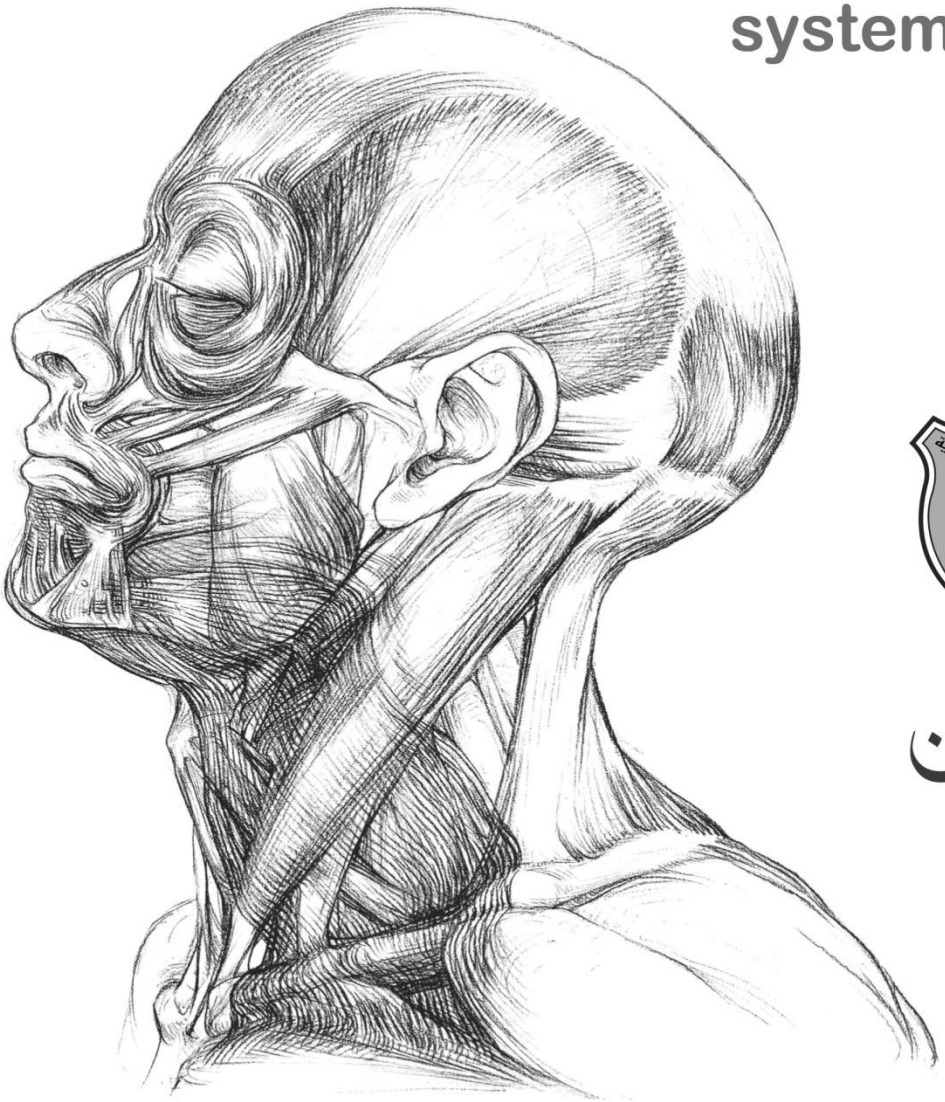
The skin & Musculoskeletal system



PHARMACOLOGY

SLIDES ☐
SHEET ■
LECTURE # 6

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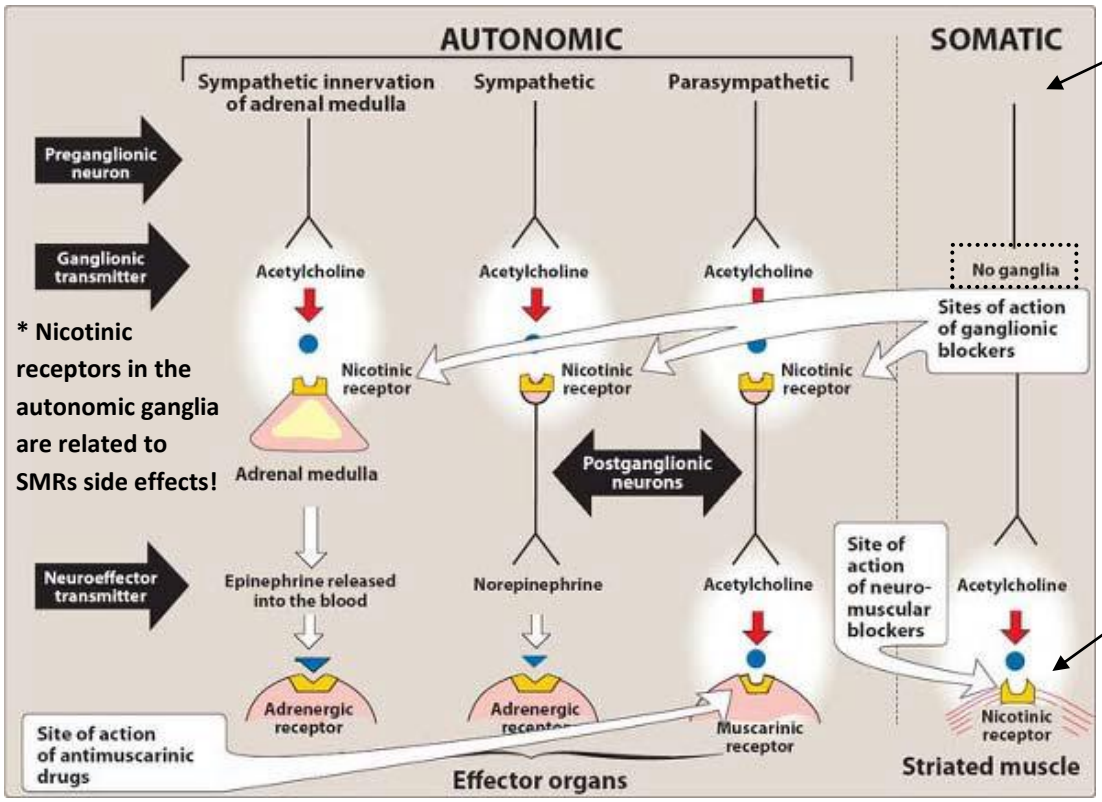
Today we are going to talk about skeletal muscles relaxants; Why do we use them, their types ,where, how does each type work and much more.

*Before you start: this sheet follows an order slightly different than the record and the slides“Order and figures are obtained from the same source ” , what’s in the slides is copied, but here you’ll better understand and order your ideas.



A bit of physiology first!

Today’s lecture :D

Figure 5.2 Sites of actions of cholinergic antagonists [(1)]

- In this figure focus on : Neurotransmitters binding the effector organ, **NTs in the ganglia** (All are Ach.) , Types of Ach. Receptors (nicotinc, muscarinic). Where do nicotinic receptors exist???“ FOCUS on the muscles”

** Now we are going to review the action potential in neuromuscular junctions:

When we have an activation action potential in the presynaptic motor neuron, the concentration of calcium is going to increase due to Na+ entry, leading to exocytosis of neurotransmitters (Ach. molecules) into the synaptic cleft, then Ach. will bind to its receptor (nicotinic) on the postsynaptic membrane and activate it.

Nicotinic receptors (Na+ chemichal gated channels) are composed of 5 subunits forming an ion channel: 2 alphas α ,1 beta β, 1 gamma γ and 1 delta δ. In addition, each receptor has two binding pockets for acetylcholine between its subunits so I

