بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 7

Muscle Relaxants Pt.2

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Peripherally Acting Skeletal Muscle Relaxants

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The next 10 slides from the previous lecture

History of Skeletal Muscle Relaxants

- Curare (antagonist of the nicotinic receptors at NM junction) is a common name for various plant extract alkaloid arrow poisons (it was used as a poison arrow for hunting by causing paralysis of the animal muscle) originating from Central and South America.

- Source: *Chondrodendrone tomentosum* and *Strychnos toxifera.* (Don't worry about these).

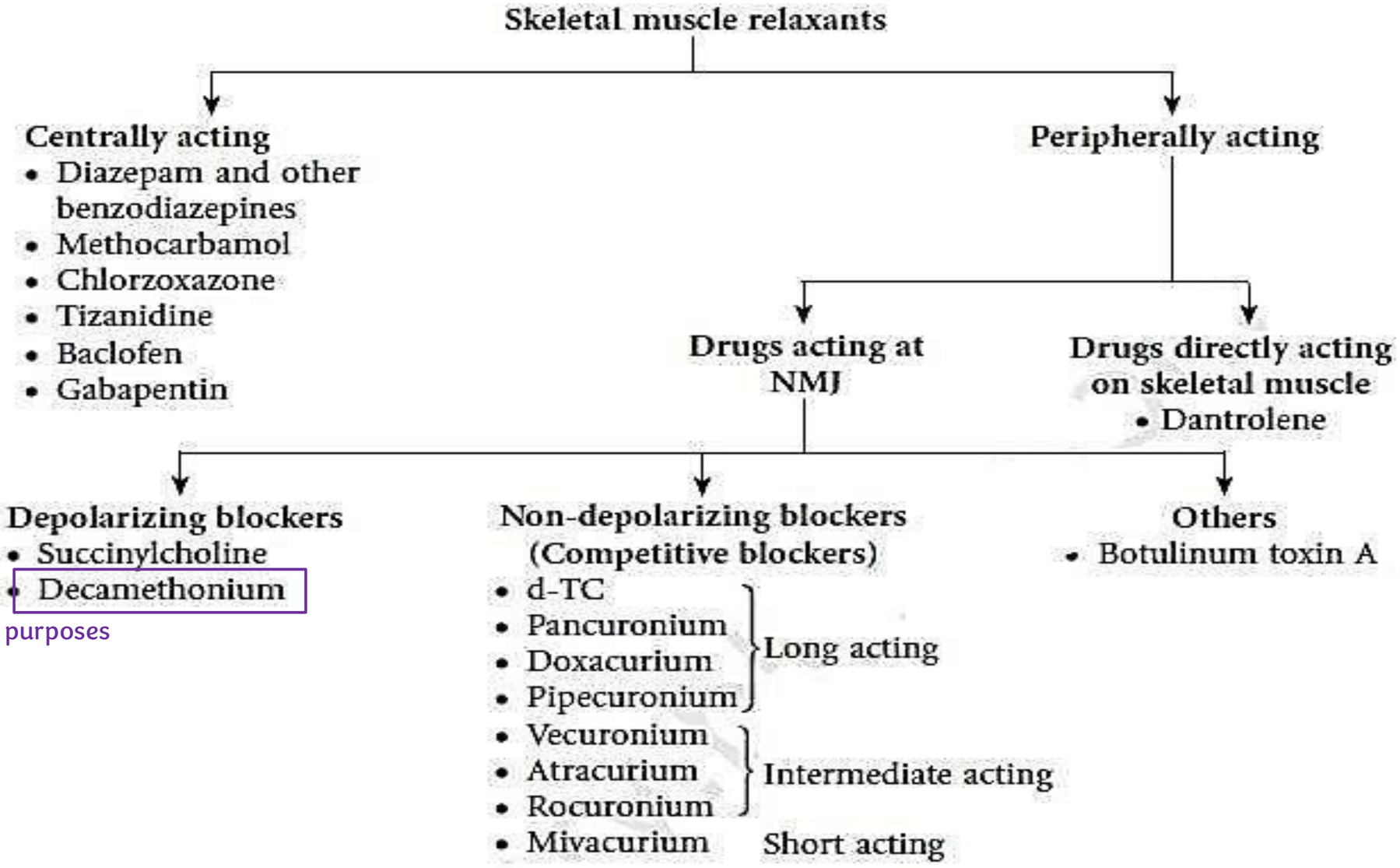
- Tubocurarine name because of packing in "hollow bamboo tubes"

History of Skeletal Muscle Relaxants

- That make us thinking : **Why this paralytic poison didn't affect the person who ate the animal that was injected with this poison?**

  - **It can't be absorbed** due to its structure (highly polar compound) and that's why those drugs **are given IV when being used as a muscle relaxant.**

Classification



Only used for research purposes

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

- Acetylcholine is a major neurohumoral transmitter at **autonomic**, **somatic** and **central nervous system, it is secreted (present) at :**

1) All preganglionic sites (Both Parasympathetic and sympathetic).
   - When we study drugs later and their side effects, we are going to find that their side effects is related to being **non-selective for Ach receptors** on both Sympathetic & Parasympathetic.

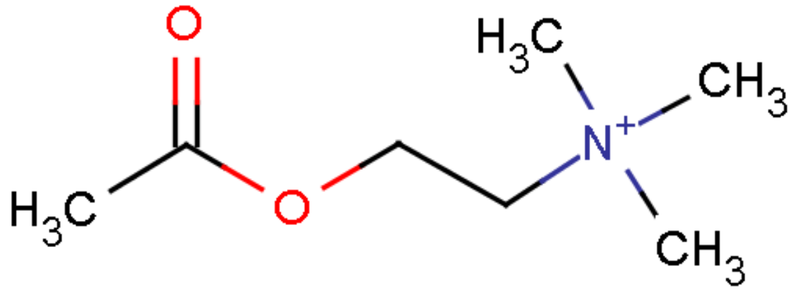
2) Skeletal Muscles. **(The effector cells of NMJ).**
   - We have 2 types of Ach receptor, the M Type (Muscle type) and N type (Nerve Type) [remember that we have a specific selectiveity toward one type, so if we are using a drug with high does we may lose selectivity and it start affecting the other receptor type and we start to see adverse effect.

