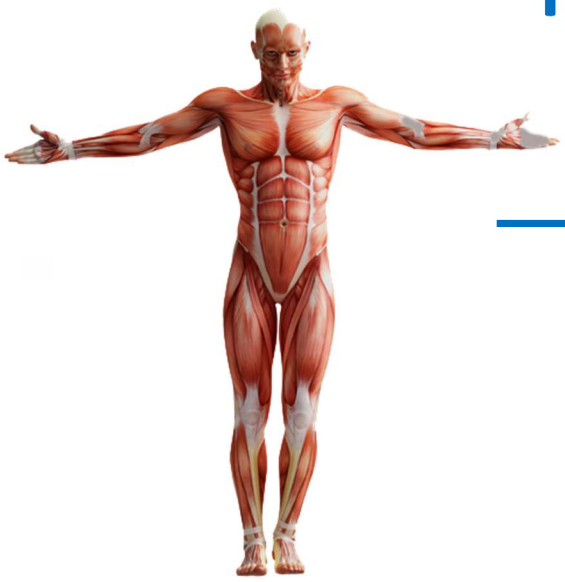
Musculoskeletal System



Pharmacology

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بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

Skeletal Muscle Relaxants

Why are Skeletal muscle relaxants important clinically?

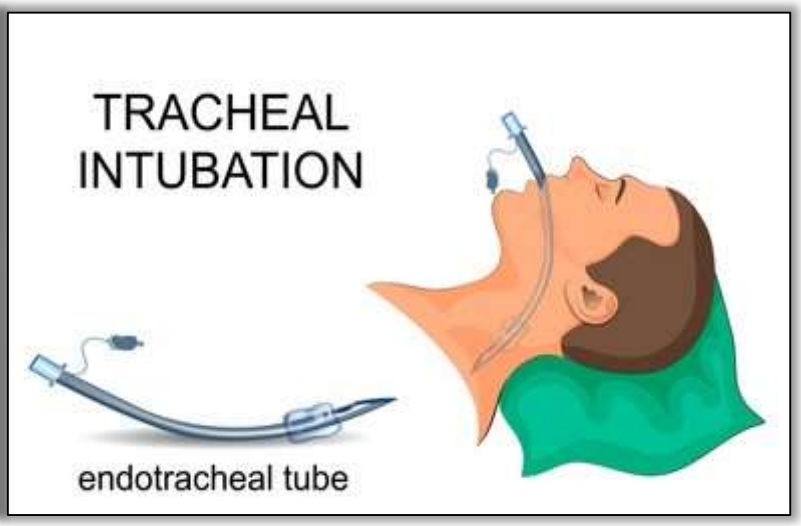
These drugs are important in the process of administration of general anesthesia to optimize surgical conditions. Additionally, they would cause a facilitation of the mechanical ventilation process (You must remember from the previous lecture that inducing a muscle paralysis or muscle relaxation this will ease up the endotracheal intubation for the patient to ensure adequate ventilation). Also, they would optimize the surgical working condition and environment.

There are 2 different groups of skeletal muscle relaxant (Two different therapeutic groups):

Those used during surgical procedures and in the intensive care unit (ICU) to produce muscle paralysis (i.e., neuromuscular blockers) or in the case of general anesthesia and those mainly work peripherally.

On the other hand, there is another group (i.e., spasmolytics and antispasmodics), that is used to reduce muscle spasticity of painful conditions such as multiple sclerosis, or cerebral palsy, or inflammation of the bursa, or some of the conditions of rheumatoid spondylitis.

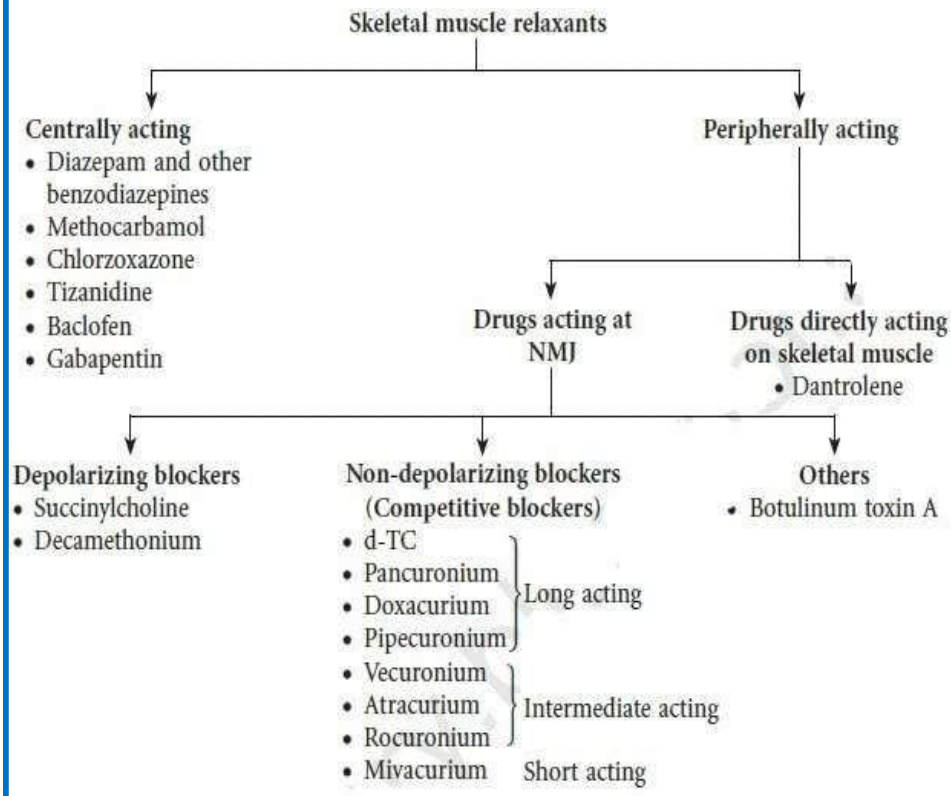
Dantrolene, spasmolytic agent, an agent that has no significant central effects and is used primarily to treat a rare (hereditary) anesthetic-related complication, malignant hyperthermia.



