Review Article

Comprehensive Review on Structural Elucidation of Local Anesthetic and It's Adverse Effects

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ABSTRACT

Drugs that are classified as local anesthetics abolish the conduction of nerve impulse in afferent and efferent nerve fibers. So that any signal or stimulus are not transmitted effectively to the brain, so motor signal is not transmitted effectively to other effector organ such as muscles. Acute or Chronic pain or sensation of pain during procedures can be prevented by applying local anesthetics. Understanding about our Physiological nerve fiber and transmission of pain sensation is very much important for mechanism of action of local anesthetic. Mainly, Local anesthetics involved with nerve ending or surrounding nerve trunk and combined with the sodium ion (Na+) channel sites on the nerve membrane. They affect membrane action potential as well as depolarizing state by reducing Na+ passage through the sodium ion channel, though blocking both generation and conduction of nerve impulse. In the same way blocking both generation and conduction of sensory nerve impulse. Local anesthetics used for dental surgery; post operation pain remove. Here, we focused on review of research progress on local anesthetics, various aspect of mechanism of action, design, synthesis route, adverse or toxicological effect of new molecules (Local anesthetic).

Keywords: Local anesthetics, Nerve fiber, Acute or chronic Pain, Nerve trunk, Depolarized, Action potential, Post operation.

INTRODUCTION

Local anesthetic produces their therapeutic effect via nervous system. Nervous system main function to receive ongoing Stimulation and the transmit stimulus through nerve cell or neuron.[1] A neuron is a single cell typically consist of cell body connected with axon terminal through axon hillock.[2] Axon Terminal is the part of presynaptic component of the nerve synapse and also contain some specific number of neurotransmitters to be released upon stimulus of action potential "message".[2] Most of the case, axon is too long in size for transmitting the signal to the terminal ending by the principle of simple chemical diffusion.[1] Though message received by the neuron cell body is transmitted as electoral impulse to nerve terminal or axon terminal or nerve ending.[3]

The electrical potential or action potential or nerve impulse is most of the case generated at the axon hillock region of the cell body where the axon emerges[1]. Then electrical impulse is conducted through the nerve by changes in the charges distribution across the neuronal membrane[4]. The rate at which impulse will be conducted that depends on the thickness of the axon and the presence or absence of myelin.[3] So Myelinated neuron (120 m/s) can transmit impulse more quickly than non-myelinated neuron(10 m/s)[4].

Ion movement(ca2+,k+,Na+) through the neuron due to the result of electrical potential difference between inner and outer surface of the cell membrane.[1] At resting condition neurons have resting potential of about -70 mV. This means that inside of neuron have more anionic charge than external portion of neuron.[2]. For starting of transmitting impulse through the neuron, internal charge of neuron should be increased to about 20 mV to -50 mV (Firing Threshold).[3] During action potential neuron internal charge should be increased to +35 mV (Depolarized).[3]

From Resulting of action potential, nerve impulse reaching from axon hillock to the terminal end of neuron.[2] So, result in release of neurotransmitter from nerve terminal that cross the synaptic cleft to the adjacent neuron or effective neuron.[4] Then produce a positive sensation t (That is inhibited by local anesthetic through inverse mechanism).

History Behind Local Anesthetics

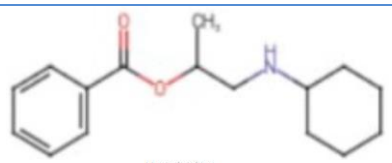
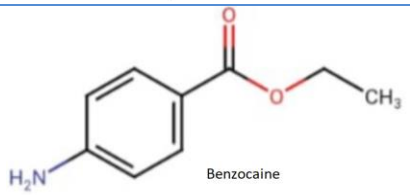
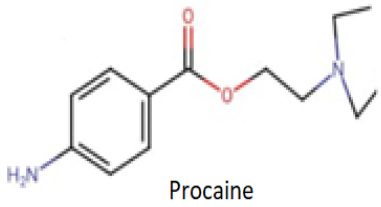
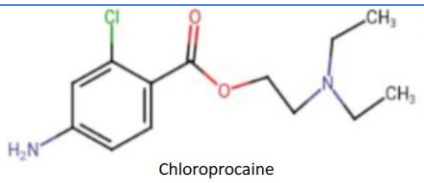
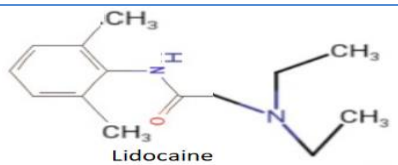
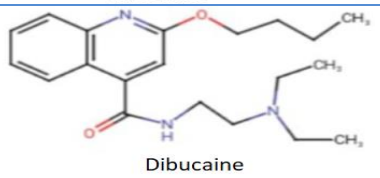
The first local anesthetic, cocaine was discovered to have anesthetic properties in the late 19thcentury. At first cocaine found in the leaves of the coca shrub (Erythroxyloncoca).[5] Then, Albert Niemann first extracted cocaine in1860, he had tested his newly extracted compound.[6] Sigmund Freud have studied cocaine's Pharmacological actions.[5] Then Carl Koller have introduced cocaine into ophthalmological surgery as local anesthetics in1884.[6] Besides that, cocaine is used as infiltration and conduction block anesthesia that is proved by Halstead.

