MSS

PHARMACOLOGY

Lec 6

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Peripherally Acting Skeletal Muscle Relaxants

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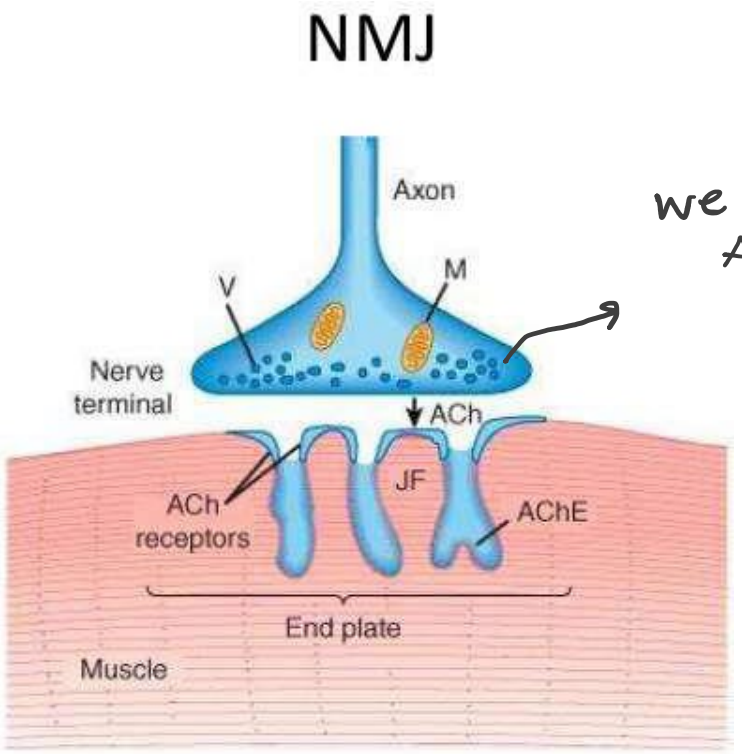
past:

Question: The use of succinylcholine for patients with spinal cord injuries or burn victim patients is not recommended?

if they are given succinylcholine we will activate too much receptors resulting in further paralysis + it will cause hypercalcemia and this leads to heart arrest

Because these patients have some motor function loss so the body increases the expression of accessory Ach receptors which are present in the smaller cleft of postsynaptic nerve terminal to compensate the loss and have stronger contraction.

Neuromuscular Junction (NMJ)



we have prejunctional Ach receptors
- fast forward mechanism
Once Ach binds to prejunctional receptors that stimulates the release of more Ach

* The blocker can inhibit prejunctional receptors and inhibit this mechanism

That is called Ach fading

Non-Depolarising Drugs

doesn't do any effect on the signaling mechanism of the cell
net effect = zero

antagonists

- Competitive Blockers having no intrinsic activity

they will bind to the channel and prevents Ach binding

- These are of 3 types based on their activity:

Duration depends on the way the drugs are metabolized or excreted

–Long Acting : d-TC, Pancuronium, Pipecuronium, Gallamine (Kidney Excretion)

+ pencuroni

–Intermediate : Vecuronium, Rocuronium, Atracuronium (eliminated by liver)

* no excretion in the kidney → faster

metabolized by the liver + Hoffman elimination (hydrolysis)

–Short Acting : Mivacuronium, Ropcacuronium (inactivated by plasma cholinesterase)