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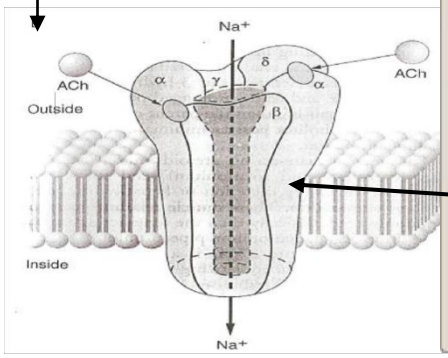
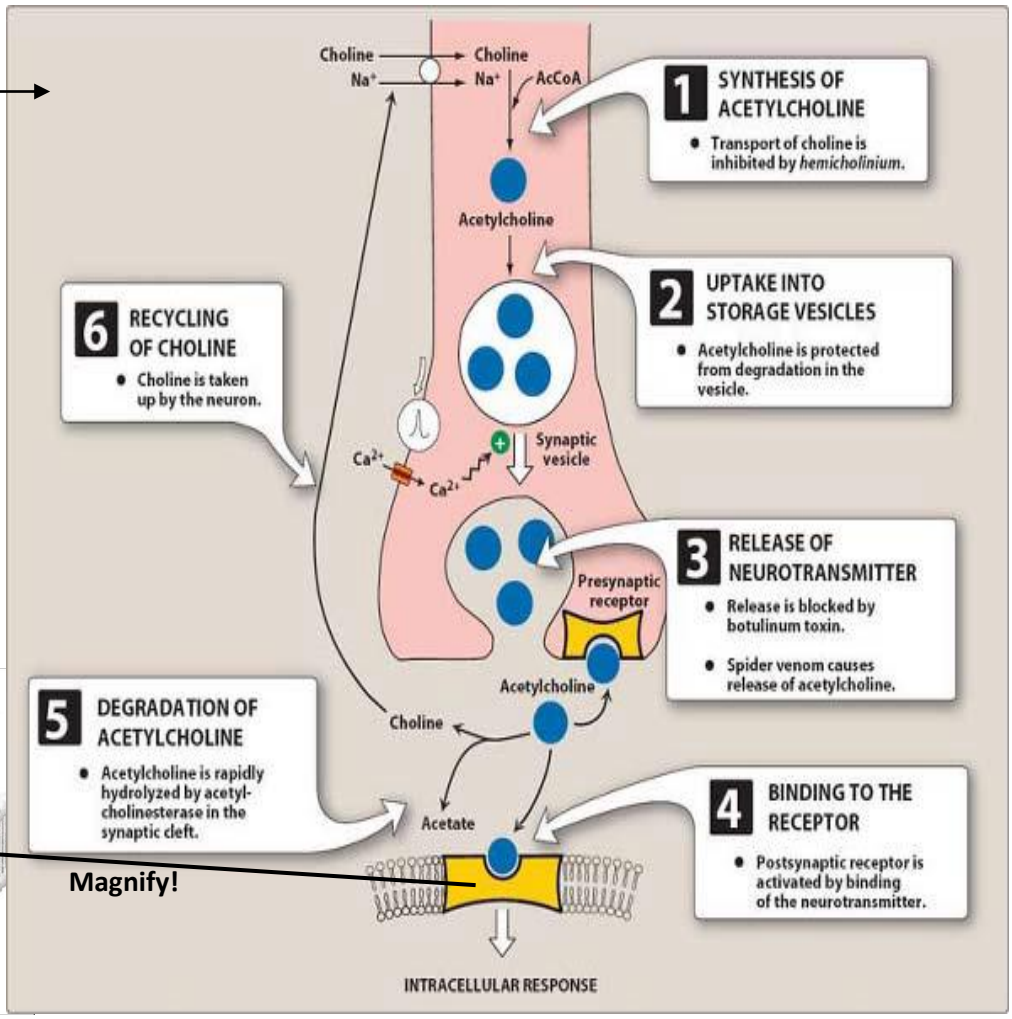
need 2 acetylcholine to open "activate" the channel which will cause the influx of sodium into the muscular cell, the entry of sodium is going to activate another channel called Na+ voltage gated channel leading to propagation of the action potential to the whole motor unit , increasing intracellular Ca+2 by releasing it from sarcoplasmic reticulum and importing it from the outside, " Calcium initiates attractive forces between actin and myosin causing them to slide alongside each other which is the contractile process" – Guyton medical physiology 13th edition, p.78

Figure 4.3 Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A(2)

**** Pay no attention to process-inhibiting drugs!**

Observe : number of Ach. Pockets and **direction**of Na+ movement .





Magnify!

- After reviewing sparks of Physiology, guess… Why to use SMRs?? They're **mainly** used for muscle spasm (tetanus), and with general ansthesia but <u>not to replace it</u>.

1. SMRs are administered with general ansthesia in the same time when preparing the patient for the operation. General anesthesia will make him unconscious "not to move" while SMRs are going to relax the muscle; because it'll be easier to perform operations when the muscles are relaxed to ease up the intubation for ventilation(التنفس الأنبوبي) during the operation.Also, Because if muscles were kept able to contract, we're not going to be able to insert ventilation tubes !!

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2. During the operation, when you cut through the patient to reach deep tissues, you're going to move muscles around, so it's better to " swim" between relaxed muscles than between stenized (مشدودة) .

* 0.00min-8.05min / Slides 1-3

There are 3 groups of skeletal muscle relaxing drugs we are going to talk about:

1. Neuromuscular blockers: They are going to interferetransmission of Ach. to the skeletal muscle end plate by interacting with the channel and preventing its **cholinergic**activation.They're composed of two subgroups:

a. Non-depolarizing drug
b. Depolarizing drugs
2. Spasmolytics" briefly in this lecture "
3. Directly acting drugs: Act on the CNS directly or affect Ca+2 concetration in the muscle ." to be discussed next lecture"

Nueromuscular Blocking Agents

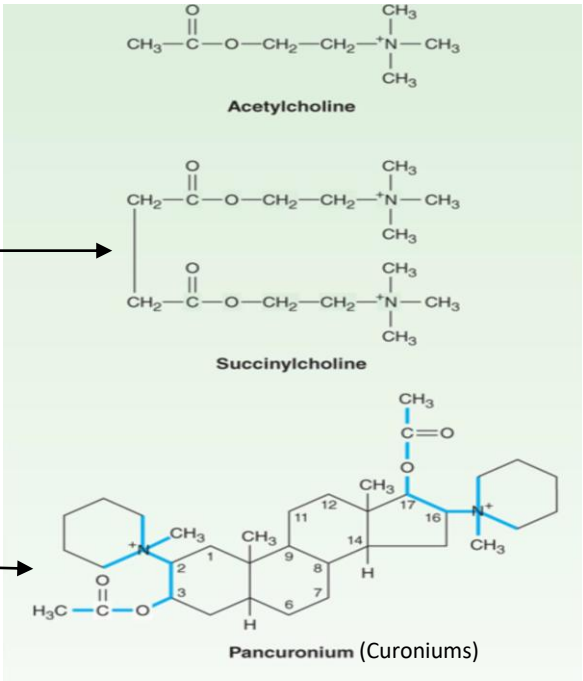
1* Chemistry of Neuromuscular blockers

-These drugs have one or two quaternary nitrogens. Therefore, they are highly polar and very **poorly lipid soluble,** so they can't cross the blood-brain barrier,and there is no central side effects of these agents to worry about, except a non- depolarizing drug called atracurium " to be detailed ".