Comparison Of Structure Activity Relationship of Different Local Anesthetic:

In local anesthetic, lipophilic portion is essential for the activity, binding to Domain of the Na+ Channel, potency etc.[8] This lipophilic portion of the molecule is consisting of aromatic group directly attached to the carbonyl group (Amino ester series) or 2,6 dimethyl-phenyl attached to carbonyl group through Amino group (Amino amide series).[9,10]

Chemical Classification Local Anesthetic Drug

Table 1: Chemical Classification Local Anesthetic Drug

SL No	Derivatives name	structure of the drug	Properties of the drug	Ester Linked or Amide Linked
1)	Benzoic Acid Derivatives	 Hexylcaine	a) White powder. b) Soluble in both water as well as chloroform. c) Local anesthetic agent consider as soluble in all purpose.[7]	Ester linked
2)	P-Amino Benzoic Acid Derivatives	 Benzocaine	a)White crystalline powder. b) soluble freely in alcohol and slightly soluble in water.[7]	Ester linked
	P-Amino Benzoic Acid Derivatives	 Procaine	a)White crystalline powder or colorless crystalline powder. b)Soluble in both alcohol and water. c)Low local irritation as well as low systemic toxicity.[7]	Ester Linked
	P-Amino Benzoic Acid Derivatives	 Chloroprocaine	a)Water soluble but insoluble in alcohol.[7]	Ester Linked
3)	Anilide derivatives (2,6 Xylidins)	 Lidocaine	a)White crystalline powder. b)Soluble in water but freely soluble in alcohol.[7]	Amide linked
4)	Miscellaneous	 Dibucaine	a)White crystalline powder. b) soluble in water, alcohol and chloroform. c)It has slightly odor. d)It is slightly hygroscopic.[7]	Amide linked

