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Overview on Neuronal Excitability and Clinical Connections

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ABSTRACT: Like muscle fibers, neurons are also electrically excitable. This excitable cellexhibits electrical potential difference across the cells. This communication is done by two types of electrical signals: (1) Graded potentials and (2) Action potentials. The production of graded potentials and action potentials depends on resting membrane potential and presence of the ion channels. The electrical signals are produced by the different types of ion channels that include leak channels, ligand gated channels, mechanically gated channels, voltage gated channels. To communicate with another parts of the body and their integration is done by this action potentials. The clinical interrelation with the voltage gated channels includes neurotoxins and local anesthetics. Neurotoxins are specific blockers of voltage gated sodium channels whereas the local anesthetics are non-specific sodium channels blockers. A concise information about the relation between neurotoxins and deep discussion on the types of ion channels and there functioning issummarized here.

KEYWORDS: Ion channels; graded potentials; action potentials; depolarization; repolarization; hyperpolarization; neurotoxins; local anesthetics

I. INTRODUCTION:

Neuron excitability is the basis for the conversion of the stimulus into electrical signals i.e. action potentials. The potential is the result of difference of ion concentration between interstitial fluid and the extra cellular space[1]. The first part of the axon which is near to the axon hillock is the main trigger zone from which the signals are sent to the other parts of the neuron[2]. To understand the potential propagation, we need to discuss about the channels which help the movement of the stimulus.

There are four types of ion channels that help in the production of electrical excitation. These ion channels allow the ions to move out and in the plasma membrane allowing in creating difference in electrochemical gradient. The ions i.e. cations and anions move across ion channels. The electrical current is produced with the movement of the ions[3]. Different types of ion channels are explained in the following

1. **LEAK CHANNELS:** The leak channels open and close randomly based on the concentration of ions. There is more k+ ion channels than Na+ ion channels. These are present mostly in all types of neurons,axons, dendrites.[4]
2. **MECHANICALLY GATED CHANNELS:** These open and close based on the mechanical stimulation due to vibrations mainly from the sensory receptors. They are present dendrites of touch,pressure,pain receptors[5]
3. **LIGAND GATED CHANNELS:** The channels open and close when the ligand bind with the receptors. Ligands include neurotransmitters, hormones etc. These are mostly present in dendrites of sensory neurons, dendrites and cell bodies of interneurons and motor neurons.[6]
4. **VOLTAGE GATED CHANNELS:** These open and close in accordance with the membrane potential difference. These are very important in generation of action potentials.These are present in all neurons without any exceptions.[7]

The main targets in local anesthetics are voltage gated channels more specifically sodium ion voltage gated channels. The mechanism of blocking the channels will be discussed in detail after explanation of action potentials.

Resting membrane potential build up when there is difference between number of ions in interstitium and ECF. When there are equal number of positive and negative ions inside and outside the membrane leads to neutral potential called resting membrane potential. The units are volts or millivolts (1mV=0.001V) and is measured using instrument called voltmeter. A typical average value is -70mV here the minus describes that there is a high concentration of negative ions inside the cell when compared with extracellular fluid[8]. Resting membrane potential appears due to following factors

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1. **Unequal distribution of ions:** A difference of concentration leads to potential. ECF is rich in Na+ and Cl- whereas intracellular fluid has K+ and phosphates in the form of ATP, amino acids in proteins. As we already discussed there are more K+ leak channels when compared with Na+ leak channels so more and mor K+ ions move out of membrane making inside negative. In this way there creates and potential difference.
2. **ELECTROGENIC NATURE OF Na+-K+ ATPase**: More K+ outflux and less Na+ influx but eventually again K+ leak back down the concentration gradient. Na+-K+ ATPases expel three Na+ for each two K+. In this way more positive ions are removed from membrane making it more negative.
3. **INABILITY FOR ANIONS TO MOE OUT OF CELL**:There are no specific channels for anions to move in and out so the potential difference cannot be neutralized.[9]

ACTION POTENTIALS: This is the sequence of steps in which there is a production and propagation of impulse due to changes in ion concentration and leading to open and closing of ion channels based on type and concentration of ions present inside and outside the membrane
There are following phases in action potential propagation which include

DEPOLARISING PHASE: In this phase voltage gated Na+ ion channels open rapidly leading to influx of high amounts of Na+ ions into cell. This makes the membrane potential from -70mV to -55mV then gradually making it to +30mV.

REPOLARISATION PHASE: Now the inactivation gate of Na+ ion channels close and K+ channels open making membrane potential to again reach the resting membrane potential.