- The main function of these drugs is to block nicotinic receptors, so they'll have to have a shape that can interact with these receptors , that's why They'll have **double acetylcholine molecules** (remember # of pockets) linked either by :

1- End to End →

2-Concealed, bulky semi- rigid ring systems. →



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1-Non-depolarizing agents (Ach. Antagonists):

They are either steroid derived or Isoquinilone derived, this arises differences in their metabolim and excretion.

The first drug that was found to be capable of blocking the skeletal neuromuscular junction was **Curare**, which the native hunters of the Amazon in South America used to paralyze the prey . The chemichal ingredient of this poison was discovered later which was Tubocurarine, **The father !!**

- Tubocurarine: it's the prototype and considered the father of this group.

1.Mechanism of Action:

1. Compete with acetylcholine at the nicotinic receptor sites at the NMJ.

2. In high doses, can enter the pore of the ion channel to cause a more intense blockade.

3. Can also block prejunctional sodium channels (to be mentioned again in page 9) to interfere with the mobilization of acetylcholine at the nerve ending.

Tubocurarine MOA :

1-It binds to the endplate nicotinic cholinoceptors without exciting them, acting as a competitive antagonist towards Ach.

2-Muscular paralysis develops within about 4 min. d-Tubocurarine does not penetrate into the CNS.

3-The patient would thus experience motor paralysis and inability to breathe, while remaining fully conscious but incapable of expressing anything.

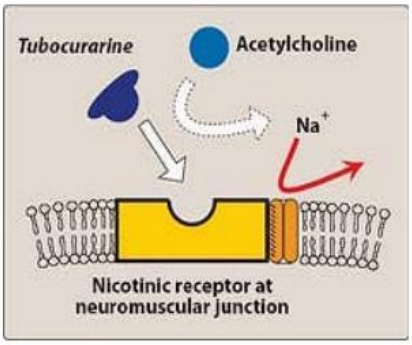


Figure 5.9 Mechanism of action of competitive neuromuscular blocking drugs [4]

2.Pharmacokinetics:

1- Must be given parentrally (not to be given orally) because they are very polar.

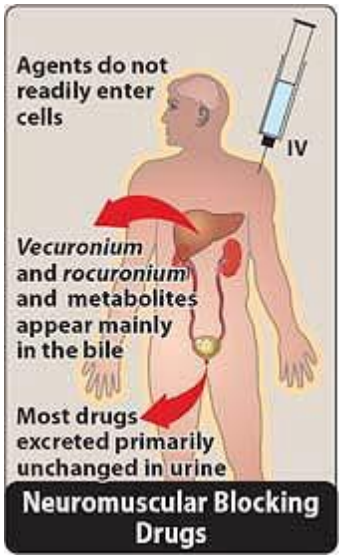
Getting back to native Americans, how were they able to eat the prey and still not affected by curare toxin and paralyzed ?! Since it's really polar, it won't get absorbed back from the GIT to even reach the circulation to act on the muscles !!

Figures pointed at (1 - 5) are taken from Lippincott illustrated reviews- Phamacology 6th edition

2- They're mainly either excreted unchanged by the kidney or metabolized by the liver(Steroidal type).

** Exception 1: **Mivacurium** is metabolized by cholinesterases.

Exception 2 : **Atracurium is the only durg which is broken down in a spontaneous reaction (HOFMAN ELIMINATION) into its by-products. It's spontaneously broken down to Laudanosine. Atracurium is not used with ICU patients , WHY? Because its toxic metabolite can reach the CNS and if it accumulated (like in ICU example below) it can provoke **seizures** (sudden attacks like a stroke).



- Figure 5.10 Pharmacokinetics of the neuromuscular blocking drugs [3]

3-Pancuronium leads to generation of metabolite called hydroxy Pancuronium with different effect than pacuronium. How? Pancuronium relaxes the muscle for a certain period while its metabolite gives 40% of that effect, which will not produce wanted effect (will not reach minimum therapeutic concentration to be effective).

Also, If a patient was kept in the ICU, given pancuronium for a long period of time, alot of metabolites will accumulate , so even after getting out of ICU , for a certain time the effect of this metabolite is going to stay in the body more than the original drug and many muscles will still be PARALYZED!

Q: Isn't the steroidal drug supposed to become more hydrophilic and excreted faster when metabolized to hydroxy- drug??