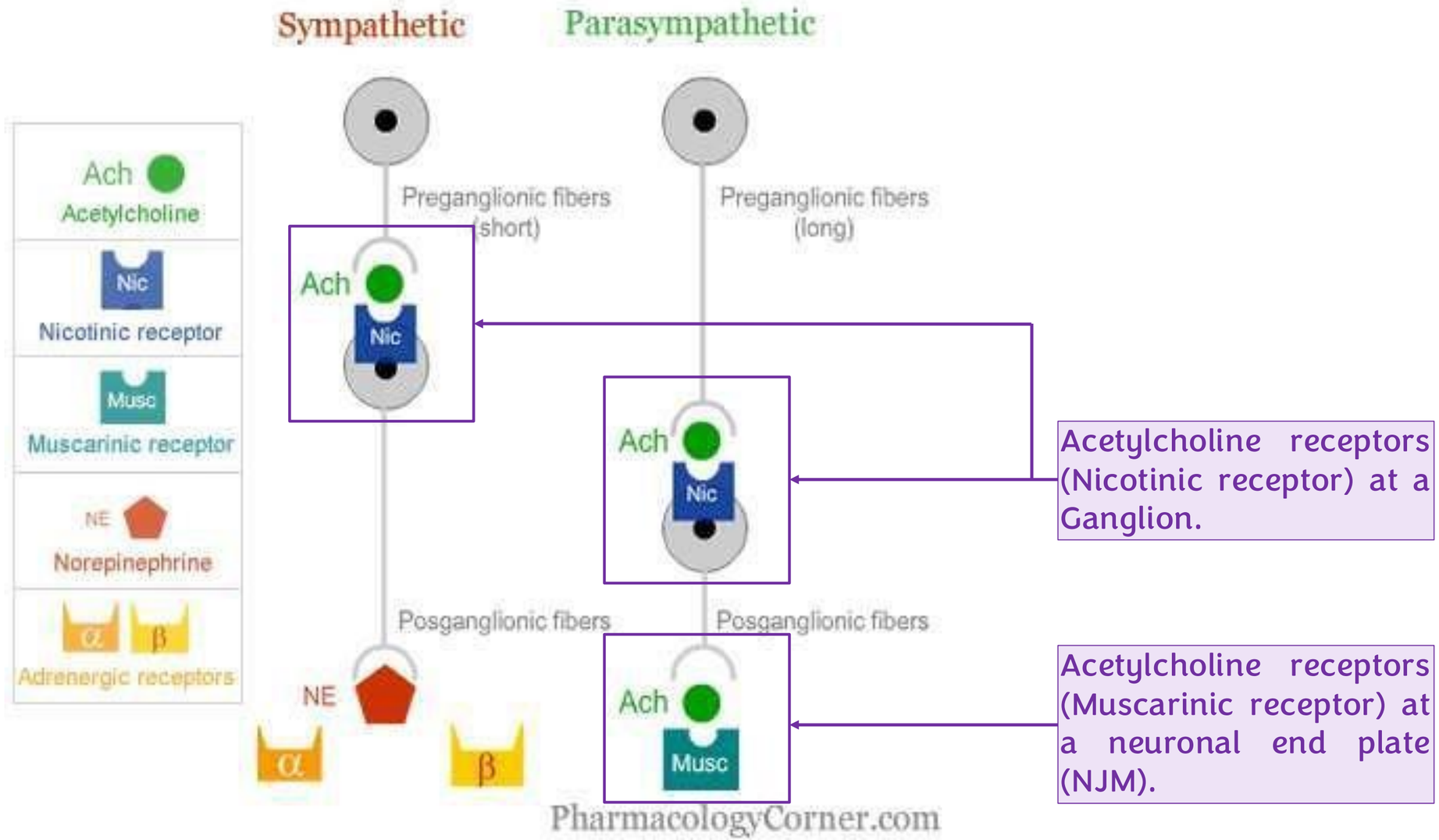
3) CNS: Cortex Basal ganglia, spinal cord and others (Many drugs that are used for Alzahimers are related to Ach).

Acetylcholine

- Parasympathetic Stimulation → Acetylcholine (ACh) release at **neuroeffector** junction → biological effects Sympathetic stimulation → Noradrenaline (NA) at neuroeffector junction → biological effects.

Acetylcholine





Acetylcholine receptors (Nicotinic receptor) at a Ganglion.

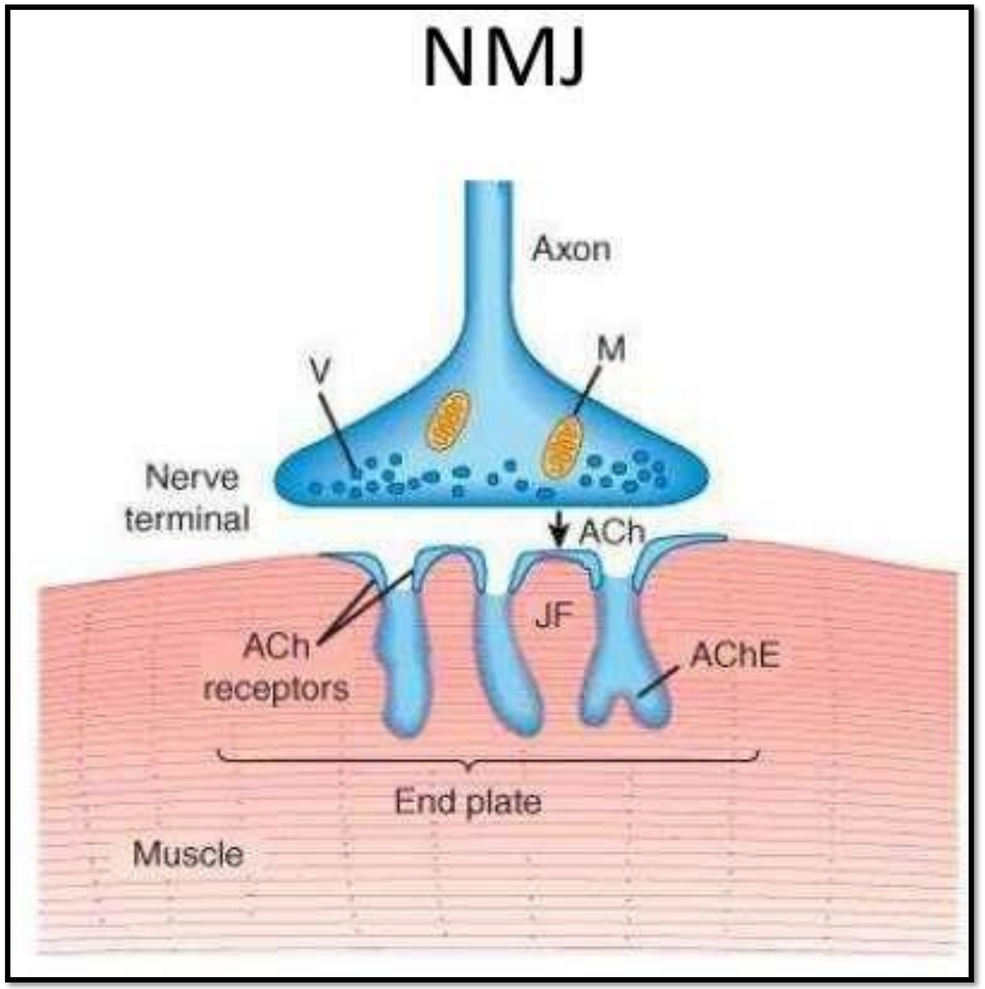
Acetylcholine receptors (Muscarinic receptor) at a neuronal end plate (NJM).