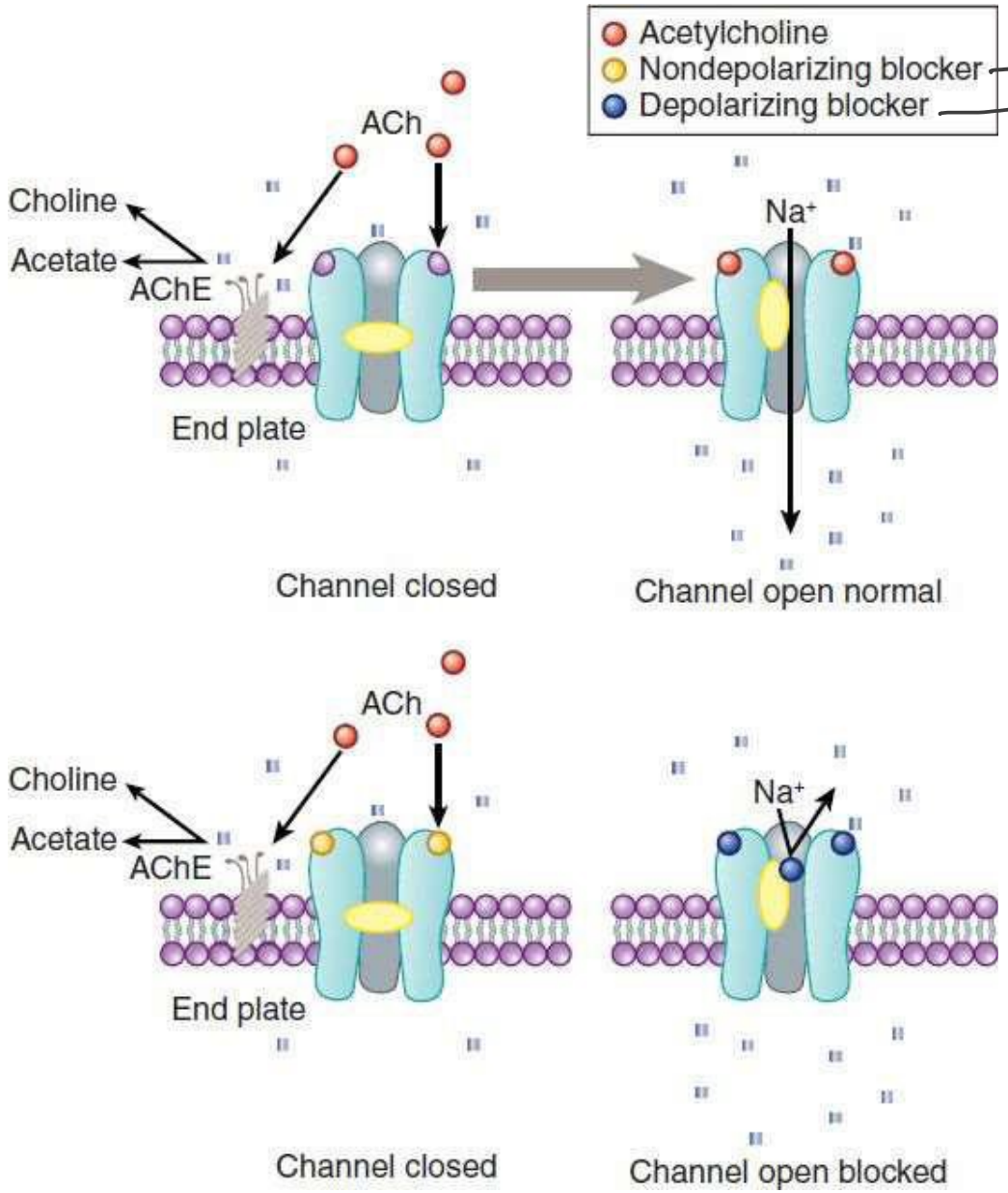
very quickly

Which drug to use depend on the patient:

- patient with kidney disease don't use a drug that is excreted in the kidney because that will lead to toxicity.
- patients with liver disease don't use drugs that is metabolized in the liver

exception : Atracuronium (mainly eliminated by hydrolysis) so it can be given to them

Represents binding locations for different drugs



bind to Ach binding site

Bind to the inside of the channel: keeping the channel open preventing further steps of repolarization.

Effects of Non-depolarizing blockers

they have different effects depending on the dose.

- **Low Doses:**
  - –Competitive antagonists of ACh
  - –Action reversed by ACh ecterase inhibitors → Neostigmine, physostigmine
- **Large Doses**:
  - –Ion Channel is blocked
  - –More weakness of neuromuscular transmission
  - –Action could not be reversed by ACh esterase inhibitors → Because when high dose part of the drug is inside the channel and cannot be accessible by AchE inhibitors
- **Other actions:**
  - –Can block pre-junctional Na+ channels and interfere with mobilization of ACh at nerve endings → This is called Ach fade

Mechanism of Action

Highly polar so we take them IV

- 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 → there's still action potential because these non depolarizing blockers are competitive Antagonists of Ach (so Ach effect is still found).
- Action can be overcome by increased ACh concentration or blocking of acetylcholinesterase
- They also block prejunctional ACh on motor nerve endings (Ach fade)

Non-depolarizing Drug: d-Tubocurarine

- 1 •st agent to undergo clinical investigation
- •purified curare – *Chondodendrom* tomentosum
- •ED_{95}= 0.5mg/kg → conc. of the drug that will give 95% of the maximal effect
  - 95%. ← almost the maximum effect
  - ← effective dose
- •undergoes minimal metabolism- is excreted
  - %10 -in urine
  - %45 -in bile
  - * most of the drug will be excreted in the kidney without metabolism ← so these percentages are for the metabolites not the whole drug
- •excretion impaired in Renal Failure

CVS Effects:

Cardiovascular side effects

① It blocks the nicotinic receptors present in the ganglia so they block the sympathetic activation of BV
↓
prevent vasoconstriction of BV resulting in relaxation and hypotension.