History

During the 16th century, when the European explored the New America and found that natives in the Amazon regions were using a chemical, or a drug, or a poison that it was called curare, they would put that on the tip of the arrow. This arrow poison will produce skeletal muscle paralysis, to kill animals and hunt them. Hence, the name of the first non-depolarizing skeletal muscle relaxant came from which is called Tubocurarine because they used a hallow bamboo tubes (looked like a tube).

Classification



We classify them into centrally acting and peripherally acting, peripherally acting is either working on the neuromuscular junction or skeletal muscle directly and we have within it the dantrolene which is directly acting on the skeletal muscle. Drugs acting at NMJ either they were an agonist or antagonist. So, we have two main groups:

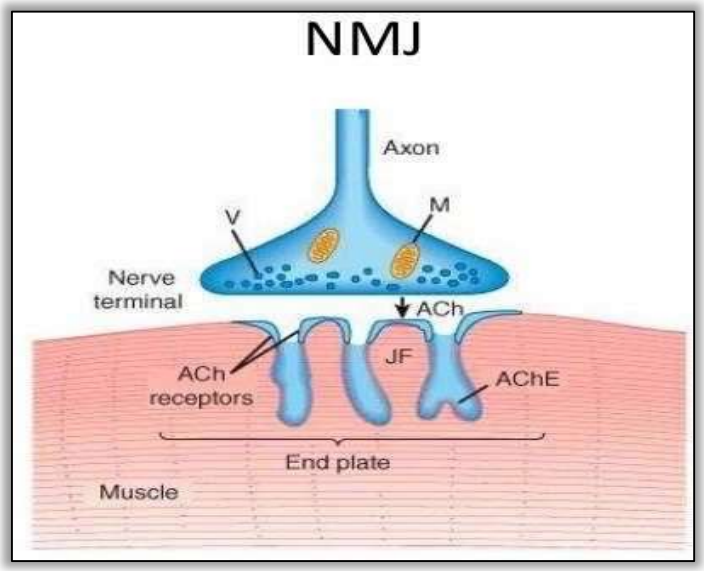
- The depolarizing blockers and in this group, we have succinylcholine and decamethonium (isn't used as much today - still available for research use).

- The non-depolarizing blockers we have divided them into 3 groups (long acting, intermediate acting and short acting).

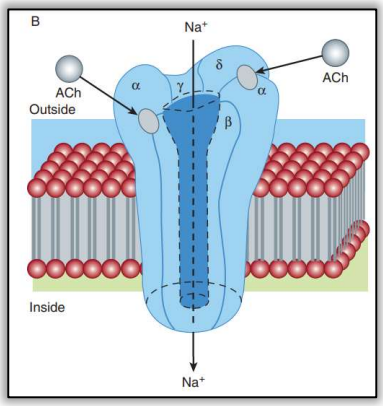
Neuromuscular Junction (NMJ)

Let's try to remember how acetylcholine activate its receptor. Acetylcholine is released from the nerve terminal when we have an action potential. The arrival of an action potential at the motor nerve terminal causes an influx of calcium and release of the neurotransmitter acetylcholine. Acetylcholine then diffuses across the synaptic cleft to activate nicotinic receptors located on the motor end plate.

What kind of acetylcholine receptor do we have ? The main kind that is available is the one which is found on the skeletal muscle end plate. And we are here talking only about the neuromuscular junction. We aren't here talking about the sympathetic or parasympathetic NS sites.



Nicotinic receptor structure



The adult N_M receptor is composed of five peptides: two alpha peptides, one beta, one gamma, and one delta peptide. We need the binding of two acetylcholine molecules to receptors on the α-β and δ-α subunits causes opening of the channel.

Induced by binding of two acetylcholine to their receptors, the subsequent movement of sodium and potassium through the channel is associated with a graded depolarization of the end plate membrane. This change in voltage is termed the motor end plate potential. *The magnitude of the end plate potential is directly related to*

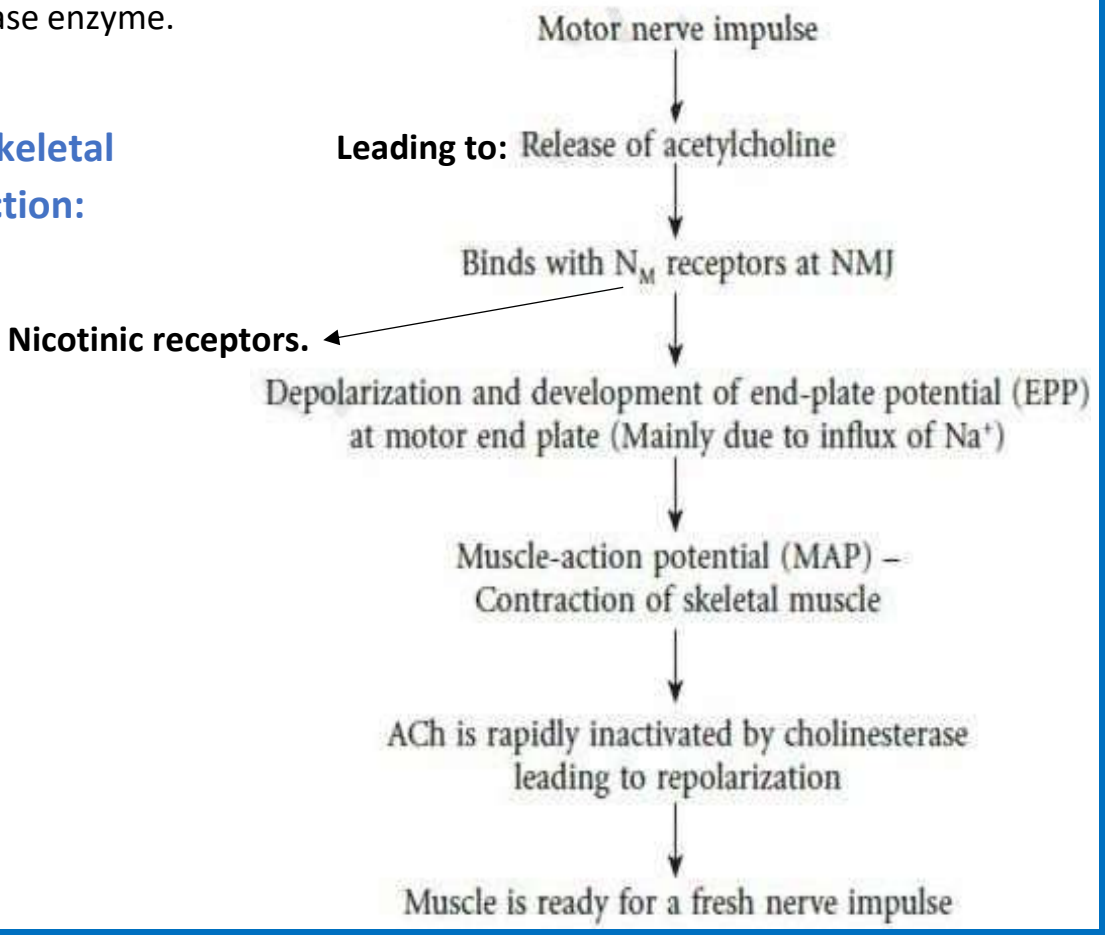
the amount of acetylcholine released (Explanation below). Muscle contraction is then initiated by excitation-contraction coupling.

