Hashemite University
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Scientific Team
الفريق العلمي

PHARMACOLOGY

Lecture : 5

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Neuromuscular junction

We will discuss in this lecture some of the drugs that work on the neuromuscular junction and examples on skeletal muscle relaxants .

Nervous system is divided into :

1.autonomic(sympathetic and parasympathetic)

2.somatic

The sympathetic and parasympathetic transmit their signals through :

1. Preganglionic

2. postganglionic

The main neurotransmitter that is released from the preganglionic fibers into the autonomic ganglia is acetylcholine

So preganglionic nerve terminals release acetylcholine at the of ganglia to activate them.

In response to ACh. The major receptor are the nicotinic receptor.

The difference between sympathetic and parasympathetic . That the sympathetic postganglionic neurons are nor adrenergic neurons meaning that they release nor epinephrine at the effector organs .

So the the receptors that respond to nor epinephrine release at the effector organs in the case of the sympathetic system are adnergic receptors such as alpha and beta receptors which vary depending on that tissue .

The postganglionic neurons or nerve fibers that emerge from the parasympathetic ganglia are cholinergic neurons means that they use acetylcholine as the main neurotransmitter at the target tissues and in that case the main receptor of that response to acetylcholine released from the postganglionic neurons are cholinergic muscarine receptors .

The autonomic nervous system including both of its division is highly involved in the regulation of many functions in the body (respiration , regulation of the circulation of blood pressure and heart rate). The focus of this lecture is understanding the drugs that work on the somatic nervous system and these are the nerve fibers that emerge from the spinal cord and innervates skeletal muscle and they are mainly involved in the control of movement .

Unlike the autonomic nervous system transmission through the somatic system doesn't involve ganglia so there is no ganglia in the somatic nervous system , these fibbers emerge directly from the spinal cord and they directly stimulate the effectors organs which are the skeletal muscles .

The nicotinic acetylcholine receptors has different variants , there are muscle type nicotinic acetylcholine receptors that are diff. from the neuronal type or the necrotic receptors located at the parasympathetic and sympathetic ganglia .

The receptors that blocks the muscle type nicotinic receptors are selective photoreceptors and have minimal effect on the autonomic nervous system

The nicotinic receptors is a pentamer meaning that it consists of five subunits (alpha,beta,delta,gamma) and in between these five major units we have a central pore and that makes the nicotinic acetylcholine receptor an ion tropic receptor because this pore act as a channel that allows the influx of ions from the outside or the extracellular compartments to the intracellular compartment .

The nicotinic receptor it is a legand-gated ion channel which means that it will only allow the transmission of ions across the membrane , the ligand for nicotinic receptors is ACh. So only the binding of ACh to the nicotinic ACH receptor the ion pore will open allowing ions to diffuse freely from the extracellular comp. to the intracellular comp.

The activation of the nicotinic ACH receptor by ACh leads to influx of sodium into the interior of the cell and that is usually accompanied by efflux of potassium so in a resting state of a membrane the rapid influx of sodium throughout the nicotinic receptor to the anterior of the cell will result in depolarization of the membrane potential so the main effect of

nicotinic ACh receptor activation is the depolarization of the postsynaptic membrane

The neuromuscular junction consists of nerve terminal from a somatic nerve that conjuncts the position with the effector skeletal muscle

The nerve terminal contains an abundance of vesicles containing ACh stored in the nerve terminal and ready to be released upon the arrival of the nerve impulse or an action potential so when a nerve impulse or an action potential arrives at the terminal of the somatic nerve that action potential results in depoleriaztion of the membrane and it allows the rapid influx of calcium ions into the nerve terminals resulting into the release of ACh from the vesicles into the synaptic cleft

so the rapid influx of calcium upon the arrival of the nerve impulse it's a very important step that regulates the release of ACh into the synaptic cleft.

Once the ACh is released into the synaptic cleft it can freely move and bind to the nicotinic ACh receptor located at the surface of the skeletal muscle and when ACh binds to the receptors that allows the ion pore to open and for sodium ions to move freely to the interior of the skeletal muscle resulting in depolarization of the postsynaptic skeletal muscle and that results in muscle contraction

So how ACh is synthesized secreted and degraded is formed from choline and accytel Coa and that reaction is catalyzed by the enzyme choline acetyltransferase after acetylcholine is formed in the somatic nerve terminals it is packaged or stored in vesicles that protect Ach from being degraded and these synaptic vesicles are stored ready to release its contents of acc into the synaptic cleft upon the arrival of the action potential and the inward influx of calcium ions .

one of the drugs that work on the last step of the release of neurotransmitter is botulinum toxin which is a bacterial toxin that results is paralysis and the way that botulinum toxin works it blocks the release of Ach from the pre synaptic terminals

Neuromuscular-blocking Agents :

1. Agonists (depolarizing type)

2. Antagonists (nondepolarizing type)

1. Nondepolarizing (Competitive) Blockers

• Curare

• Used by native South American hunters • "paralyzes prey"

Other Neuromuscular drugs used largely in clinical medicine :

1. Cisatracurium 2. pancuronium 3. rocuronium

Mechanism of action At low doses

• Competitively block Ach at nicotinic receptors (no stimulation) and that results in the prevention the depolarization of muscle cell membrane because that will not allow any sodium ion to mobilize to the inside of the cell . Binding of these non-depolarizing agent to the nicotinic receptors does not activate the receptor they act as a classical antagonist at the receptor and as result these drugs cause muscle paralysis .

How can you overcome/reverse this effect (pharmacologically)?