Answer: Yes, and these metabolites will be further metabolizedand they'll eventually be eliminated, but when talking about **long periods of administration** , then accumulation will overweigh the rate of elimination, and because the metabolite has a longer half-life than the parent drug, a persistant paralysis will be seen for a certain period after getting out of ICU .

3. Drug interactions:

Suppose a patient had an overdose of pancuronium, all of his muscles even the respiratory muscle will be relaxed, he's also anesthetized. How are we going to wake him up? What would be the suitable antidote (opposing drug) ? ... thinking of Ach? Remember that it degrades very quickly so it won't reach and be useful !!!

Figures pointed at (1 - 5) are taken from Lippincott illustrated reviews- Phamacology 6th edition

The answer is: I give neostigmine (or physostigmine) which is an acetylcholine esterase inhibitor. Neostigmine will inhibit degradation of Ach. , thereby increasing Ach. concentration existing naturally in the body, and in the NMJ synaptic cleft especially, causing a fired up competition with pancuronium that'll sure be won by Ach. , Ach. will takeover finally and will rebind to its receptor to activate the muscle!

** Refer to illustration in slide 16 for better understanding.

2-Depolarizing agents (Ach. Agonists):

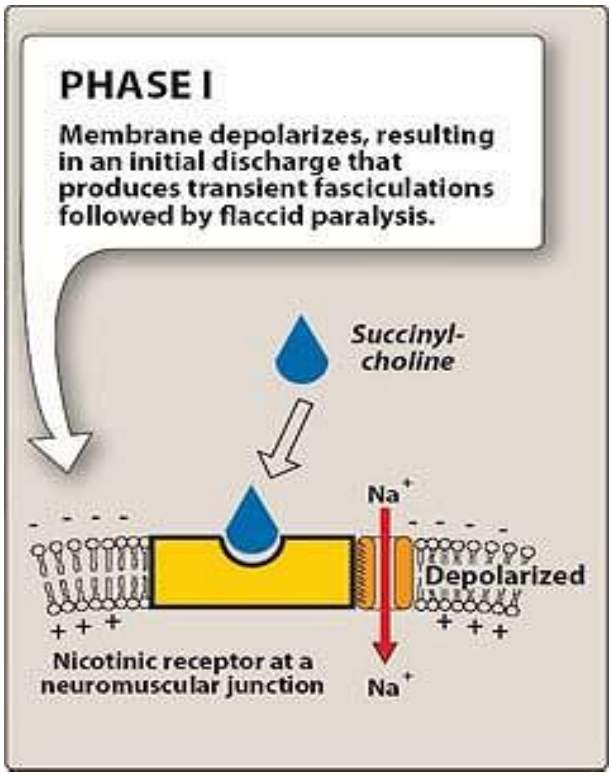
1. These drugs are structural analogues of acetylcholine , this inturn reflects their short half life!!

2. They are also used parentrally.

3. Mainly used in short procedures, or when we need fast onset of relaxation.

- Examples: **succinylcholine** " Mainly used" and Decamethonium.

1. Mechanism of action :



(A)

**** Initial discharge : initial flow of Sodium to the inside**

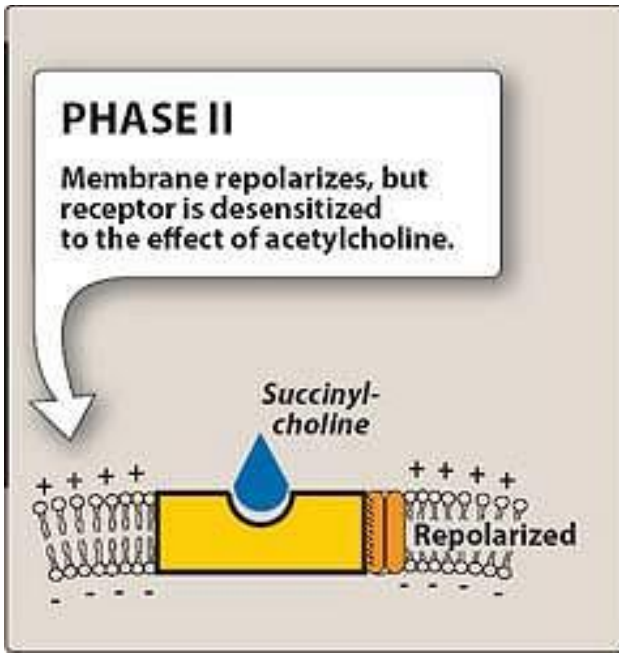
-Phase I Block(depolarizing):

succinycholine reacts with nicotinic receptors to opens the channel and cause depolarization of the motor end plate which will spread to adjacent membranes, causing contractions of muscle motor units.

-Can enter the channel to produce a prolonged "flickering" of the ion conductance (always active).

-The depolarized membranes remain depolarized " no repolarization in this phase so we can't reactivate the muscle ", and unresponsive to subsequent impulses causing paralysis which is augmented (increased) by cholinesterse inhibitors.