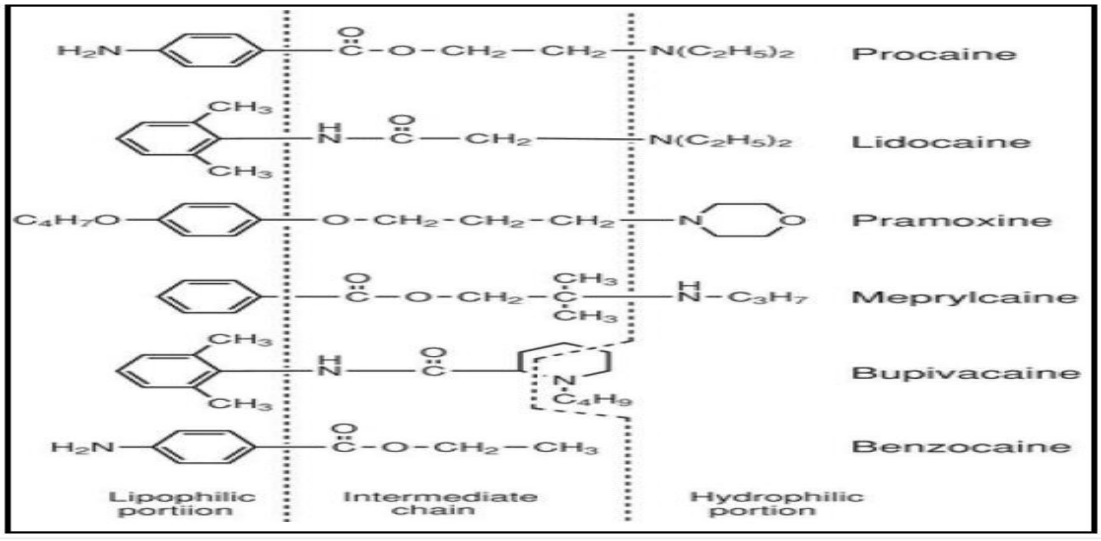
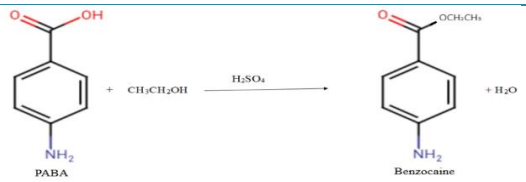
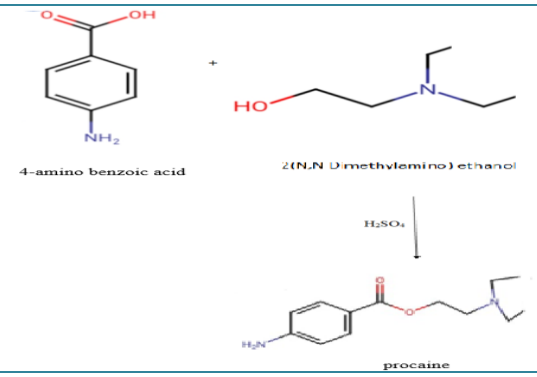
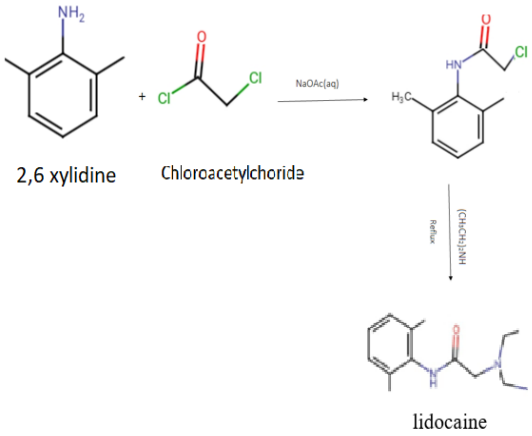
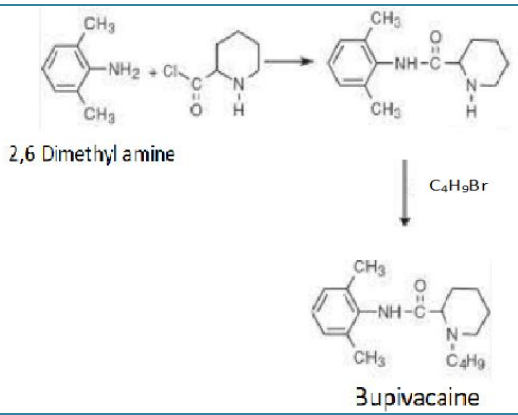


Figure 1: Comparison of Structure activity Relationship of different local anesthetic[8]

Local Anesthetics Synthesis and SAR:

Table 2: Local Anesthetics and SAR

SL NO	Local anesthetic name	synthesis	SAR (Structure Activity Relationship)
1)	Benzocaine		a) In benzocaine, aromatic moiety with amino group (Aniline) is lipophilic so it is essential for potency, activity, and also for binding with DIV domain of Na+ channel. [7] b) Carbonyl moiety is essential for proper activity of local anesthetic.[11] c) Ester moiety helps to local anesthetic for affinity to binding with Na+ channel.[12] d) Terminal ethylene moiety increases lipophilic character of local anesthetic so activity has to be increased .[13,14]
2)	Procaine		a) Procaine has aromatic ring with amino group (Aniline) that is lipophilic in nature so potency as well as activity of procaine is increased [7]. b) Tertiary amin in procaine is hydrophilic in natureso hydrophilic portion in procaine increased aqueous solubility of procaine.[15] c) Carbonyl group in procaine is essential for activity of procaine as local anesthetic [16] d) Ester moiety in procaine increased affinity to binding site of Na+ channel .[7,17]
3)	Lidocaine		**Aryl group** i) Aryl group attached to the carbonyl group(sp^2) through amino group.[18,19] ii) Methyl group at 2 and 6 position of phenyl group increase the activity of the compound and also increases the steric hindrance to hydrolysis the product .[20] iii) Any substitution on the phenyl group increases the potency by inducing zwitterion configuration in the molecule.[18,20] **Amino-alkyl group:-** i) Amino group (Tertiary amine group) have a capability to form salt formation and also this amine group is hydrophilic.[9,19] ii) Tertiary amine group is important for less irritating compound because primary and secondary amine group have irritating characteristic.[19,20] **Carbonyl group:-** Carbonylgroup is necessary for activity of local anesthetic.[20]
4)	Bupivcaine		**Aryl group:-** a) Phenyl group is essential for increase the activity of bupivacaine .[19] b) If hetero cyclic ring is present in place of phenyl ring then activity also increase.[19] **Amino-alkylgroup:-** a) If amino alkyl group is hetero cyclic ring the activity and potency will be increased.[20] **Carbonyl group:-** a) Oxygen group increase the potency of the compound.[20]

