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RESEARCH ARTICLE

Survey the Effect of Sodium Channel Voltage to Prevent the Production of Action Potential in order to Create a Local Anesthetic and its Simulation by MATLAB Software

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Abstract

In this study, survey the sodium channel effects on blocking the conduction of action potential and Simulation of sodium channel voltage reducing process have been explored. The simulation has been performed by using the Matlab software. First by using Hodgkin Huxley equations and simulation of them, action potential waveform is obtained which indicates that the nerve signals can be transmitted by it. The next step is when the pain is felt in the body and we will use anesthetics drugs to relieve pain. After using drugs, we know that the more, the effect of drugs on the body to create a local anesthetic increases, Sodium channel voltage is reduced and this will continue until the voltage reaches to zero and at this moment, the sodium channel is closed. Thus, sodium ions can not pass through the sodium channel and the action potential will not be producted and propagated inside of the axon. As a result, the body doesn't feel pain and in other word, local anesthesia occur and this is clear in the simulation.

INTRODUCTION

Neurons usually transmit information through two mechanisms of electrical and chemical signals. usually information within a neurons is transmitted by electrical signal that is propagated by the action potential. This is the resting membrane potential before the action potential begins. The membrane is said to be polarized during this stage because of the –70 millivolts negative membrane potential that is present[1]. When the membranes of neurons is stimulated, A depolarization causes the opening of the voltage gated Na+ channels. At this time, the membrane suddenly becomes very permeable to sodium ions, allowing tremendous numbers of positively charged sodium ions to diffuse to the interior of the axon[1]. This causes the flow of sodium ions into the cell . Then, when the Na+ concentration gradient is balanced between inside and outside the cell, the penetration of Na+ is stopped. Na+ channels are closed and become temporarily insensitive to depolarization. Subsequently, voltage gated K+ channels open and allow movement of potassium ions is given. Then the membrane potential come back to the resting state. This phenomenon is called action potential and takes only a few milliseconds[2],[3] .An action potential causes partial depolarization of adjacent areas, activating voltage gated Na+ channels in the adjacent areas and thus, causes propagation of the action potential along the axon.

Local anesthetics block the function of voltage gated Na+ channels and thus block conduction of action potenials. In other word, local anesthetics are drugs used to prevent or relieve pain in specific regions of the body. Currently used local anesthetics bind to voltage gated Na+ channels in peripheral nerves, block sodium movement through sodium channel, and thus block nerve conduction[4]. According to the above description, with simulation of sodium

channel voltage, we show that by reducing the sodium channel voltage, action potential will not be able to produce. Thus, the nerve impulses are not transmitted and cause numbness.

2.Material and Methods

2.1 Local anesthesia

Local anesthetics are a group of drugs that they have ability to prevent the entry of sodium ions into the axon. Also prevents the production and propagation of action potential inside of axon .Their other actions, however, such as prevention of axonal sprouting and effects on G-protein-coupled receptors and on conductance of ions in addition to sodium that might be important in the management of pain[5].

Noci receptors in the sensory nerve terminals which are stimulated by various factors and convey the pain to the posterior horn of the spinal cord . In the posterior horn of the spinal cord and with release of neurotransmitter like glutamate, secondary neuronal excitation[6]. The action potential is sent for processing or response of central nerves system will produce. Local anesthetics with Inhibition of sodium channels, prevent to production and propagation of action potential. Thus, action potential will not reach the end of the nerve and neurotransmitter transporter, will not be able to produce the sense of pain and sensory nerve terminals transmit pain message to the higher centers and inhibit the sense of pain , Of course this is reversible, no pain is felt.

2.2 Mechanism of action

Local anesthetics reversibly bind to voltage gated Na+ channels, blocking Na+ movement through the channels, and thus block the action potential and neural conduction. At adequate dosage, these drugs should reversibly inhibit conduction of all neurons. Both the pharmacological effects and most toxic effects of local anesthetics arise from this mechanism[4].