Figures pointed at (1 - 5) are taken from Lippincott illustrated reviews- Phamacology 6th edition



(B)

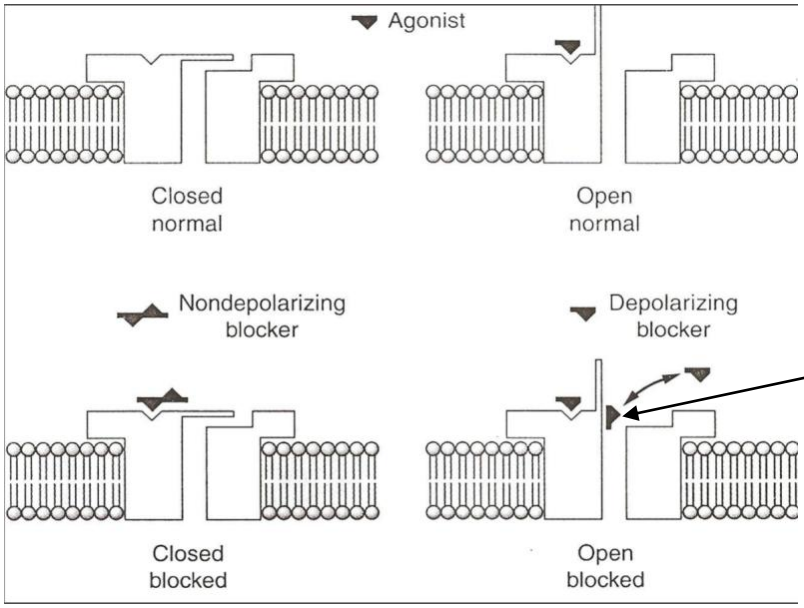
-Phase II Block(desensitizing): with continued exposure, depolarization decreases and the membrane becomes repolarized and can not be depolarized again because it is desensitized " made less sensitive to stimuli".

-This may be due to blockade of ion channel (done by an amount of drug) , which might be more important than the action of the agonist at the receptor (done by the other amount) , i.e. the channels behave as if they are in a prolonged closed state.

-This phase is reversed by acetylcholinesterse inhibitors.

Figure 5.12 Mechanism of action of depolarizing neuromuscular blocking drugs[5]

Why did repolarization happen in this phase?? Because of potassuim leakage to the outside of the cell. Keep it in mind when reaching contraindications.



Observe the blockade mentioned earlier !

2. Pharmacokinetics of succinylcholine :

1-Extremely short duration (5-10 minutes then it'll start to break down) so sometimes it's given by continuos infusion to maintain longer duration of effect .

Figures pointed at (1 - 5) are taken from Lippincott illustrated reviews- Phamacology 6th edition

2-Metabolized by cholinesterases (pseudocholinesterases) in the plasma and liver.

3- Only a small percentage reaches the neuromuscular junction, where it diffuse away into the extracellular fluid.

4- **The BEST feature : fast onset of action** " within 30sec" , How ?Through the blood to site of action, a bit of it will be destructed in the plasma but the remaining fraction once it reaches muscles it quickly acts on them!!

[Note: The duration of action of *succinylcholine* is dependent on diffusion from the motor end plate and hydrolysis by plasma pseudocholinesterase.] L.I.R – parmachology 6th edition.

5- Succinyl choline can be combined with pancuronium to prolong duration .

6-Some patients have a genetically abnormal variant of plasma cholinesterase.

-Dibucaine Number: is a measure of the ability of a patient to metabolize succinylcholine (as you remember from the first semester, we have fast metabolizer and slow metabolizer and this applies to the choline esterases).You have to make this test to patients in order to know if they are slow metabolizers to prevent the accumulation of the dose, or if they're fast metabolizers to change the drug because it won't reach effective dose level .

8- In cases we can't use it, we use rocuronium **in High doses** (to produce fast onset of action because it's an intermediate reacting drug) as an alternative.

-The table in slide 11 is not for memorizing, In slide 12 you need to know that depending on the structure of drugs, you can determine which is suitable for your operation.

Ex. drugs metabolized in the kidney have the longest half life while drugs metabolized in the liver then excreted from the kidney have an intermediate half life.

3. Contraindications:

1. Mutations in Metabolic enzyme(**plasma cholinesterase) :** [Genetic variants in which plasma cholinesterase levels are low or absent leads toprolonged neuromuscular paralysis.] L.I.R – parmachology 6th edition.

2. Patients with burns or traumas : If a burn or trauma victim was brought to the hospital and he needs an operation, you have to be aware and recall that burns or

Figures pointed at (1 - 5) are taken from Lippincott illustrated reviews- Phamacology 6th edition

neurological traumas (that cause hemiparalysis) cause upregulation of a type of receptors called prejunctional " extrajunctional" nicotinic receptors . they are nicotinic receptors that usually exist in small numbers in the muscle end plate, and they're upregulated as compensatory effect. In case we used Succinyl choline, **Hyper kalemia** (increased K+ loss) will be the result which can be fatal to the patient . "*Succinylcholine* increases potassium release from intracellular stores. This may be particularly dangerous in burn patients or patients with massive tissue damage in which postassium is beenrapidly lost from within cell"L.I.R – parmachology 6th edition.