Local Anesthetics Uses and Adverse Effects:

Table 3: Local Anesthetics Uses and Adverse Effects

Sl No	Local Anesthetic Name	Uses	Adverse Effect
1)	Benzocaine	i)Benzocaine is used for relieve pain from toothache, sore, sore gums/throat, mouth/gum injury.[21] ii)It is used to reduce sensation during dental procedures, injections, or other minor procedures that cause pain and discomfort.[22] iii)Benzocaine is used to relieve local pain such as insect bite, sunburn, other minor burns or sore throat.[23,24] iv)Benzocaine is used as a treatment for premature ejaculation.[25] v) Benzocaine can help to lower the excessive level of sensation that can contribute to early ejaculation.[26]	a) Benzocaine has life threatening side effect that is methemoglobinemia that's why unknown symptom occurred like cyanosis, hypoxia, dyspnea.[27] b) Some other adverse effect of benzocaine is bradycardia, hypotension, cardiac arrest, convulsion, drowsiness, dizziness, edema, allergic reaction etc. [28] c)Hypersensitivity occurred in children and elderly people .[28,29] d) Benzocaine may cause tenderness, itchiness, edema to applied portion of skin.[30]
2)	**Procaine**	i) Procaine most commonly used for spinal anesthetics.[31] ii) Procaine produces the greatest vasodilation of all clinically used local anesthetics.[32] iii) Procaine is used for infiltration anesthesia.[33] iv) Procaine can be used as epidural anesthetics.[34] iv) Procaine can be used as in sensation of any pain.[35]	a) Allergic reaction (Difficulty breathing, closing of the throat, swelling of the lips, tongue, face, or hives) .[36] b) Chest Pain or slow or irregular heartbeats.[37] c) Dizziness or drowsiness.[38] d) Anxiety or restlessness.[38] e) Nausea or vomiting [36] f) Trembling, shaking or seizures (convulsions)[38]
3)	**Lidocaine**	i) Lidocaine has been used as a wide range as local anesthetic[39,8]. ii) Lidocaine is usable where local anesthetic with intermediate duration of action is needed[39]. iii) Lidocaine is used as antiarrhythmic agent in some cases[39,8].	a) Tachycardia in major case and bradycardia in minor case.[40] b) Depressive mood, depressive mood with paranoid.[41,42] c) Visual and auditory hallucination.[43] d) Dizziness, light headiness, drowsiness, limb paranesthesia, visual disturbances.[44,45] e) Blurred vision, confusion, disorientation, cognitive difficulties.[46,47]
4)	**Bupivacaine**	i)Bupivacaine is used for local infiltration peripheral nerve block, epidural and caudal blocks.[48] ii)Bupivacaine sometimes used in combination with epinephrine to prevent systemic absorption and extend the duration of action.[49] Iii) Bupivacaine is used as local anaesthetics during labor.[50] iv)Sometimes used in post-operative pain management. [51]	a) chills or shivering, headache, back pain.[52] b) Dizziness sexual dysfunction, restlessness, anxiety, vertigo, tinnitus.[53,54] c) Convulsion, myoclonic jerks, coma, cardiovascular collaps.[55,56] d)Ringing in the ears, changes in vision, low blood pressure, irregular heart rate.[57,58]

CONCLUSION

After completing the review paper about local anesthetic, we can conclude that local anesthetic has enough function in nerve blocking through Na+ channel, voltage gated sodium channel, Potassium channel, in minor case calcium channel. But some adverse effect, toxicity have been arising during nerve block such as paralysis, hypotension, respiration failure, systemic toxicity etc. So that there have many things that we should correct like maintain proper local anesthetic with minimum systemic toxicity, hypotension, respiration failure etc. proper administration of local anesthetic with proper dosage has vital role in adverse effect, if there have any mismatch then that will lead to dead of the patient. Local anesthetics plays a vital role in modern medical science. It acts by blocking peripheral nerves or by inhibiting the nerve terminals. It mainly used surgery and relief from pain after surgery. The above study described mechanism of action, pharmacokinetics and pharmacodynamics of different local anesthetics.

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