Na+ channels are heterotrimeric transmembrane proteins, consisting of α (Mr~260 kDa), β1 (36 kDa) and β2 (33 kDa)subunits. The α subunit contains four homologous domains (I-IV), each domain contains 6 α-helical transmembrane segments (S1-S6). The S5 and S6 segments of the four domains form a pore that allows the passage of Na+ ions. The voltage sensor is located in the 4th transmembrane segment of each domain which is rich in positively charged residues. The loop between domain III and IV serves as an inactivation gate which folds to block the pore shortly after opening of the channel. The binding site for local anesthetics is located in the S6 transmembrane domain of segment IV close to the intracellular side of the membrane[4].

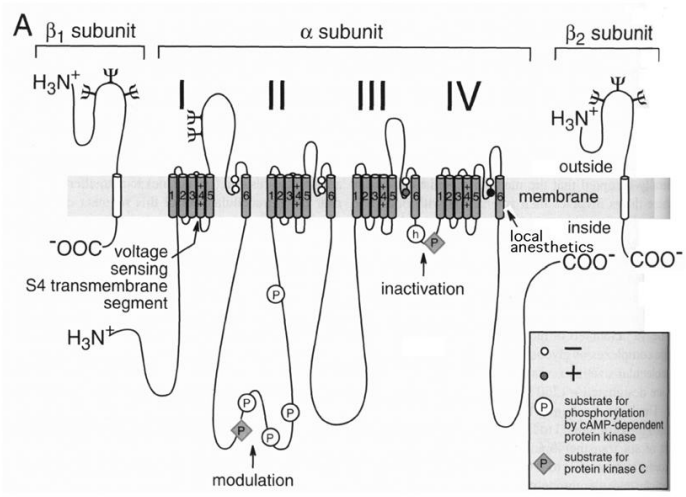


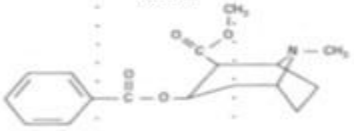
Fig1. Schematic of the voltage dependent sodium channel [4]

2.3 Chemistry of local anesthetic

Today, the local anesthetics that most widely used include procaine, lidocaine, bupivacaine and tetracaine. Most of the drugs consist of a hydrophobic group (often an aromatic ring) connected by an intermediate chain (containing an ester or amide bond) to an ionizable group (usually a tertiary amine group)[4],[7].

Local anesthetics are weak bases. The pKa for most local anesthetics is in the range of 8.0-9.0. A balance of charged and uncharged forms is present in the body. The ratio between the cationic and uncharged forms of these drugs is determined by the Henderson- Hasselbalch equation (Log (cationic form/uncharged form) = pKa-pH). The uncharged form is more lipophilic and thus more rapidly diffuses through the membrane. However, the charged form has higher affinity for the receptor site of the sodium channel[4],[8].

Table1.structure and properties some of ester and amide local anesthesics [4]

	Lipophilic — Intermediate chain — Amine substituents	Potency (procaine=1)	Duration of action
Esters			
Cocaine		2	Medium
Procaine (novocain)		1	Short
Tetracaine (pontocaine)		16	Long
Benzocaine		surface use only	
Amides			
Lidocaine (xylocaine , etc)		4	Medium
Mepivacaine (carbocaine , Isocaine)		2	Medium
Bupivacaine (maracaine)		16	Long
Etidocaine (duranest)		16	Long
Prilocaine (citanest)		3	Medium

3. Simulation

In this section, simulation of action potential waveform and sodium channel voltage decrising process is performed. Since the sodium ion is one of the most important and influential in generating action potentials and conduction of nerve impulses, the action potential waveform for sodium channel voltage changes caused by the use of anesthetics, is simulated.