If we have enough change in the action potential or the voltage this will lead to propagation of the muscle action potential leading to contraction of the skeletal muscle and usually as you remember this happens by excitation-contraction coupling.

Explanation: If the potential is small, the permeability and the end plate potential return to normal without an impulse being propagated from the end plate region to the rest of the muscle membrane. However, if the end plate potential is large, the adjacent muscle membrane is depolarized, and an action potential will be propagated along the entire muscle fiber.

The released acetylcholine is quickly removed from the end plate region by both diffusion (away from the area) and enzymatic destruction by the local acetylcholinesterase enzyme.

Physiology of Skeletal Muscle Contraction:



Actually, we have at least two additional types of acetylcholine receptors been found within the neuromuscular apparatus or junction. One type is located on the presynaptic motor axon terminal, and activation of these receptors will cause mobilization of additional transmitter for subsequent release by moving more acetylcholine vesicles toward the synaptic membrane. When we use a nicotinic receptor antagonist (inhibition) such as Tubocurarine can lead to the fading of the signal that we can note. The second type of receptor is found on extra junctional cells and is not normally involved in neuromuscular transmission (aren't usually activated in normal conditions). So, we have the main kind and then we have 2 additional kinds; one on the presynaptic motor axon terminal, the 2nd type is found on the extra junctional cells, we said that isn't normally functioning in the neuromuscular transmission. However, under certain conditions (e.g., burned victim, prolonged immobilization, thermal burns), these receptors may proliferate sufficiently to affect subsequent neuromuscular transmission and contraction.

Peripherally acting: Neuromuscular Blockers

- **Depolarizing Blockers – mimic the action of acetylcholine (ACh)**
  - The main example we have is: Succinylcholine (SCh) is the only drug used clinically.
  - The prototypical depolarizing blocking drug is succinylcholine.
  - Agonists of the nicotinic receptor at the skeletal muscle end plate.

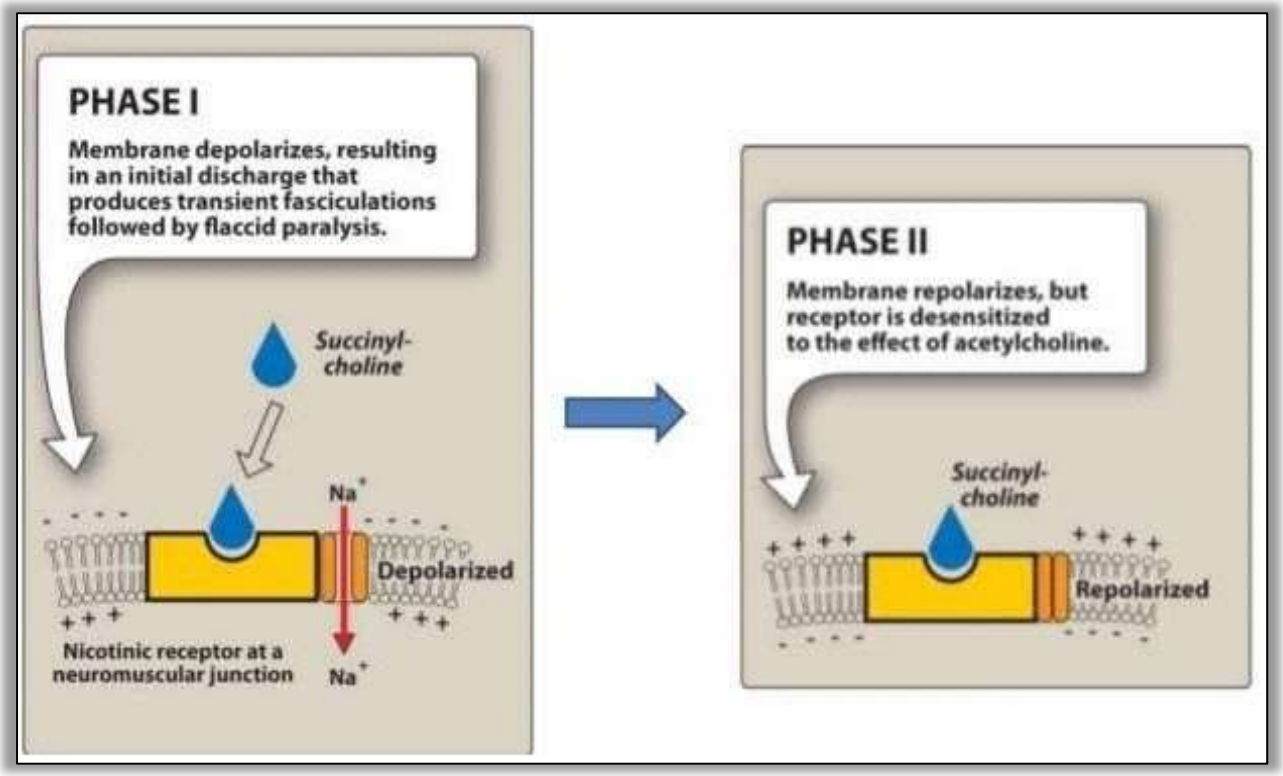
  - **Non-Depolarizing – interferes with the action of ACh**
  - Competitive Inhibitors - Blockers - (Antagonist)
  - Further divided into short, intermediate and long acting non-depolarizing drugs
  - So, they will prevent the binding of acetylcholine and prevent the contraction of the muscle.