Increase acc concentration at the neuromuscular junction or in case if you stimulate the muscles fibers themselves with electrical stimulation (experimentally)

Mechanism of action At high doses

• block the ion channels of the motor endplate for more prolonged period further weakening of acc on the nicotinic receptors , further weakening of neuromuscular transmission ….. that results in prolonged period of muscle paralysis … it can't be reversed either increasing the concentration of acc or through direct electrical stimulation f the muscle

Actions

The main action is to cause muscle paralysis . not all the muscles have the same sensitivity to these drugs

• Inequal muscle sensitivity • Small rapidly contracting more sensitive

Acting first

↘

face and eye → fingers, limbs, neck, and trunk muscles →intercostal muscles → diaphragm

Pharmacokinetics:

• Given IV (sometimes IM)

• Very poor membrane penetration (including BBB)

• Mostly, action is elimination is by redistribution

• Variable onset/duration of action of different members of this class

Note here that some drugs such as buchuronium and rocharonium can undergo some hepatic metabolism and they are excited in feces and that's why they might need some dose adjustments when taken with other drugs that are also metabolized by the liver or in patients with hepatic disease , so these agents exert their paralyzing effects very fastly they have a rapid onset of action

The time that the patient needs to recover muscle function following the cessation of drug treatment is highly voluble between these drugs for example it takes 40 min. To restore 25 % of the maximal response with atacurium but that is longer with cisatracurium and it is spontaneously becames degraded in the plasma and is the only non-depolarizing neurotransmitter that can be used safely without dose adjustments in patients with renal failure because they are execrated in urine except of cisatracurium that’s why we use the cisatracurium with patients that have multi system failure

Drug interactions

1. Cholinesterase inhibitors: e.g., neostigmine → overcome the action of nondepolarizing NM blockers. Remember low vs high dose.

2. Halogenated hydrocarbon anesthetics: e.g., desflurane → enhance the neuromuscular blockade

3. Aminoglycoside antibiotics: e.g., gentamycin → inhibit ACh release from cholinergic neurons

4. Calcium channel blockers: may increase the neuromuscular blockade

Sugammadex

Is used as an antidote to the action of the neuromascular blockers terminate the effect of both

• Selective relaxant-binding agent

• It is a very bulky large drug that can be used to terminates the action of both: rocuronium and vecuronium

• Wraps the NM blocker in 1:1 ratio it means that each sugammadex will bind in the circulation to a molecule of rocuronium or vecuronium and then it prevents it from getting into the neuromascular junction to exert their action

• Rapid reversal of neuromuscular blockade or treat cases of toxicity when neoromascular blockers are given in high doses that can cause (muscle paralysis, respiratory failure)

Depolarizing Blockers

• These drugs act as an agonists at the nicotinic receptors but they result in muscle paralysis so they work like ACh → depolarize the membrane of the muscle fiber meaning that they bind to the nicotinic receptors and they cause depolarization of the post synaptic membrane they are similar to Ach in structure .Ex: Succinycholine

• So how are they different?

Succinycholine can bind to the nicotinic receptors for a more prolonged period so it has a very long duration of action It forms a stable binding with the receptor and it is more resistant to degradation be acetylcholinesterases and they can depolarize the muscle fiber.

Mechanism of action

• Succinylcholine attaches to the nicotinic receptor and acts like ACh to depolarize the junction

• Succinylcholine is more resistant to degradation by AChE

• Succinylcholine persists at high concentrations in the synaptic cleft

• Produces constant stimulation of the receptor

• How is it degraded then? By pseudocolonysterasis

Mechanism of action

• Phase I: opening of nicotinic receptor associated Na+ channel and that results in depolarization of the post synaptic membrane in the same way that Ach will do , so Succinylcholine benid an antagonist to the receptor will bind to the receptor and cause sodium ions to flux in → fasciculations : transient twitching of the muscle

• Phase II: continuous binding leads to receptor desensitization means that it blocks any signals coming from released ACh → flaccid paralysis

Actions:

• Brief muscle fasciculations (causes muscle soreness) → flaccid paralysis

• The respiratory muscles are paralyzed last

• Redistribution to plasma is necessary for metabolism (therapeutic benefits last only for a few minutes).

• The Succinylcholine is not metabolized by the cholinesterases located at the junction so that allows the agent to bind to the nicotinic receptors for a longer period of time

Pharmacokinetics

• IV

• Short duration of action (onset ~ 30 seconds)

• Eliminated by redistribution and hydrolysis by plasma pseudocholinesterases.

• Drug effect disappears upon discontinuation

Adverse effects

A. Malignant hyperthermia

-rare, life-threatening condition

-caused by excessive skeletal muscle aerobic metabolism

-circulatory collapse ,extremely elevated body temperature that can progress into failure of the circulation and that will lead sometimes to death

-antidote: dantrolene (it can be used in cases of severe malignant hyperthermia that develops suddenly)

B. Apnea

-due to paralysis of diaphragm

-due to rapid to rapid release of K+(because of this rapib releasing the more prolonged paralysis takes place)

C. Hyperkalemia

-Succinylcholine increases potassium release from intracellular stores into the extracellular space and into the blood and that can cause

problems in patients with electrolyte imbalances or those who take drugs such as digoxin or they have the uritecks or patients with chronic kidney failure

Therapeutic Uses of Neuromuscular Blockers

Main Therapeutic Use: Adjunct to General Anesthesia

- Muscle relaxation: orthopedic, abdominal surgeries

- Facilitation of intubation, mechanical ventilation

- Succinylcholine during electroconvulsive therapy