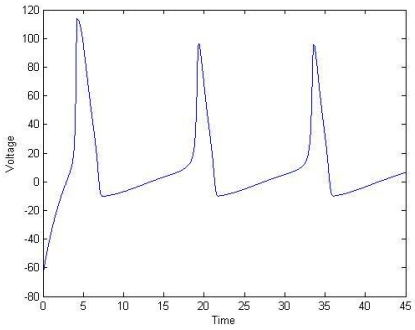


Fig2.Action potential

Simulation of action potential due to the sodium channel voltage changes as follows.

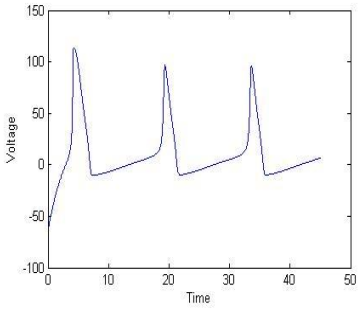


Fig3.Action potential when V_{na} =50 mv

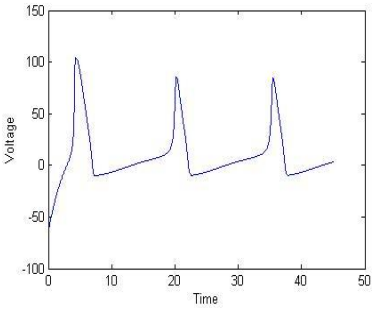


Fig4.Action potential when V_{na} =40 mv

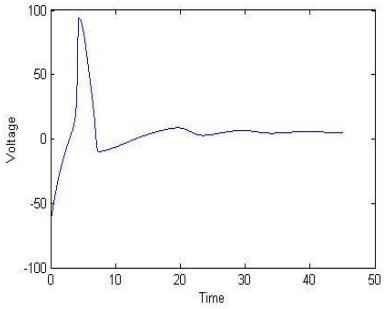


Fig5.Action potential when V_{na} =30 mv

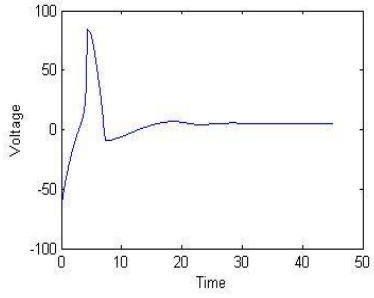


Fig6.Action potential when V_{na} =20 mv

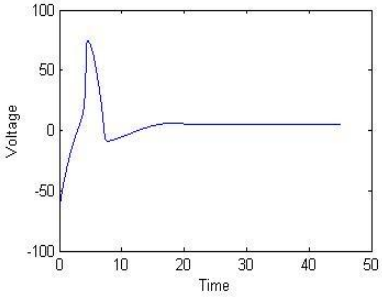


Fig7.Action potential when V_{na} =10 mv

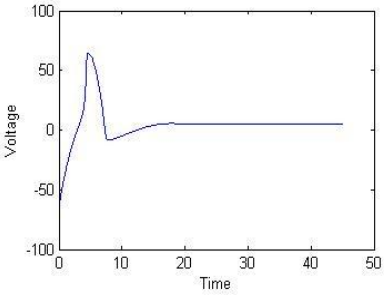


Fig8.Action potential when V_{na} =0 mv

The results show whatever sodium channel voltage decreases, Action potential waveform starts to change and continues until the sodium channel voltage reaches to zero and action potential can not be generated , thus the nerve signals, will not be able to be transferred within the axon. In other word, Due to the lack of pain creation, we can say that numbness has occurred.

Result and Discussion

In this paper, the simulation of Hodgkin Huxley equations is performed and the waveform of action potentials that are based on sodium channel voltage change obtained. we see that when the anesthetic drugs are used, changes in cell membrane occurs or in other word anesthetic drugs reduced sodium channel voltage. The voltage reduction leads to closure of the sodium channel and sodium ions will not be able to pass through the channel and action potential can not be produced in this case and in other words we can say that is blocked . By blocking the action potential, nerve signals are not transferred and no pain will not be felt in the body and local anesthesia occur.

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