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

➢ This process occurs in two phases :

- Phase I: During Phase I (depolarizing phase), they cause muscular fasciculations (ارتعاشات في العضلة) while they are depolarizing the muscle fibers.

- Phase II: After sufficient depolarization has occurred, the muscle is no longer responsive to any more stimuli from acetylcholine that is released by the nerve ending so it becomes paralyzed, 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 diaphragmatic movements.

• Short duration of action (5-10 minutes). Sometimes, this is wanted (when we want to do a fast procedure). So, we can have recovery of the patient from this drug fast on.

• Dose 1-1.5mg/kg

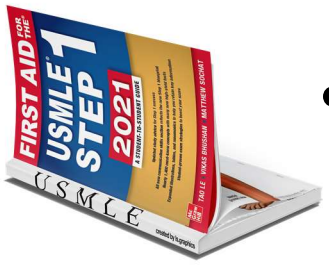
• Usually, because it has a short duration of action it's used as continuous infusion occasionally .

Disadvantages:

- Cardiovascular: unpredictable BP, heart rate and arrhythmias (This is especially evident when administered with a general anesthetic agent (Halothane). So, Succinylcholine can predispose or cause cardiac arrhythmia when administered with halothane because the drug stimulates the choline receptors including the nicotinic receptor as both the sympathetic and the parasympathetic ganglia and the muscarinic receptor in the heart.)
- Fasciculation.
- Muscle pain.
- Increased intraocular pressure: Administration of succinylcholine may be associated with the rapid onset of an increase in intraocular pressure (<60 seconds), peaking at 2–4 minutes, and declining after 5 minutes.
  The mechanism may involve tonic contraction of myofibrils or transient dilation of ocular choroidal blood vessels. Despite the increase in intraocular pressure, the use of succinylcholine for ophthalmologic operations is not contraindicated unless the anterior chamber is open ("open globe") due to trauma.

- Increased intracranial pressure.
- Hyperkalemia: k+ efflux from muscles which can be life threatening in Cardiac Heart Failure, or patient with diuretics… etc.

Patients with burns, nerve damage or neuromuscular disease, closed head injury, and other trauma may develop proliferation of extrajunctional acetylcholine receptors. During administration of succinylcholine, potassium is released from muscles, likely due to fasciculations. If the proliferation of extrajunctional receptors is great enough, sufficient potassium may be released to result in cardiac arrest.



Succinylcholine:

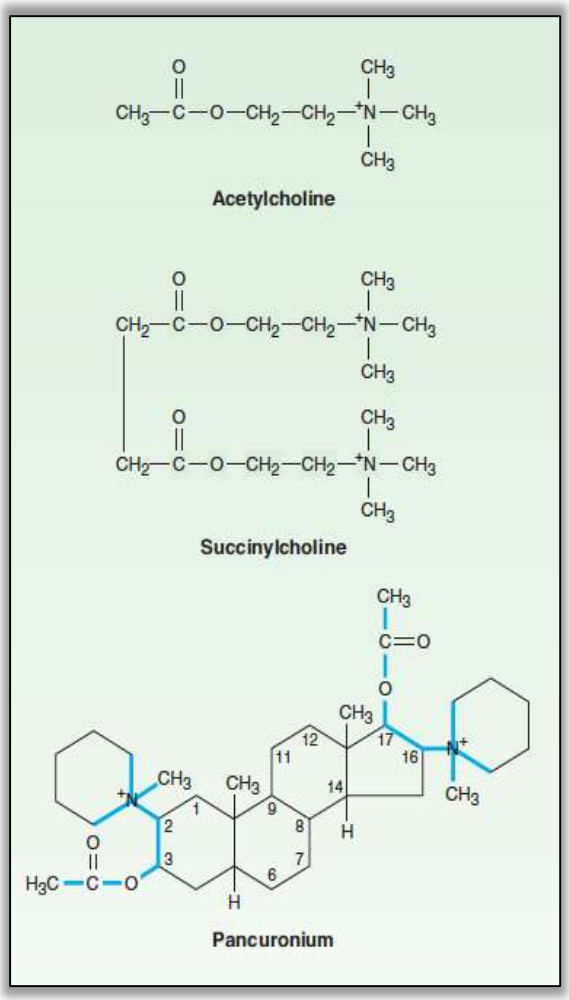
— Strong ACh receptor agonist; produces sustained depolarization and prevents muscle contraction.

Reversal of blockade: Phase I (prolonged depolarization) — no antidote. Block potentiated by cholinesterase inhibitors.
Phase II (repolarized but blocked; ACh receptors are available, but desensitized)—may be reversed with cholinesterase inhibitors.

Complications include hypercalcemia, hyperkalemia, malignant hyperthermia.

Chemistry & PK

All these agents have a structure that is mimicking the structure of acetylcholine (E.g., succinyl is two acetylcholine molecules linked end to end. Another example (Pancuronium) also has a hidden double acetylcholine structure labeled in blue (the figure below) and this is embedded with a rigid ring system .



Non-Depolarizing Drugs

- Competitive Blockers having no intrinsic activity (antagonist of the nicotinic receptor)
- 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).*
  - *ShortActing : Mivacuronium, Ropcacuronium (inactivated by plasma cholinesterase)*

Why do we have these differences in the half-life of these drugs and the onset of action? This is related to their metabolism and excretion.