Neuromuscular Junction (NMJ)

1) Release of transmitters occurs when **voltage-sensitive calcium channels in the terminal membrane are opened**, allowing an influx of calcium.

2) The resulting increase in intracellular calcium causes fusion of vesicles with the surface membrane and exocytotic expulsion of acetylcholine and co-transmitters into the junctional cleft.

3) The released ACh will bind to **nicotinic receptors (Ligand gated sodium channels)** on End plate, resulting in opening of the channel → Sodium influx → depolarization → Calcium channels opening (on Sarcoplasmic reticulum and on Sarcolemma) → Muscle contraction (as we learned in Physio MID).



➢ The main ways of ACh intact is by Acetylcholinesterase enzyme.

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

We have cholinesterase in the synaptic cleft but they are also found in the plasma (Pseudocholinesterase) its important when we talk about half life of some drugs we gonna use

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

Peripherally acting: Neuromuscular Blockers

- **Depolarizing Blockers** – mimic the action of acetylcholine (Ach)
  - Agonists
  - Succinylcholine (SCh) is the only drug used clinically

A drug that binds to a receptor usually has a structure similar to the endogenous ligand so that it can fit into the receptor binding site.

· If a drug produces the **same effect as the endogenous ligand**, it is called an **agonist**.

· If a drug **blocks the action of the endogenous ligand**, it is called an **antagonist**.

· In the case of neuromuscular junctions, drugs act on the **nicotinic acetylcholine receptors (Nm receptors)**.

Depolarizing Block - Succinylcholine

Remember:
Affinity refers to the **ability of the drug to bind to the receptor.**
Intrinsic activity refers to the **ability of the drug-receptor complex to produce a biological response.**

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

meaning the effect produced is **less than the maximal response produced by acetylcholine but still is doing the effect .**

- It acts on sodium channels, open them and causes initial twitching (brief muscle contractions) and fasciculation.

•It does not dissociate rapidly from the receptors resulting in prolonged depolarization persistent depolarization leads to inactivation of Na+ channels. As a result, **new action potentials cannot be generated.**

This prevents further muscle contraction and leads to **skeletal muscle relaxation (paralysis).**

Depolarizing Block - Succinylcholine

What do we observe when succinylcholine is administered?

- Administration of **succinylcholine initially produces contraction of skeletal muscle**.

What is the difference compared with acetylcholine?

- The contraction produced by succinylcholine is **weaker than the normal contraction produced by acetylcholine (ACh)**.

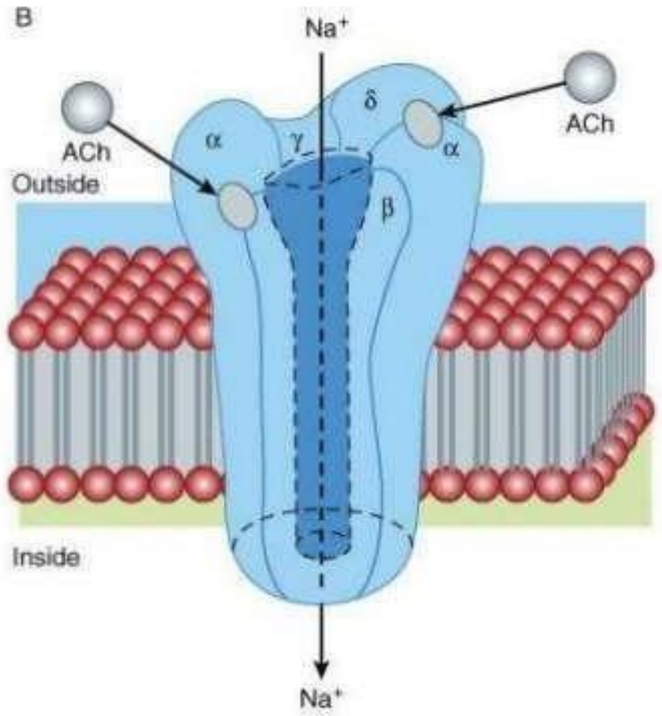
- However, the important difference is that **succinylcholine remains bound to the receptor for a longer period of time**.
- Because the drug **keeps the ion channel open**, the muscle membrane remains **continuously depolarized**.

- This leads to **repeated muscle contractions initially**, until the muscle fibers become **unable to generate further contractions**.
- Eventually, this results in **neuromuscular blockade and muscle relaxation**.

❖ **Important: All these effects are temporary and reversible; nothing is permanent.**

Mechanism of Action: Succinylcholine

Nicotinic ACh Receptor



These drugs are **depolarizing agents**, meaning they produce **effects similar to acetylcholine (ACh)** at the neuromuscular junction.

- They bind to the **nicotinic acetylcholine receptors (Nm receptors)** on skeletal muscle.

- By activating these receptors, they **open sodium (Na^+) channels**, causing **membrane depolarization**.

- This results in **initial skeletal muscle contractions**, which appear as **muscle twitching (fasciculations)**.

- Unlike acetylcholine, these drugs **do not dissociate rapidly from the receptor**.

- Because the drug remains bound for a longer time, **prolonged depolarization occurs**, leading to **inactivation of voltage-gated Na^+ channels**.

- As a result, the muscle **cannot repolarize and cannot respond to further stimulation**, which ultimately leads to **muscle paralysis**.