* 8.05min- 34.15min/ slides 4-19

2* Clinical use of neuromuscular blockers:

1.Muscle relaxation during surgical procedures.

2.Endotracheal intubation.

3.Maintain controlled ventilation: when administering general anesthetics along with SMRs the patient will fall asleep, and will not be able to breathe on his own " the respiratory muscle is paralyzed" , so we'll have to give artificial ventilation.

3* Neuromuscular blockers interactions:

1. Potentiated by inhaled anesthetics : General anesthetics like Isoflurane, halothane are type of Halogenated hydrocarbon anesthetics that make the patient unconscious.

Anesthetics as well as succinyl choline can induce a lethal condition known as **Malignant hyperthermia.** Hyperthermia is a sudden and prolonged release of calcium with massive contraction , lactic acidosis due to fast anaerobic massive contractions producing lactic acid, finally leading to increased body temperature.

The main cause is still unknown but scientists think it may be because of a mutation in a gene coding for a receptor called Ryanodine receptor; a receptor that exists on the surface of the sarcoplasmic reticulum, so if any of the above where administered to a patient with the mutation , there'll be an exaggerated release of calcium in the muscle leading to continuous contractions. Be very careful when administering both!!

2. Potentiated by aminoglycosides (Type of antibiotics) and calcium channel blockers (drugs used to treat hypertension).

Figures pointed at (1 - 5) are taken from Lippincott illustrated reviews- Phamacology 6th edition

3. Can block autonomic ganglia at higher doses. Get back to the figure in page 1 to see which type of receptors and neurotransmitters exist there, VERY SIMILAR ???!

4. Respiratory paralysis

4* Actions of Neuromuscular Blockers (NMBs) :

1-Skeletal Muscle Paralysis:

Depolarizing Drugs: Action starts by transient muscle fasiculations over the chest and abdomen within 30 seconds ;Paralysis develops rapidly (within 90 seconds), the arm, neck, and leg muscles followed by the respiratory muscles ; Blockade lasts less than 10 minutes.

2-Cardiovascular Effects:

Normally, doctors warn smokers that continuous cigarette intake " massive amounts of **nicotine**" will threaten their lives and predispose their body to cardiovascular diseases like hypertension, Why??

When talking about blood vessels, which Autonomic system is mainly responsible of controlling them ?? YES , without hesitation it's **the sympathetic system**, a vasoconstrictor when activated! .. Now you can understand smokers example.

So mainly NMBs will act as blokers for all autonomic ganglia. Also, they can enhance histamine release which is a vasodilator , together they mainly in cardiovascular system (CVS) will cause **Hypotension**" lowering blood pressure in blood vessels".

Of course not all NMBs produce effects to the same extent, some drugs don't affect CVS like the VCR group -->"**V**acuronium , **C**is-Atracurium, **R**ocuronium "

Conclusion : CVS effects are mediated by autonomic or histamine receptor; Both sympathetic and parasympathetic ganglia and muscarinic receptors in the heart can be stimulated; Usually cause hypotension, which can be attenuated " reduced" by antihistamines.

3-Hyperkalemia: In patients with burns, nerve damage, or neuromuscular disease, head injury, and other trauma; Can result in cardiac arrest, Why? To always remember, potassium is important in the balance between sodium and potassium in th heart, so any **increase in leakage to the outside** like in this condition would result in cradiac arrest and arrhythmia!

Figures pointed at (1 - 5) are taken from Lippincott illustrated reviews- Phamacology 6th edition

4-Increased Intraocular Pressure: Due to tonic contraction of myofibrils (they affect ocular muscles contractions) or transient dilation of ocular blood vessels (remember they block sympathetic) that cause elevation in pressure inside the eye. So they're contraindicated in Glaucoma "increased intraocular pressure"

5-Increased Intragastric Pressure: In obese, heavily muscled, diabetics, traumatic patients, fasiculations of succinylcholine can cause regurgitation and aspiration of gastric contents (entering of materials such as pharyngeal secretions, food or drink, or stomach contents into the larynx and lower respiratory tract from the trachea)

6-Muscle Pain: Due to unsynchronized contractions of adjacent muscle fibers just before the onset of paralysis.

* 34.15 Min – 40.50 min / slides 20-26 " almost there :D "

Spasmolytics

- These drugs are **not used in operations**, but are used to treat muscle spasm in the body.

-We use this type of drugs for :

1-neurologic diseases such as multiple sclerosis.