Pharmacokinetics of Nm blockers (Non-Depolarizing Drugs)

• Polar quaternary compound –

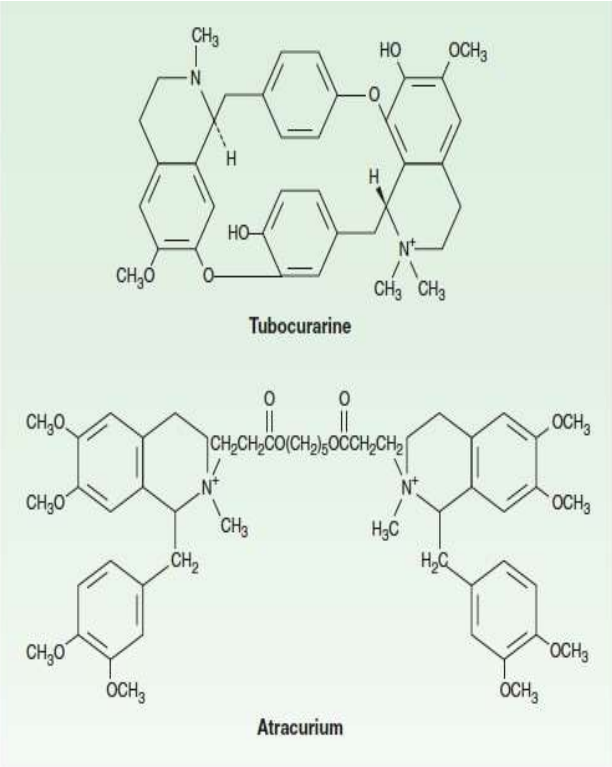
A) Not absorbed orally (Because they are polar they don't cross intestinal wall. So, that is why they don't given orally and this can explain why the people who were using this poison to kill the animal won't be affected by the poison once they consume the meats of these animals because if you eat the drug or eat the muscle that has been injected with that drug it won't be absorbed through your intestinal membranes and thus it won't harm the body)
B) Do not cross cell membranes, Blood Brain Barrier, or placental barrier, so we give these drugs parentally or sometimes we can give them as an intramuscular injection!

• Low Volume of distribution – always given intravenously or rarely intramuscular. They mainly stay in the bloodstream.

Non depolarizing agents are subdivided into 2 groups we have **Isoquinoline neuromuscular blocking agents (2 Examples: Tubocurarine, Atracurium – Figure Below)** and then we have the **Steroid neuromuscular blocking agents (2 Examples: Pancuronium and Vecuronium – illustrated in the figure below).**

All steroidal muscle relaxants are metabolized in the liver. All steroidal muscle relaxants are metabolized to their 3-hydroxy, 17-hydroxy, or 3,17-dihydroxy products in the liver. The 3-hydroxy metabolites are usually 40–80% as potent as the parent drug. Under normal conditions, we don't have enough quantities of that metabolite that is partially active to give us a significant effect of neuromuscular blocking. However, in certain cases if we have a patient that's present in the intensive care unit for several days this 3-hydroxy metabolite can accumulate and can result in prolonged paralysis because it has actually a longer half-life that the parent compound. Now, it's very important to differentiate between the half-life of these drugs. As we said, we have a long acting, short acting and intermediate acting. One of the intermediate acting steroid muscle relaxant is the **Vecuronium** and this drug is mainly excreted through the bile or it

is metabolized in the liver before it's eliminated and these are more commonly used than the long acting steroid kind such a s **Pancuronium.**



Structures of two isoquinoline neuromuscular blocking drugs. These agents are nondepolarizing muscle relaxants.

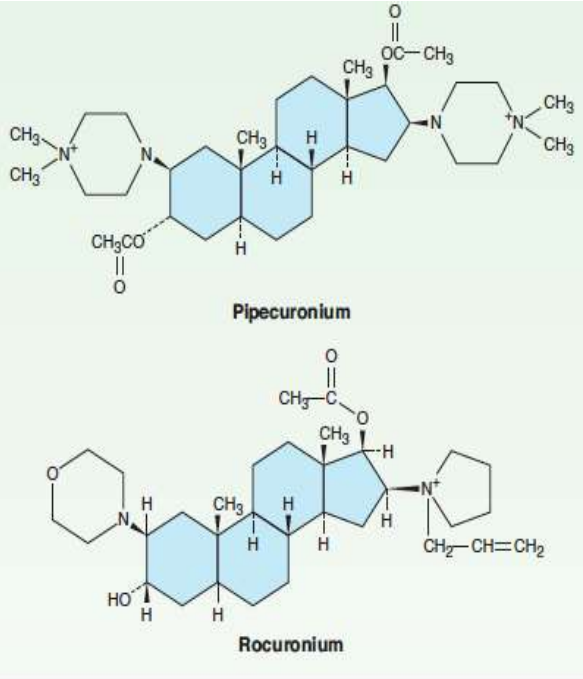
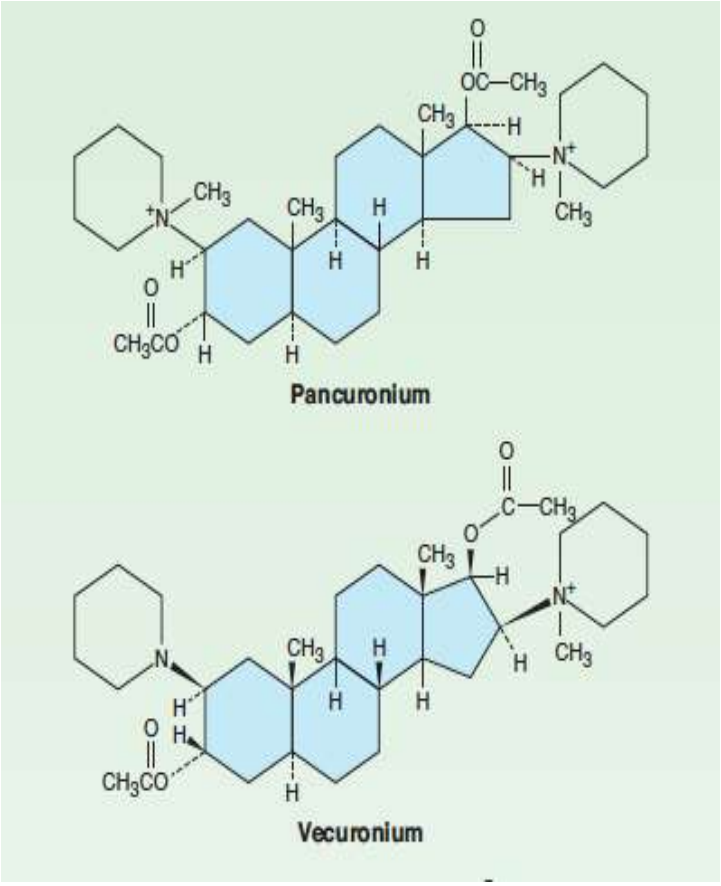


