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SECTION 9. Chemistry and chemical technology.

SURVEY THE LOCAL ANESTHETIC DRUGS MECHANISM AND ITS EFFECT ON SODIUM VOLTAGE CHANNEL

Abstract: *The transmission of nerve impulses inside of axon done by action potential wave and pain is felt in body. Since the sodium ions have a key role in production of action potential wave, in order to prevent of pain feeling creation, we use local anesthetic drugs, because they have ability to prevent of entry of sodium ions into axon and also prevent of production and propagation of action potential wave inside of axon. Hence, in this paper three kind of local anesthetic drugs base on lasting effect, structure and some properties of them in order to produce local anesthetic have been explored. Also action mechanism of these drugs and how they can effect on sodium channel and some common methods of local anesthetic production presented. Finally, it can be seen that by using local anesthetic drugs, sodium channels blocked and the action potential will not be producted and propagated inside of the axon. As a result, the body doesn't feel pain and local anesthetic occur.*

Key words: *Local Anesthetic, Action Potential, Axon, Sodium Channel, feeling pain.*

Language: *English*

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Introduction

Local anesthetics (LA) are agents which cause local temporary intensitivity with fully preserved consciousness due to reversible paralysis of peripheral sensory nerves. They affect the cellular membrane in which they block the sodium channels and inhibit the creation and transmission of the nervous impulse along the nervous fiber. The application method of local anesthetics and the way of their action depend on their physicochemical properties (stability, solubility, pKa), which are in connection with the protein-binding properties[1],[2],[3],[4]. Although given locally, local anesthetics may exert a systemic effect, as they are transferred through blood to other areas (kidneys, liver). These systemic effects which are dependent to the concentration of local anesthetics in the blood usually cause sedation, nausea, vertigo and anxiety. Local anesthetics are used in surgery, dentistry, ophthalmology and cardio-therapy. They are also used for the temporary relief of pain from insect bites, burns, and other types of surface wounds [5],[6],[7].

Local anesthetic

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 [8],[9]. Other actions of these drugs, however, such as anti-inflammatory actions by interaction with G-protein receptors [10], are also thought to be relevant to their use to prevent or treat pain.

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[11]. 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 [8].

Physical and chemical properties of local anesthetics

According to chemical structure, local anesthetics can be: alkaline esters, ethers, ketones, amides and anilides . A molecule of a local anesthetic consists of a hydrophilic part which is connected to the lipophilic part via the alkyl interchain and an amide or ester group (Fig1)[2],[5],[7]. Physicochemical properties of local anesthetics affect the potency, speed of origination, depth and lasting of local anesthetic action. The chemical characteristics of local anesthetics' molecules directly affect their clinical characteristics. Drugs which contain an ester group metabolize easier and are less toxic (procaine and chloroprocaine)[12]. The lipophility determines the relative potency, while binding to blood plasma proteins has an influence on the lasting of the effect. pKa, i.e. pKb values directly correlate with the beginning of the local anesthetic effect. According to above mentioned properties, we can classify the local anesthetics which are used clinically into three groups[1]:

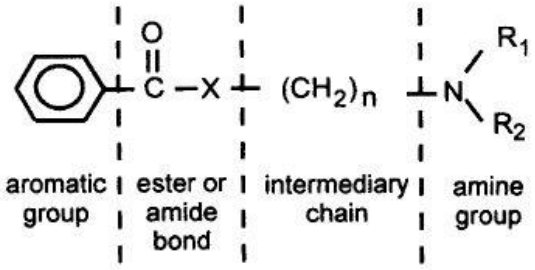

Figure 1 - Basic general structure of local anaesthetics [13].

1. Moderate potent anesthetics with shortlas ting effects (chloroprocaine and procaine)

Some of properties of procaine is as follow:

A. Ineffective topically
B. Must be administered by injection (usually with epinephrine to delay absorption)
C. Plasma esterases degrade it rapidly
D. Can cause allergic reactions

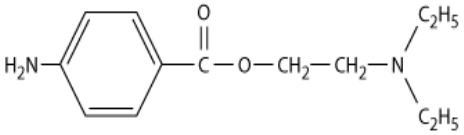

Figure 2 - Structure of Procaine.