- ① hypotension frequently even at doses < ED95
- ② histamine released (skin flushing frequently)
- ③ autonomic ganglionic blockade- manifests as hypotension

② Histamine results in bronchoconstriction and more respiratory secretions that can affect the intubation process
↓
So we give antihistamine to reverse the effect of histamine.

Clinical Use:

Good for long operations

- long duration of action(60 to 120 mins) and CVS effects restricted its use
- used as "precurarization"
  ↓
  we give d-tubocurarine before succinylcholine to prevent the pain (at first succinylcholine causes fasciculation of the muscles).

Non-depolarizing Drugs

•Gallamine

• –Less potent than curare

• –Tachycardia

•D-Tubocurarine

1 –hr duration of action

• –Histamine releaser (Brochospasm, hypotension)

• –Blocks autonomic ganglia (Hypotension)

•Atracurium

• –Rapid recovery

• –Safe in hepatic & renal impairment → partially eliminated by hydrolysis reactions

• –Spontaneous inactivation to laudanosine (seizures)

laudanosine: CNS stimulater (if accumulates it can cross BBB).

short acting (metabolized by plasma choline esterases)

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

less CVS effects

Heart
- SA node → parasympathetic tone
  - * we block the main reason bradycardia resulting in tachycardia
- contraction → sympathetic

Summury

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

only underlined is required

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

we take it IV

•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

short acting (10 min)

• Succinylcholine Succinylmonocholine Succinc acid + choline (plasma cholinesterase): 3-5 min

rapid onset

• In some – generally determined abnormality and deficient pseudocholinesterase Paralysis & apnoea

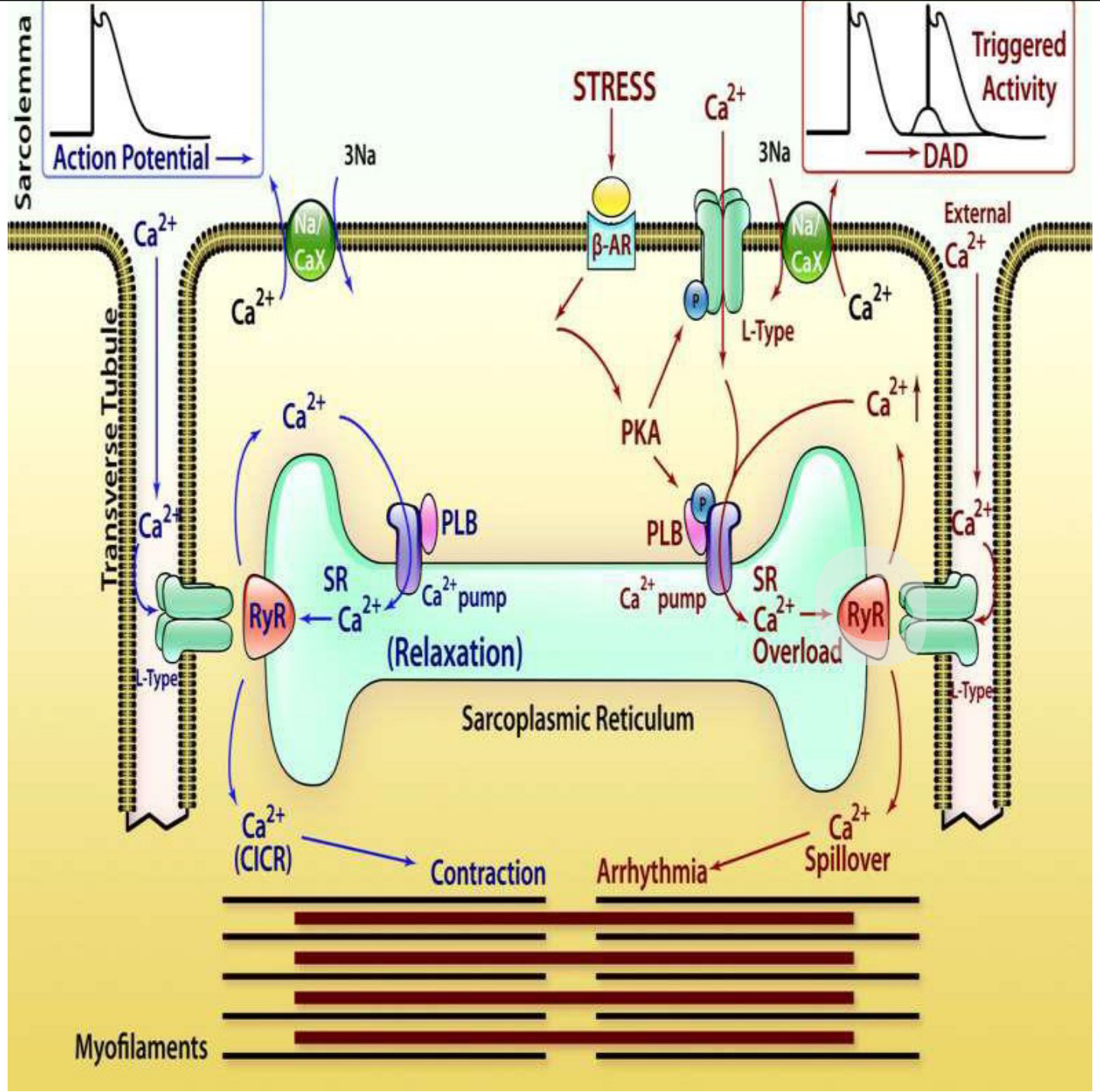
works directly on the muscle's mechanism of contraction