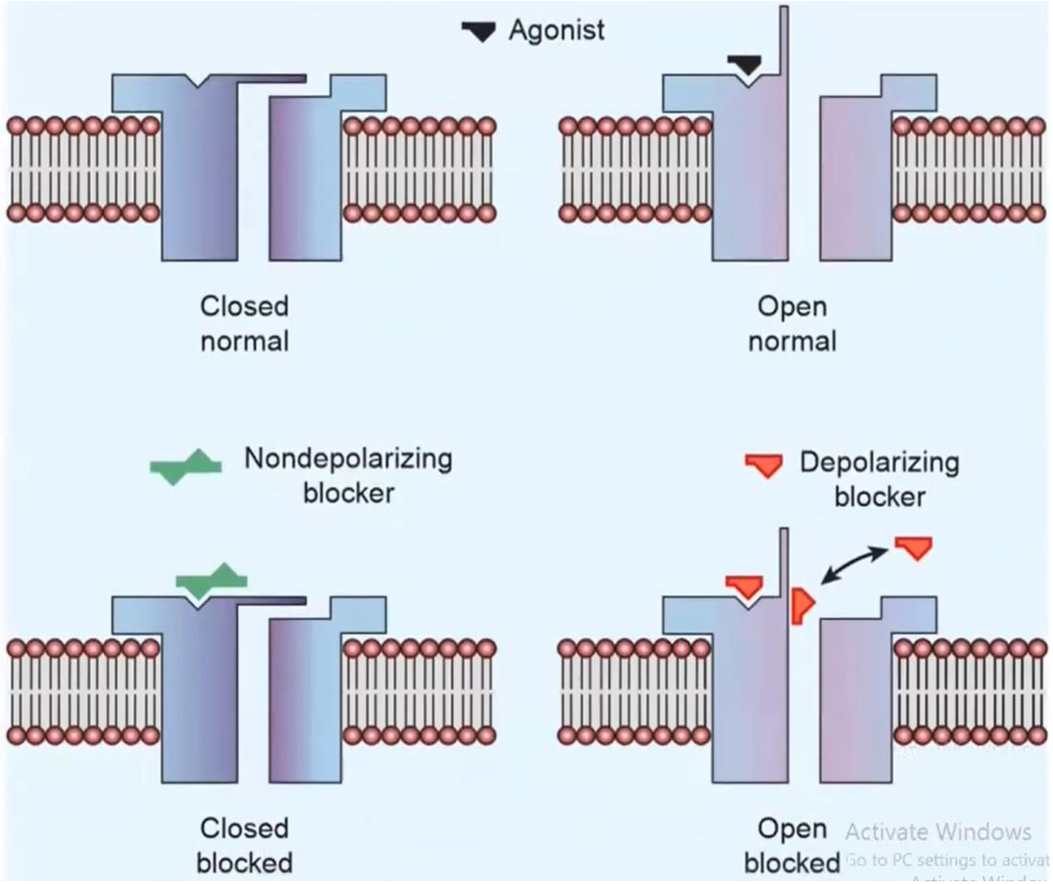
Mechanism of Action: Succinylcholine

❑ Receptor Interaction

- In the diagram, **black represents acetylcholine (ACh)** and **red represents the depolarizing drug**.
- Both molecules are **structurally similar**, allowing the drug to **bind to the same receptor site**.
- However, the depolarizing drug **remains bound to the receptor and keeps the ion channel open longer**.
- This causes **repeated initial contractions**, but eventually **prevents another cycle of depolarization**, leading to **neuromuscular blockade and muscle paralysis**.

❑ Non-Depolarizing Drugs

- The **green molecule represents a non-depolarizing neuromuscular blocker**.
- These drugs **bind to the same receptor binding site**, meaning they have **affinity for the receptor**.
- However, they **do not activate the receptor**.
- Therefore, the ion channel **does not open**, and **sodium influx does not occur**.
- As a result, **acetylcholine cannot bind and activate the receptor**.
- These drugs **do not cause depolarization** but instead **prevent muscle contraction**.
- Because contraction is blocked, the final effect is **skeletal muscle relaxation.**



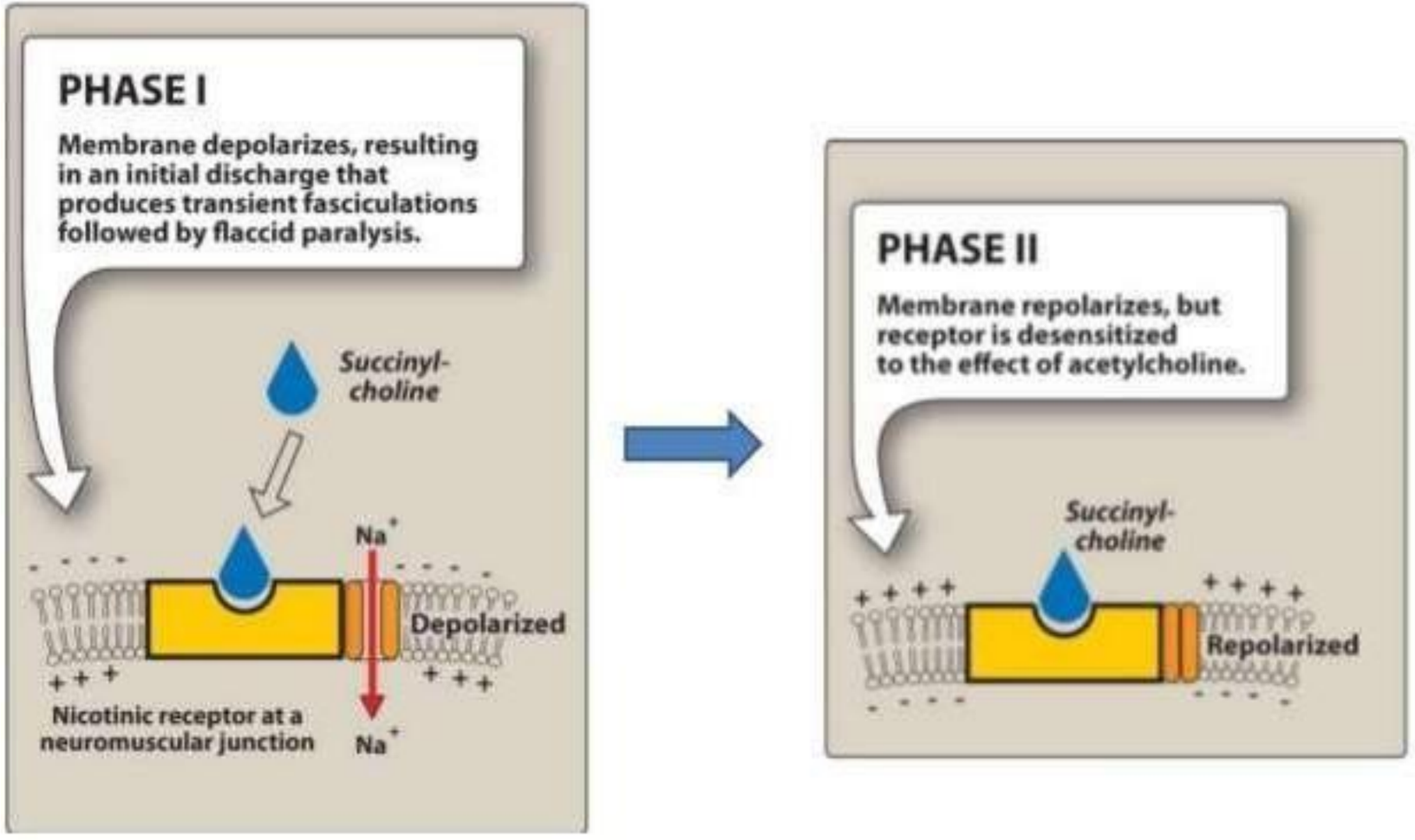
Depolarizing drugs:
Bind + activate receptor → depolarization → fasciculations → paralysis
Non-depolarizing drugs:
Bind but **do not activate** → block ACh → no contraction → relaxation

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 **sustained depolarization and excessive prior contractions**.) sets and the muscle is no longer responsive to Ach released by the nerve endings.