2. Moderate potent anesthetics with moderatelasting effects (prilocaine, lidocaine and carticaine)

Some of properties of lidocaine is as follow:

A. Amide-type drug
B. Topical or injection
C. Rapid and prolonged anesthesia
D. Allergic reactions rare
E. CNS and cardiovascular toxicity can result

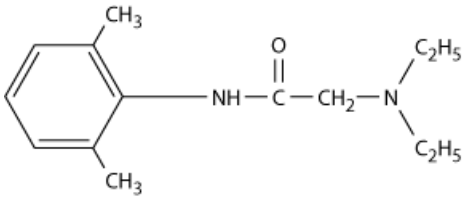

Figure 3 - Structure of Lidocaine.

3. High potent anesthetics with long lasting effects (etidocaine, tetracaine, ropivacaine and bupivacaine) [1],[14],[15].

Some of properties of lidocaine is as follow:

A. prolonged duration of action; up to eight hours when combined with epinephrine. It is therefore used whenever long action is required (post-op analgesia; prolonged surgery etc).

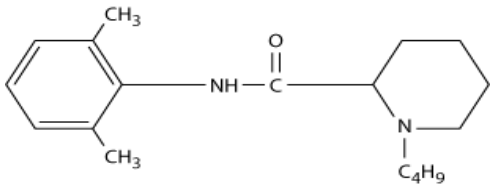

Figure 4 - Structure of Bupivacaine.

The Mechanism of Action

The mechanism of action of local anesthetics is achieved by a reversible block of the sodium channels in the cellular membrane of the nerve cell and the influx of sodium ions into the cell[7]. Among the most important stabilizers there are many substances used clinically as local anesthetics, including procaine and tetracaine. Most of these acts directly on the activation gates of the sodium channels, making it much more difficult for these gates to open, thereby reducing membrane excitability. When excitability has been reduced so low that the ratio of action potential strength to excitability threshold (called the "safety factor") is reduced below 1.0, nerve impulses fail to pass along the anesthetized nerves[16].

Local anesthetic producing common methods

A. Surface (topical) anesthesia
B. Intrasynovial anesthesia
C. Regional anesthesia
D. Infiltration anesthesia
E. Intravenous regional local anesthetic
F. Spinal anesthesia

Effect of Local anesthetic on sodium channel

The mechanism by which local anaesthetics block voltage-gated sodium channels has been a long intriguing puzzle for electrophysiologists. The effect of these molecules depends upon membrane potential, channel conformation, pH and access to the ion-conducting pore[17].

QX 314 is a quarternary derivate of the local anesthetic lodocaine that has a permanent positive charge . it is not in clinical use but has interesting features that have helped to elucidate the mechanism of blocking Na channels . this drug blocks the channels only when applied to their intracellular side[19]. Most local anesthesics, except benzocaine, are amine compounds, which are charged at a pH below 6. The uncharged form is lipid soluble[20]. Biophysical calculations based on the electrical field across the cell membrane suggested that the binding site is at a distance from the external surface of the membrane of approximately 60% of the membrane diameter (an estimate that agrees fascinatingly well with what we now know from the moleculer structure)[21]. This finding gave rise to the first ideas about the blocking mechanism : the receptor is in the pore; the charged form acts on the receptor and the drug molecules have topass through the lipid membrane to act. Another blocking characteristic was observed at that time: nearly full size Na currents could be elicited during the first depolarizing impulse in the presence of a local anesthetic, but subsequent impulses elicited smaller an smaller peak currents. It was suggested that the drug binds cumulatively and that this block needs open channels. This accumulation of inhibition has been called use-dependent block or phasic block.

Subsequently, the guarded receptor hypothesis was proposed. Suggesting that the receptor is protected in the pore and that channel needs to be open before it can be blocked. The impact of use-dependent block became manifest at higher firing frequencies of nerve fibers, where lower concentrations of local anesthetics were needed to block compound action potentials[18] .

Conclusion

In this paper, survey the local anesthetic drugs and chemical structure of them and also some properties of these drugs which is depend on the different conditions can be used have been explored. As mentioned, sodium ions play main role in production of action potential wave and with transmission nerve signals inside of axon, lead to a sense of pain. Hence, to prevent of pain creation and its feeling, we use local anesthetic drugs and due to the properties of these drugs and with respect to the said mechanism, Sodium ions are prevented from

entering into the axon and will not be able to pass through the channel, in other word, sodium channel blocked,and action potential can not be produced. Thus, nerve signals can't transferred along the axon and no pain will be felt in the body and local anesthetic occur.

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