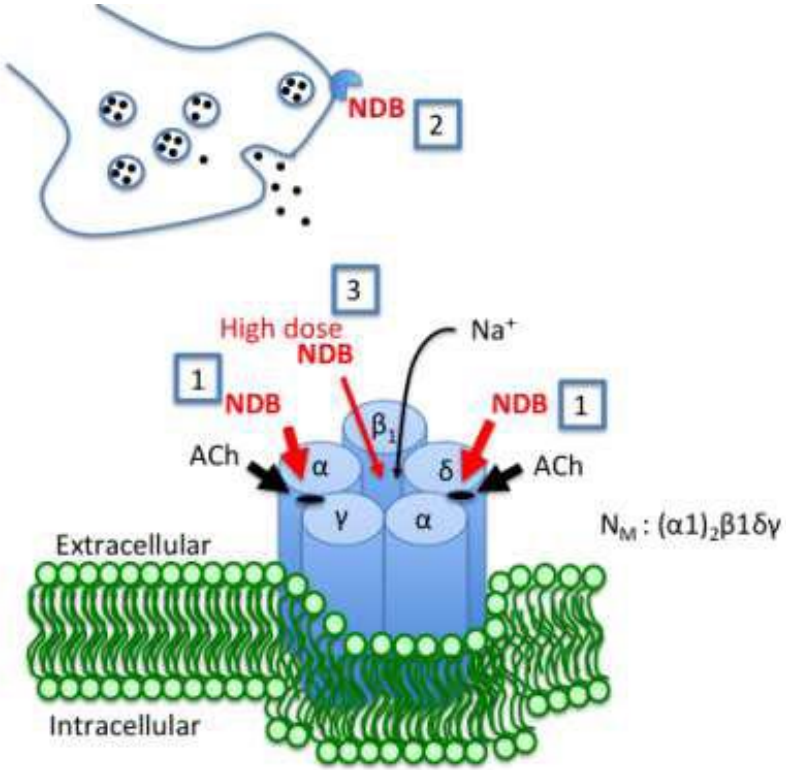
Mutations of the Ryanodine receptors

like succinyl choline

anesthetics.

Sequester Ca++

with massive contraction, this leads to lactic acidosis and increases body temperature.



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.*