Regardding phase 1

- Patients who receive **succinylcholine during induction of general anesthesia** may experience **muscle pain or soreness after surgery**.
- This occurs because succinylcholine causes **initial muscle fasciculations**, which can lead to **postoperative muscle fatigue and discomfort**.
- Therefore, **postoperative muscle pain** is considered **one of the common side effects of depolarizing skeletal muscle relaxants**.


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, especially in **emergency situations**
  - Rapid onset (1-2 min)
  - Good intubation conditions – relax jaw, separated vocal chords with immobility, no diaphargmatic movements; these effects make it easier to **insert the endotracheal tube into the airway.**
  - Short duration of action 5-10 minutes
  - Dose 1-1.5mg/kg
  - Used as continous infusion occasionally but this is uncommon because its **short duration usually makes repeated dosing unnecessary.**
  - For **long surgical procedures**, other **longer-acting neuromuscular blockers (usually non-depolarizing drugs)** are preferred.

Succinylcholine

Side effects:

- Cardiovascular: unpredictable BP, heart rate and arrhythmias.

- **Explanation of Cardiovascular Side Effects :**

Continue Next Slide

  - Nicotinic receptors are located in two major sites: the **neuromuscular junction** and the **autonomic ganglia**. In this context, the important receptors are those present in the **autonomic ganglia of both the sympathetic and parasympathetic nervous systems**.

  - Because nicotinic receptors exist in **both systems**, drugs that activate or interfere with these receptors may influence **both sympathetic and parasympathetic activities simultaneously**.

  - As a result, the cardiovascular response can be **unpredictable**. For example, in the heart these drugs may cause either **bradycardia (slow heart rate)** or **tachycardia (fast heart rate)** depending on which autonomic system is **dominant at that moment**.

  - The final physiological effect depends on the **dominant autonomic tone** in a specific organ. Different organs may respond differently. For example:

  - **Blood vessels** are mainly controlled by **sympathetic tone** because they lack significant parasympathetic innervation.

  - **The heart** receives **both sympathetic and parasympathetic innervation**, so the response may vary depending on which system predominates.

Succinylcholine

Side effects:

- Cardiovascular: unpredictable BP, heart rate and arrhythmias.

- **Explanation of Cardiovascular Side Effects :**

  - Furthermore, even within the same organ the response can differ; for instance, the **atria and ventricles of the heart may respond differently**.

  - Because of this complex autonomic interaction, these drugs can produce **cardiovascular side effects**, including:

    - **Unpredictable changes in blood pressure.**
    - **Alterations in heart rate.**
    - **Cardiac arrhythmias.**
    - Although succinylcholine primarily targets **nicotinic receptors at the neuromuscular junction**, it may also influence **nicotinic receptors in autonomic ganglia**, which contributes to these cardiovascular effects.

See Next Slide

Succinylcholine

- Succinylcholine keeps the ion channel open, so the ion movement continues, This leads to sustained muscle contraction, during which potassium (K^+) moves out of the muscle cells into the blood, resulting in **hyperkalemia**.

- **Clinical Importance of Potassium Balance :**
  - The body normally maintains potassium levels within a narrow range (approximately 4.5–5.0 mEq/L) to preserve proper physiological function.
  - **Any increase** above this range is **dangerous**, especially for the heart, because cardiac function depends on the Na^+/K^+-ATPase pump. Disturbances in potassium levels can lead to cardiac **arrhythmias**.
  - Although both hypokalemia and hyperkalemia are harmful, **hyperkalemia is more dangerous for cardiac function.**

- **Drug-Related Risk (Diuretics) :**
  - Some diuretics, specifically potassium-sparing diuretics, can increase potassium levels in the body by reducing its excretion.
  - If a patient is receiving such drugs along with succinylcholine, the combined effect may significantly increase potassium levels, posing a serious risk to the heart.

High-Risk Patients for Hyperkalemia

1. Spinal Cord Injury

Patients with spinal cord injury experience:

- ✓Loss of nerve supply to muscles → paralysis.
- ✓As a compensatory mechanism, the body increases the number of nicotinic acetylcholine receptors, including extrajunctional receptors.
- ✓These receptors become more widely expressed on the muscle membrane.

➢As a result:

1) There is increased binding of succinylcholine
2) This leads to a higher risk of potassium release and severe hyperkalemia

Therefore, succinylcholine should **not** be used in these patients.

2. Extensive Burns :

In patients with extensive burns:

- ✓Tissue damage leads to significant release of potassium.
- ✓There is also increased expression of acetylcholine receptors as a compensatory response.

➢This results in:

1) Increased sensitivity to succinylcholine.
2) Higher risk of developing hyperkalemia.

These patients are also at increased risk and **should avoid** succinylcholine.

Non-Depolarising Drugs

- Competitive Blockers having no intrinsic activity (antagonist)
- These are of 3 types based on their activity: (This classification depends on their pharmacokinetics, specifically how they are metabolized and excreted from the body)
  - *Long Acting* drugs that are mainly **excreted by the kidneys** tend to have the longest duration of action, because their elimination from the body takes more time:

d-TC, Pancuronium, Pipecuronium, Gallamine (Kidney Excretion)

  - *Intermediate* drugs that undergo **metabolism in the liver and are excreted via the liver:**