FIGURE 27–5 Structures of steroid neuromuscular blocking drugs (steroid nucleus in color). These agents are all nondepolarizing muscle relaxants.



The duration of neuromuscular blockade produced by nondepolarizing relaxants is strongly correlated with the elimination half-life. Drugs that are excreted by the kidney typically have longer half-lives, leading to longer durations of action (>35 minutes). Drugs eliminated by the liver tend to have shorter half-lives and durations of action.

Effects of Non-depolarizing blockers

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

Atracurium

Atracurium is an intermediate-acting isoquinoline nondepolarizing muscle relaxant that is no longer in widespread clinical use. In addition to hepatic metabolism, atracurium is inactivated by a fo rm of spontaneous breakdown known as **Hofmann elimination**. The main breakdown products are **laudanosine** and others related quaternary acid, neither of which possesses neuromuscular blocking properties. **Laudanosine** is slowly metabolized by the liver and has a longer elimination half-life (i.e., 150 minutes). It can crosse the blood-brain barrier, high blood concentrations of this metabolite may cause seizures and an

increase in the volatile anesthetic requirement. During surgical anesthesia, blood levels of laudanosine typically range from 0.2 to 1 mcg/mL; however, with prolonged infusions of atracurium in the ICU, laudanosine blood levels may exceed 5 mcg/mL.

Summarizing here, **Atracurium** is metabolized either in the liver or by Hofmann elimination. Once it's metabolized by this process it can produce a compound called **laudanosine**, it can be metabolized further in the liver, but it has a longer elimination half-life than the original drug. One problem with laudanosine is it can cross the blood-brain barrier, and if it reaches high enough concentration in the central nervous system -> it can develop seizures. Also, another consequence for its accumulation is that the patient under general anesthesia will need a higher dose of the general anesthetic so we must be cautious about the levels of laudanosine in the blood not to exceed five milligram per milliliter especially in patients who are in the intensive care unit and who are receiving prolonged or continuous infusion with Atracurium.

Now a solution for this problem came where we have a isomer of **Atracurium** called **Cisatracurium** and actually it became one of the most commonly used muscle relaxants in clinical practice.

Although cisatracurium resembles atracurium, but it has less dependence on hepatic inactivation, produces less laudanosine, and is much less likely to release histamine. Releasing of histamine is one of the consequences of the use of non-depolarizing neuromuscular blocking agent. From a clinical perspective, cisatracurium has all the advantages of atracurium with fewer adverse effects. Therefore, cisatracurium has virtually replaced atracurium in clinical practice.

Mivacurium

Let's talk now about one example of the short acting neuromuscular blockers: We have **Mivacurium,** Isoquinoline, it is the shortest duration of action of all the non-depolarizing muscle relaxant, but the onset of action is not that fast it is lower than succinylcholine. One other drawback of **Mivacurium** is if we want to have a larger dose in order to get a faster onset of action -> this can be associated with excessive release of histamine which can cause hypotension bronchospasm. **Mivacurium** is metabolized by plasma cholinesterase and it is not dependent on metabolism of the liver or the kidney. However, we have to remember that the patients who have renal failure usually have low level of plasma cholinesterase so the action of **Mivacurium** can be prolonged in these patients. One alternative for **Mivacurium** is **Gantacurium** which is a new class of the non-depolarizing neuromuscular blocker, it is degraded by the abduction of the amino acid cysteine and by ester bond hydrolysis. It is degraded nonenzymatically by adduction of the amino acid cysteine and ester bond hydrolysis. It has a rapid onset of effect and a very short duration of action kind of similar to succinylcholine and that can be reversed with neostigmine quickly (within 1–2 minutes), with administration of l-cysteine.

It does not cause a profound histamine release so the adverse effects related to histamine release on the cardiovascular system are less and also it doesn't cause bronchospasm or pulmonary vasoconstriction.

Rocuronium

Other examples here: Let's talk a little bit about rocuronium, it is kind of similar to Cisatracurium, it is hepatically metabolized, the duration of action is intermediate it's not as toxic as atracurium in relation to causing seizures. It is useful or indicated to be used in patients who have renal impairment.

Neostigmine and pyridostigmine antagonize nondepolarizing neuromuscular blockade by increasing the availability of acetylcholine at the motor end plate, mainly by inhibition of acetylcholinesterase.

Non-depolarizing Drug: d-Tubocurarine

- 1st agent to undergo clinical investigation.
- Purified curare – Purified from a plant called (*Chondodendrom tomentosum)*
- (The effective dose) ED_{95}= 0.5mg/kg. - Actually, when this drug is used at doses even lower than that it can result in hypotension.
- Undergoes minimal metabolism- is excreted:
    - 10% in urine.
    - 45% in 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”

Precurarization: Usually we administer a small dose of less than 10 percent of the original dose of the drug of this compound before the administration of succinylcholine and the aim of that is to minimize the complication of succinylcholine that can arise to muscle fasciculation, or increase in the intragastric pressure, or intracranial pressure.