AFTER HYPERPOLARISATION PHASE: In this phase still voltage gated K+ ion channels are open leading to more negative potential inside the cell.[10]

When there exists the first action potential being proceeding the next potentials does not stimulate another generation of next potentials.

REFRACTORY PERIOD: This is time in which another action potentialdoes not create even when there is a highly strong stimulus. In this period the inactivated gates of Na+ ion channel does not open so there is no creation of any action potential[11].

Now coming to the action of local anesthetics and neurotoxins

LOCAL ANESTHETICS:

LOCAL ANESTHETICS act mainly by preventing the entry of Na+ ions into the membrane. As the ions doesn't enter cell the membrane does not undergo polarization and does not allow the cells to propagate the stimulus. These act by increasing refractory period, and decreasing the speed of firing rate. Now let's see in detail description of local anesthetics

HISTROY: In about thousands of years back coca leaves where chewed by psychotropic patients to make them prepared before surgery. Firstly in 1860 cocaine was isolated from the leaves and prescribed for local anesthesia next in 1885 this was first used in reversible corneal ophthalmologicalsurgery. Next rapid tests where made on different substances and synthetic anesthetics where developed the first synthetic anesthetic drug was found in 1905, procaine.[12]

STRUCTURE: anesthetics contain aromatic ring attached with ester or having an amide bond (makes the drugs hydrolysis) to a basic side chain, these are weak bases (except benzocaine) with the pH value of 8-9. This range is very important as it makes them penetrate into axon and start their action.[13]

MECHANISM: When the drug is administered due to amide bond it is hydrolyzed and penetrate the nerve sheath entering axon bind with the Na+ channels specially to inactivated state and block them. When the drug is administered in low dosage it decreases the rate of action potential where as when administered in high doses it leads to completely stops firing action potentials. The unique character of these drugs includes use-dependent blocking which means the more open channels the more blocking can be observed.[14]

There are quaternary amine local anesthetics these acts when the channels are open but tertiary amine local anesthetics block even if the channels are not open so according to use, we can administer the drugs which we require.[15]

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Table 1:[16]

DRUG	ONSET	DURATION	PLAMA HALF LIFE	IMPORTANCE	ADRs	METHODOF ADMINISTRATION
Cocaine	Medium	Medium	Nearly 1 hour	Rarely used, mainly in upper respiratory tract	CVD, CNS	Infiltration anesthesia
Procaine	Medium	Short	Less than 1 hr	No longer used	CNS: anxiety, respiratory depression, restlessness CVD: bradycardia, vasodilation	Infiltration anesthesia
Mepivacaine	Rapid	Medium	Nearly 2hrs	Less vasodilation administered without vasoconstrictor	As procaine	Infiltration anesthesia
Lidocaine	Rapid	Medium	Nearly 2 hrs	Widely used	Less tendency to cause CNS effects	Surface, nerve block, epidural, spinal, intravenous anesthesia
Tetracaine	Slow	Moderate	Nearly 2 hrs	Mainly before venipuncture	As lidocaine	Nerve block
Bupivacaine	Slow	Long	Nearly 2hrs	Widely used	As lidocaine but more cardiotoxicity	epidural
Atricane	Rapid	Short	Only half an hour	Used in dentistry	As lidocaine	surface

ADVERSE REACTIONS: The main effect can be seen on cardiovascular system and on central nervous system leading to arrythmias and depression and respiratory system related problems. Dizziness, headache, blurred vision, numbness are also experienced.[17]

EXAMPLES include Cocaine, Procaine, Lidocaine, Bupivacaine, Tetracaine, Prilocaine [18]etc.… let us see in detail with each drug.

II. DISCUSSION:

The physicians should calculate the maximum dose with accordance with body weight and along with the previous complications. When there is a need to decrease concentration of anesthetics then it is diluted with sterile injectable saline also addition of epinephrine improves safety and then administered.Technique of injection is also important for safety of patient this include inspiration before injection that is necessary to decrease the adverse reaction(rise in serum levels). This is done by using 22- or 25- gauge needle for scalp and 25- or 27- gage needle for face and neck. In this way anesthetics are very important in each and every surgery.[19]

III. CONCLUSION:

Hence from the above discussion I conclude that property of neuronal electrical excitability is the main important in generation and propagation of action potentials which are essential for the communication of neurons in nervous system. Initiation of potential depend on the voltage gated Na+ ion channels which are mostly located in sensory receptors like touch, pain, hear. So, blocking these Na+ ion channels will make the axons do not respond to stimulus and do not undergo excitation. In this way local anesthetics doesnot create pain when administered to patient before undergoing surgery.

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