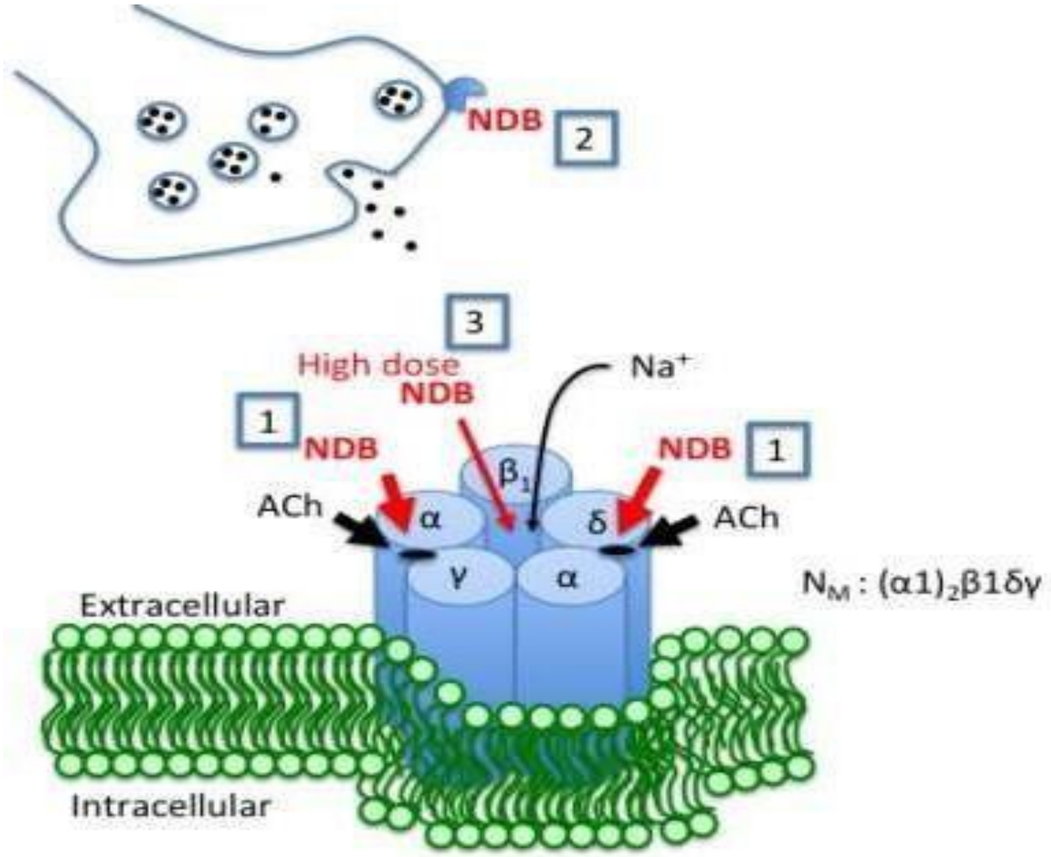
Vecuronium, Rocuronium, Atracurium (eliminated by liver)

- *Short Acting* drugs are **metabolized by cholinesterase** enzymes:

Mivacurium, Ropcacuronium (inactivated by plasma cholinesterase)

Succinylcholine has a very short half-life due to metabolism by 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: Non-depolarizing Block in Muscles

At the neuromuscular junction:
Nerve activation leads to the release of acetylcholine (ACh).
ACh binds to its binding site on the α-subunit of the nicotinic receptor.
When a non-depolarizing blocker (NDB) is administered:
It competes with ACh for the same binding site.
It has **affinity but no intrinsic activity**, so it does not activate the receptor.
Therefore, it acts as a **competitive antagonist.**

- In pharmacodynamics, "**competitive**" means:

Increasing the concentration of one ligand allows it to **outcompete** the other for receptor binding.

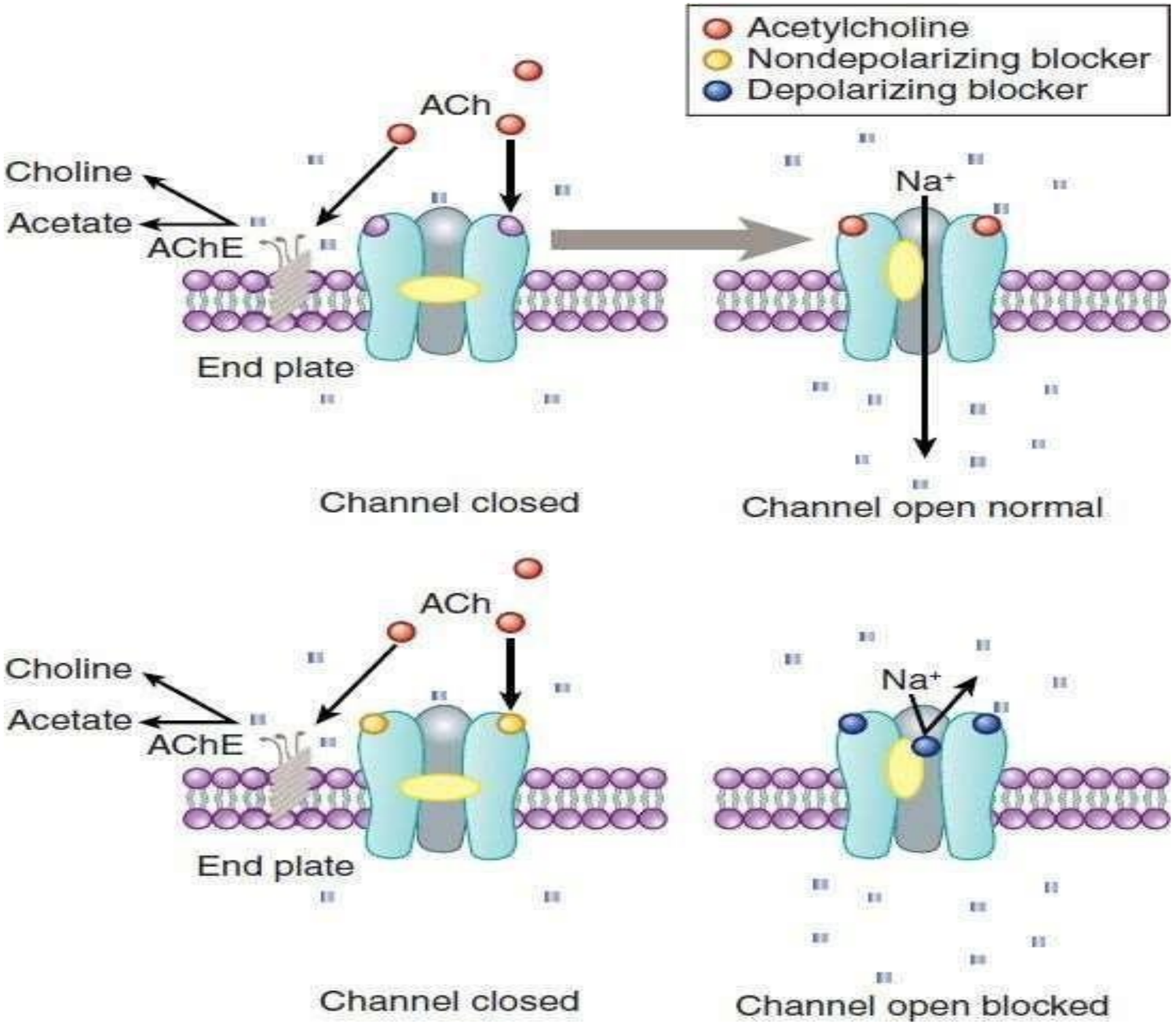
Clinical Application :
If a patient is given a non-depolarizing drug such as d-Tubocurarine (long-acting) and the procedure ends earlier than expected:
We need to reverse the muscle relaxation. This requires administering an antidote.

Mechanism of Reversal :
To reverse the effect, we need to increase acetylcholine levels so it can compete with the blocker.
Direct administration of **ACh is not used clinically because it is rapidly degraded in the body.**
Instead:
- We administer an acetylcholinesterase inhibitor (e.g., **Neostigmine**).
- This inhibits the breakdown of ACh, leading to an increase in its concentration.