2-acute injuries such as spinal cord damage and muscle inflammation" in muscle stiffness "

- Our goal of therapy is to reduce spasticity and pain while retaining function, we don't want to make central decrease in muscle contraction - some drugs we'll discuss later will centrally weaken the muscle- , here we just want to decrease contraction without losing the muscle function ..

- Examples on Spasmolytic drugs:

1.Diazepam: Valium - Famous trade name
- Acts at GABA receptors in the CNS(works centrally).
GABA is an inhibitory neurotransmitter, if GABA receptors were activated, an activation of the inhibitory pathway; then reduction of motor neuron activity; finally muscle relaxation will occur.
–Sedative to reduce patient stress " it won't make him unconscious but will put him in a state of amnesia ; a partial loss of memory ". Instead of using general

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anaesthesia which wouldn't be necessary in minor surgeries like in dentistry "wisdom teeth extraction" we use Valium to help relaxing the muscles for drilling and other steps, and for the patient to **respond to you** when interfering the oral cavity .

- A risk of dependence on some patients "happens with all central acting drugs".

2.Baclofen: activates inhibitory pathway as well .

– Acts at $GABA_B$ receptors, resulting in hyperpolarization and presynaptic inhibition through reducing Calcium influx.

– Can also reduce spasticity by inhibiting the release of substance P in the spinal cord. Substance P has an inhibitory effect on the spinal cord, so it reduces muscle spasm specially spinal muscles.

– Less sedative, but can cause drowsiness.

– Can be given intrathecally for spinal anaesthesia.

– Can reduce craving in alcoholics and in migraine.

3.Tizanidine:

– Related to clonidine " centrally acting α2 agonist used to treat hypertension "

– α2-adrenoceptor agonist

- A bit of physiology again : we know that the neurotransmitters existing in the sympathetic system is adrenaline (epinephrine)/noradrenaline (norepinephrine). its receptor which is adrenergic receptor has subtypes; α1 on blood vessel walls ,α 2 existing on sympathetic nerve endings presynaptically to control NEP release, and β. When NEP molecules bind presynaptically after their release from presynaptic neuron, they activate α2 receptor and work as feedback inhibitions to prevent further release .

– Presynaptic and postsynaptic inhibition of reflex motor output.

- Indications: Spasm due to multiple sclerosis, stroke " post-stroke muscle tension " , amyotrophic lateral sclerosis

- The exact mechanism of relaxation isn't will understood but what we know is that it prevents cetrain brain stimuli from increasing motor functions that is normally done by adrenaline .

- Pharmakokinetics: renal and hepatic elimination, duration, 3–6 h

- Toxicities: weakness of the muscles because it works centrally , sedation, **hypotension** " remember effect of blocking sympathatic system" .

4. Gabapentin : Not to be required now!

It's a drug to treat seizures and epilepsy, it's mainly used as last resort when other SMRs won't work .. like in a condition called Myalgia " chronic muscle pain " . We don't use it much due to its side effects and the chance of addiction.

Figures pointed at (1 - 5) are taken from Lippincott illustrated reviews- Phamacology 6th edition

5. Dantrolene:

– Related to phenytoin, an antiepileptic.

– Interferes with excitation-contraction coupling in the muscle fibers by interfering with the release of activator calcium by binding with the ryanodine receptor (ryr) channel of the sarcoplasmic reticulum " it inhibits the receptor function that causes hyperthermia " .

– Useful in treatment of malignant hyperthermia " considered the **antidote** of succinyl choline; refer to page 9 "

**40.50 min- 48.24 min/ slides 27 – 33

Test your understanding: Taken from L.I.R pharmacology 6th edition, p.75

1.Which of the following is correct regarding the neuromuscular blockers?

a. Cholinesterase inhibitors reduce the effects of nondepolarizing NMBs.

b. Nondepolarizing NMBs are administered orally.

c. Effects of depolarizing NMBs can be reversed using cholinesterase inhibitors.

2. Which of the following is correct regarding drug interactions with non-depolarizing neuromuscular blockers?

a. Isoflurane reduces the effects of nondepolarizing NMBs.

b. Cholinesterase inhibitors increase the effects of nondepolarizing NMBs.

c. Aminoglycosides increase the effects of nondepolarizing NMBs.

d. Calcium channel blockers reduce the effects of nondepolarizing NMBs.

3. A patient was administered a neuromuscular blocker (NMB) prior to a surgical procedure to produce skeletal muscle paralysis. This NMB drug caused initial fasciculations before the onset of paralysis. The effect of this drug could not be reversed with neostigmine. which of the following neuromuscular blockers was most likely administered to the patient?

a. Cisatracurium

b. succinylcholine

c. Diazepam

d. Tubocurarine

Answers : A, C, B

No better place than a textbox to congratulate you :P !

We hope this was an easy going sheet, If any info was to be corrected don't hesitate, we're your colleagues , better knowledge is what we always seek for ^.^

Figures pointed at (1 - 5) are taken from Lippincott illustrated reviews- Phamacology 6th edition