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

antagonist

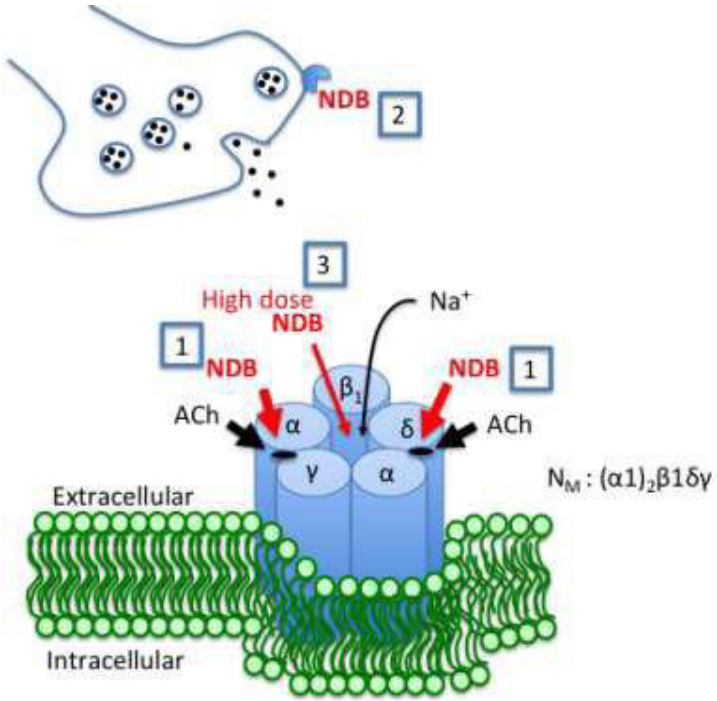
most important ion in muscle contraction


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

Malignant Hyperthermia

- Rare heritable disorder triggered by a variety of stimuli, including general aesthetics and neuromuscular blockers.
- Patients have a hereditary impairment of the sarcoplasmic reticulum to sequester calcium.
- The trigger can causes sudden and prolonged release of calcium, with massive contraction, lactic acidosis ,and increased body temperature.
- Treatment is by cooling, correcting acidosis, and dantrolene to reduce calcium release.

* mutation in Ryanodine receptor
  ↳ acts on the receptor preventing calcium release.
  when they take succinylcholine or halogenated hydrocarbons (general anasthetic agents)
  ↓
  patients will have excessive release of Ca++ due to the mutation, which will lead to aggressive and continuous contraction and this contraction will raise the body temperature (Hyperthermia)



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.*