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 (no contraction occurs), & Na+ channels remians closed
- No End Plate Potential generation in nerve endings (leading to a decrease in muscle action potential).
- Muscle Action Potential decreases
- Action can be overcome by increased ACh concentration by blocking of acetylcholinesterase
- They also block prejunctional ACh receptors on motor nerve endings – FADE PHENOMENON

Non-depolarizing blockers are **highly polar** compounds, therefore they must be administered **intravenously** (IV)because they are not absorbed through biological membranes.


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

- With prolonged use of non-depolarizing blockers :

✓ They can cause inhibition of pre-junctional nicotinic receptors.

- These receptors are present:

✓ On the nerve endings responsible for releasing acetylcholine (ACh) and also at the neuromuscular junction.

- There is a normal mechanism that helps regulate the release of ACh.
- Non-depolarizing blockers may bind to these pre-junctional receptors and block them, which leads to impaired release and mobilization of Ach.

- This results in the fade phenomenon, where:

✓ The response progressively decreases with repeated stimulation (i.e., a reduction in the effectiveness of neuromuscular transmission over time)

Effects of Non-depolarizing blockers

- **Low Doses:**
  - Competitive antagonists of ACh
  - Action reversed by ACh ecterase inhibitors (e.g., **Neostigmine, Pyridostigmine**)

- **Large Doses:**
  - Ion Channel is blocked
  - More weakness of neuromuscular transmission
  - Action could not be reversed by ACh esterase inhibitors

Increased drug concentration leads to greater competition with acetylcholine

- **Other actions:**
  - Can block pre-junctional Na^+ channels and interfere with mobilization of ACh at nerve endings (i.e., decreases ACh mobilization)

Non-depolarizing Drug: d-Tubocurarine

considered the prototype of non-depolarizing neuromuscular blockers.

- 1st agent to undergo clinical investigation
- purified curare – *Chondodendrom tomentosum.*
  (natural extract, not important)
- ED_{95}= 0.5mg/kg
- undergoes minimal metabolism- is excreted
  - %10in urine
  - %45in bile (main route)

  Despite partial renal excretion, it is classified as a long-acting drug.

- excretion impaired in Renal Failure

REMEMBER :

ED (Effective Dose): the dose required to produce a therapeutic effect.

ED50: the dose that produces 50% of the maximal effect.

ED95: a dose very close to the maximum effective response.

Clinical Consideration (Renal Impairment) :
For drugs that are excreted in urine:
In patients with **renal dysfunction** or **chronic kidney disease**:
➢ Drug excretion is reduced
➢ Drug concentration in the body increases
This may lead to:
✓ Drug accumulation
✓ Longer duration of action
✓ Increased toxicity
Therefore, either **dose adjustment is required** or a **drug eliminated through non-renal routes should be selected.**

D-Tubocurarine is not highly selective for nicotinic receptors at the neuromuscular junction:
✓ It can also block nicotinic receptors in autonomic ganglia
Blocking ganglionic nicotinic receptors leads to: decreased sympathetic stimulation
Since blood vessels are mainly controlled by the sympathetic nervous system, this results in:
✓ Reduced vasoconstriction
✓ Increased vasodilation
✓ **Hypotension**.

CVS Effects:

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

- Skeletal muscle relaxants can interact with **mast cells**, leading to their degranulation and release of histamine.
- This is **not an immunological (allergic) reaction**, and it can occur in most patients.
- Histamine causes **vasodilation of blood vessels**, which leads to a **decrease in blood pressure**.

Clinical Use:

- long duration of action(60 to 120 mins) and CVS effects restricted its use (These factors have limited its clinical use, especially since it is one of the older drugs and has more CVS side effects compared to other non-depolarizing muscle relaxants).
- used as "precurarization" **SKIP THIS POINT**

Non-depolarizing Drugs

- Gallamine
  - Less potent than curare
  - Tachycardia (in contrast to Succinylcholine, which may cause bradycardia).
- 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)

Clinical Note (Related to Bronchospasm): These drugs are used during general anesthesia to produce muscle relaxation only and do not induce anesthesia by themselves. During general anesthesia, other drugs are administered in combination, such as: Antihistamines, to reduce the effects of histamine release . This is important because Histamine can cause irritation of the bronchi it can increase bronchial secretions . Therefore, antihistamines are given to reduce bronchial irritation and secretions that may be induced by drugs like d-Tubocurarine.

Laudanosine is a metabolite that can **cross** into the central nervous system (**CNS**)and cause seizures if it **accumulates** in the body. Therefore, caution is required with high doses or prolonged use of Atracurium , to avoid accumulation of laudanosine.

Non-depolarizing Drugs

- Mivacurium
  - Metabolized by pseudocholinesterase
  - Fast onset and short duration
- Pencuronium
  - Long duration of action
  - Tachycardia
- Vecuronium
  - Intermediate duration of action It is mainly metabolized in the liver.
  - Fewer side effects (no histamine release, (does not lead to accumulation of toxic metabolites) , no ganglion blockade, no antimuscarinic action)

This table highlights the most important points you need to focus on.

Non-Depolarizing

Difference between the competitive and depolarisinng muscle blocker

VERY IMPORTANT

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)

❑ **Neostigmine, how it works :**

- Neostigmine blocks cholinesterase, so it will increase acetylcholine (ACh).

- So, what will happen to succinylcholine?

✓ It will increase its effect, and acetylcholine will be more available.

✓ Notice that: While neostigmine antagonizes the effect of tubocurarine, it can augment the effect of succinylcholine.

- We said that succinylcholine does contractions (fasciculations),so when we increase acetylcholine → we increase this effect.
- So it is not an antagonistic effect, rather than potentiation effect.

Other Actions of Nm Blockers

- Automic ganglia:
  - Partial blockage of ganglia (Nm type of receptor)
  - Results in fall in BP and tachycardia (This effect is due to ganglionic blockade, not a direct effect of Succinylcholine on muscarinic receptors)
- 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. These drugs mainly act on nicotinic receptors in skeletal muscle. However, they may also affect other muscle types in the body as a side effect.