Quick Summary: Non-depolarizing Drugs.

Gallamine

- Less potent than curare
- Tachycardia

D-Tubocurarine

- 1-2 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)

Important note:
We don't have any variants in the enzymes metabolizing regarding **Tubocurarine.** On the other hand, in relation to **Succinylcholine,** we have patients who have variation in the genetic structure of the enzyme that metabolize it which is called pseudocholinesterase and usually this is determined by the dibucaine number. So, this is a test that is done for patient to determine how effective is cholinesterase functioning in their body and according to that you decide the proper dose of succinylcholine to administer for them.

You must remember that we said one of the side effects of succinylcholine that can cause cardiac arrhythmia and we said this is because it can stimulate the sympathetic, parasympathetic ganglia and the muscarinic receptors in the heart. So, usually at larger doses succinylcholine have a positive isotropic and chronotropic effect. On the other hand, we can sometimes conceive bradycardia -> if we give a second dose of succinylcholine within less than five minutes after the initial dose and this is because we have a direct effect of the muscarinic two receptors on the heart which will cause bradycardia or decrease of the contractility of the heart.

Other Actions of Nm 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 (this is because they will cause paralysis of the muscles of the iliac) But as you remember the effect of succinylcholine including the ability to increase in the intragastric pressure, usually the vesiculation will increase the pressure from 5 to 40 and this can increase the risk of regurgitation and aspiration of the gastric contact and this is very serious e.g., esophageal dysfunction or obesity patients.

This also happens more frequently in the patients who have delayed gastric emptying such as those: with type 2 diabetes patients with traumatic injury in emergency cases where they were not actually getting ready for the surgery a day ahead of time. So, they do have a gastric content.

Directly acting relaxants - Dantrolene

- Different from neuromuscular blockers, no action on neuromuscular transmission.
- Mechanism of Action: Ryanodine receptors (RyR) calcium channels (inhibition) – prevents depolarization – no intracellular release of Ca++ -> Relaxation of the muscle.
- 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 (دوخة), muscular weakness, diarrhea and hepatotoxicity at high doses.

In normal conditions:

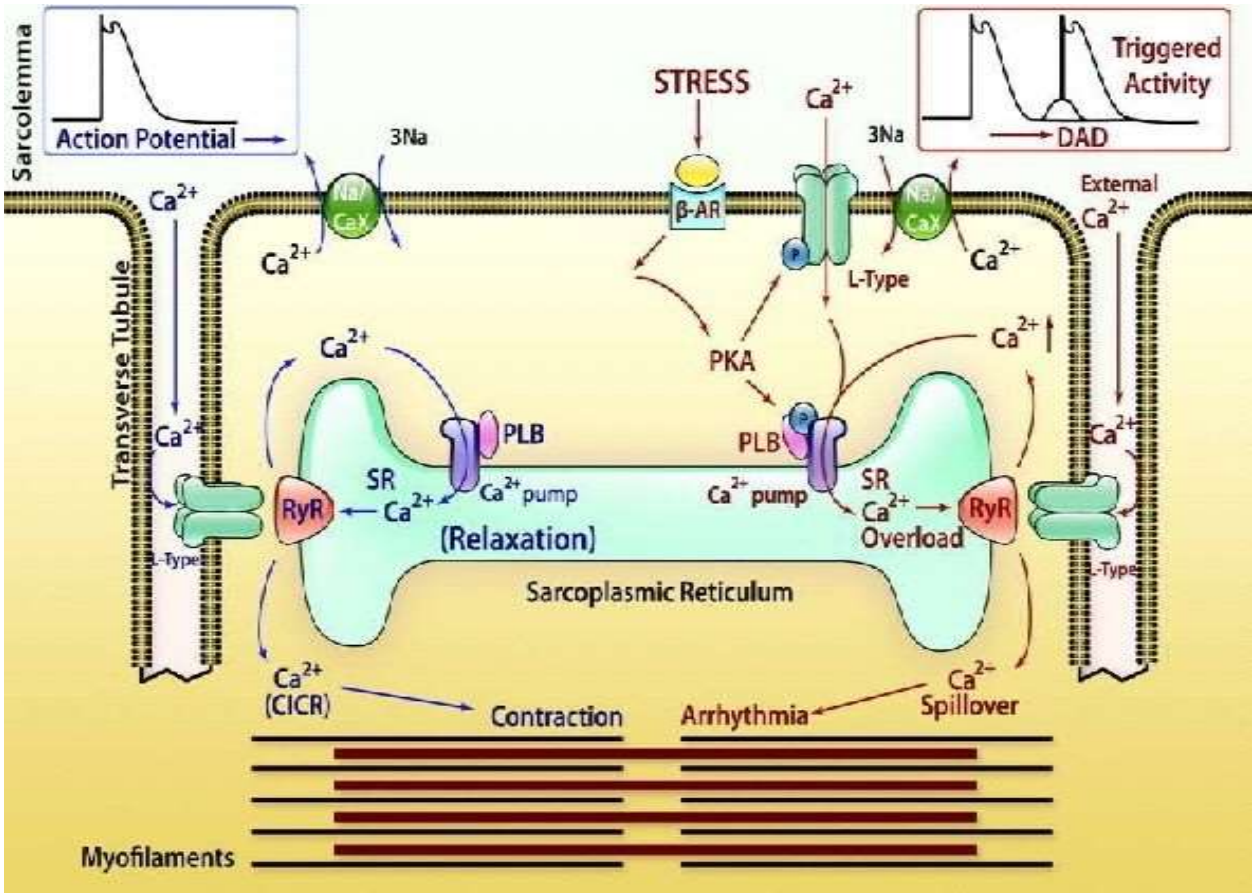
Once we have an action potential of the skeletal muscle leading to opening of the l-type calcium channels, we'll have a normal contractile response this will involve the release of calcium from the the sarcoplasmic reticulum then the released calcium causes the power streak between actin and myosin leading to the contraction of the muscle. Usually, the calcium released from the sarcoplasmic reticulum occurs through a calcium channel called the ryanodine receptor channels (now the name comes because of that plant alkaloid)