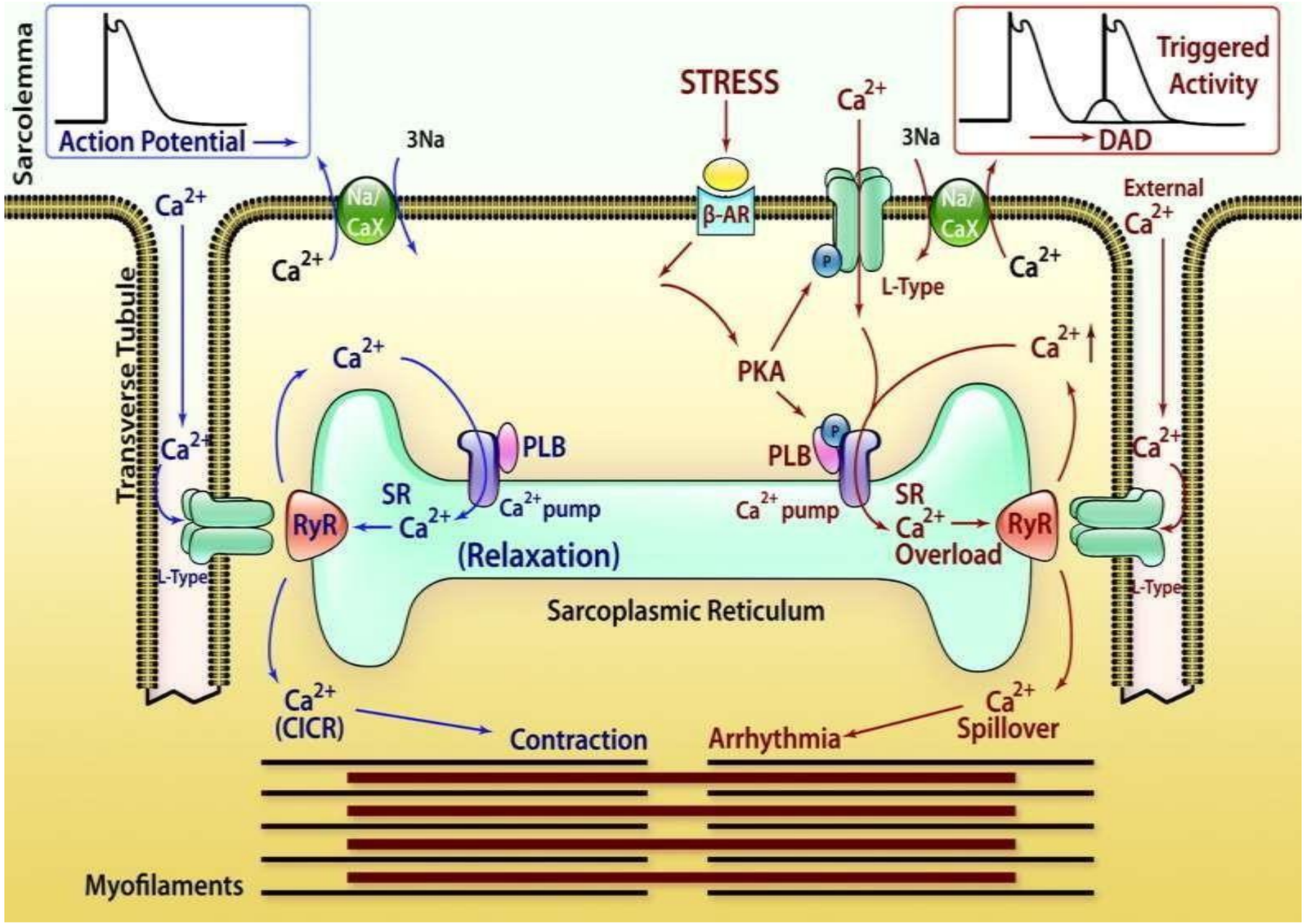
Pharmacokinetics of Nm blockers

- Polar quaternary compound - Not absorbed orally, do not cross cell membranes, Blood Brain Barrier or placental barrier, low Volume of distribution (will remain in blood)– 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 inhibitor – 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

This slide provides a brief review of the muscle action potential.



ThankYou!!!

الصورة معبرة جدًا دكتورة
💀

رسالة من الفريق العلمي (الجزء ١):

من لم يكمل صيام الستة أيام من شوال
فليتعجل فالشهر أزف على الرحيل

قال صلى الله عليه وسلم:
(من صام رمضان وأتبعه ستاً من شوال
كان كصيام الدهر)

رسالة من الفريق العلمي (الجزء ٢):

توضيح بخصوص رسالة الفريق العلمي في ملف Drugs for Gout :

محولة من
فَادعُ وَاستَقِم

#ستحذف

السلام عليكم، نشرت البارحة رسالة وُجِّهَت من دكتورة - ضمن خطاب الاضربات النفسية وإلى آخره - فيها معنى جميل وكلام طَيِّب، وتم ذكر آية (وابيضَّت عيناه من الحزن فهو كظيم)،

كان في بالرسالة ٣ أفكار / "أغلوطات" نعتقدها بمجتمعنا وكان يتم تصحيحها بدليل من الآية، أول فكرتين ما رأيت فيهم شيء وأويدهم، أما الثالثة الموضحة بالصورة - الله يجزيه الخير اللي نبّهني - ليست ضمن سياق الآية أصلًا، بعيدًا عن مدى صحتها من عدمه كفكرة لكن أتكلم عن ربطها في الآية،

فبعد (فهو كظيم) بآية، قال رب العالمين على لسان سيدنا يعقوب (قال إِنَّما أَشكو بَثّي وحُزني إلى الله وأعلَمُ مِن اللهِ ما لا تَعلَمون)

قال السعدي - رحمه الله - في تفسيره:

فقال يعقوب: ﴿إنَّما أشكو بثِّي﴾؛ أي: ما أبثُّ من الكلام، ﴿وحُزْني﴾: الذي في قلبي. ﴿إلى الله﴾: وحدَه لا إليكم ولا إلى غيركم من الخلق؛ فقولوا ما شئتم، ﴿وأعلمُ من الله ما لا تعلمونَ﴾: من أنَّه سيردُّهم عليَّ ويقرُّ عيني بالاجتماع بهم.

فـ "الأغلوطة" كما ذكرت لا علاقة لها بالآية ولا موقعها هو هذا النص، بعيدًا عن إذا كانت صح أو خطأ، بس ذكر هاي الفكرة مع سياق الآية يوحي أنه كتم سيدنا يعقوب لحزنه عن الناس وشكواه لرب العالمين هو بذاته كان سبب في ضرر - والفكرة هاي هي الخاطئة

يعني لتوضيح فكرتي بشكل أسرع:
لا أناقش فكرة إذا الكتم بشكل عام صحيح او خاطئ، الأمر هذا من منظوري - والله أعلم - أرى فيه تفصيل واذا تكلمت سأطيل (يمكن أوضح منظوري لمن أراد ويمكن لا)،

بل أناقش ربط الفكرة بالآية، وضرب مثل الكتم العام بسيدنا يعقوب، لكن كتم سيدنا يعقوب لألمه مش سبب لاصابته بالعمي،

وهذا مجرّد تنبيه لما نشرته سابقًا، نسأل الله المغفرة

والله تعالى أعلم،

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	25,35 25,36 41 41 8	- Prevents Depolarization Nonadrenaline	Atracurium Mivacurium Inhibitor (added) Deleted Noradrenaline
V1 → V2			