Dantrolene effect:

Dantrolene combines with the receptor on the channel and calls its activation. Dantrolene interfere with the release of the calcium from the sarcoplasmic

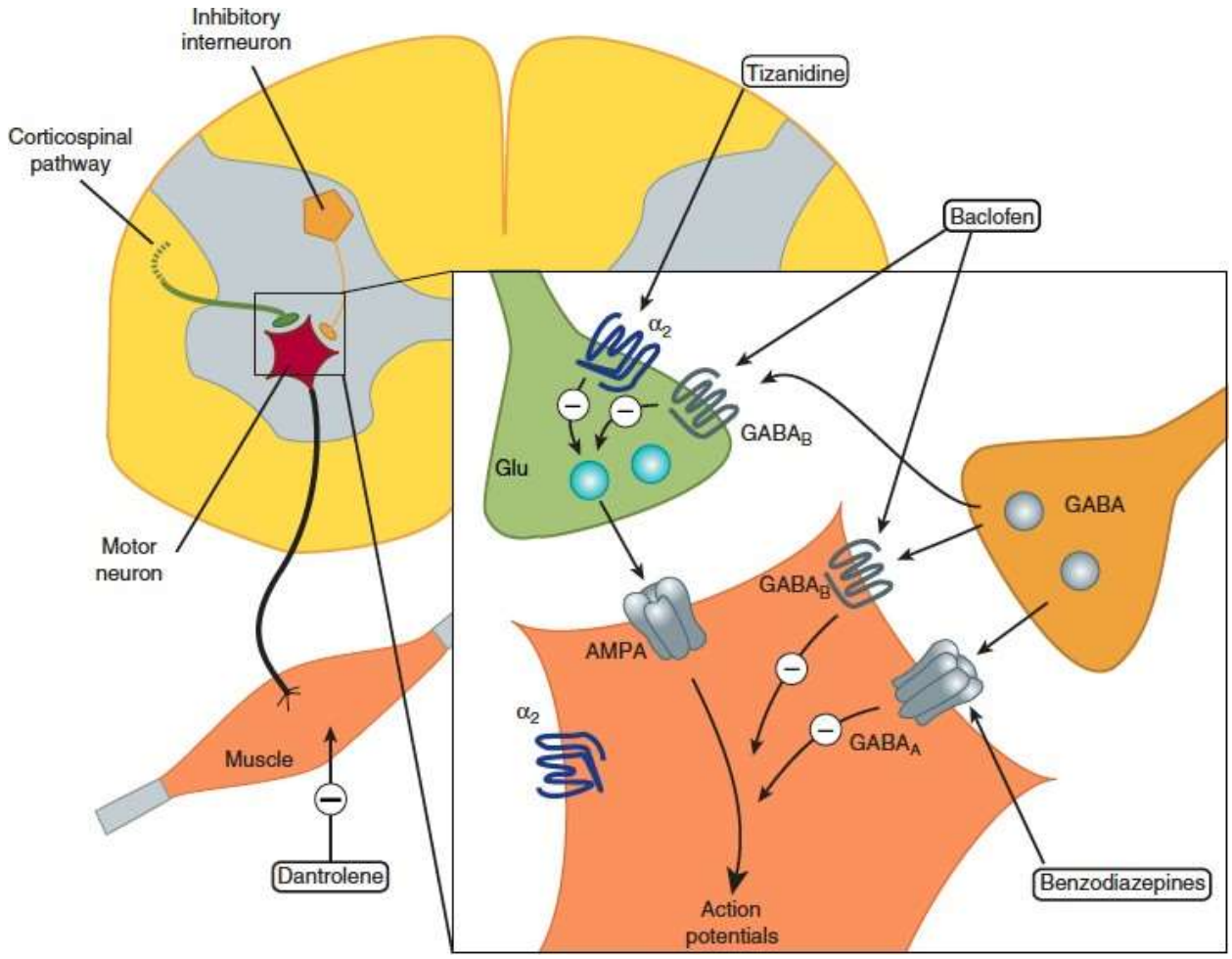
reticulum through binding to the Ryanodine r1 receptor and blocking the opening of the channel.

The motor units that contract rapidly are more sensitive to the drug effect than slower responding unit. Thus the cardiac muscles and the smooth muscles are minimally depressed using the Dantrolene than the skeletal muscle cells.



The action of the different spasmolytic drugs that are centrally working.

So, we have **Tizanidine** (alpha 2 agonist that resembles clonidine) as it has ability to reduce the muscle spasm because tizanidine resembles clonidine we would be worried about cardiovascular side effects because remember when you activate the alpha 2 pre-synaptic adrenergic receptors -> this will lead to inhibition of the release of catecholamines such as norepinephrine and epinephrine which cause lowering of the blood pressure, lowering of the cardiac contractility but actually testing has approximately 1.10 to 1.15 effect on the blood pressure than that of clonidine according to studies. So, still it does have an inhibitory suppression action on the spinal interneuron without causing changes in the intrinsic muscle properties.



Activation of these receptors by baclofen results in hyperpolarization by three distinct actions:

1) closure of presynaptic calcium channels.

2) increased postsynaptic K+ conductance.

3) inhibition of dendritic calcium influx channels.

Through reduced release of excitatory transmitters in both the brain and the spinal cord, **Baclofen** may also reduce pain in patients with spasticity, perhaps by inhibiting the release of substance P in the spinal cord.

Side effects of baclofen include: Sedation, drowsiness, Increased seizure activity has been reported in epileptic patients. So, the withdrawal from baclofen must be done very slowly.

lastly let's talk about benzodiazepine, they mainly work in the central nervous system by facilitating the action of GABA. Also, they have other mechanism of actions. So, they can serve as calcium channel blockers and can inhibit the depolarization sensitive calcium uptake also they can inhibit acetylcholine release which is important in explaining their muscle relaxant properties. Additionally, the muscle relaxant properties of diazepam are produced by inhibition of polysynaptic pathways in the spinal cord.