

Local Anesthetics

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Summary:

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.

Membrane potential and neurotransmission:

Neurons transmit information mainly by two mechanisms: chemical and electrical signals. Information within a neuron is mainly transmitted by electrical signals. Electrical signals are propagated by the action potential.

Resting neurons maintain an intracellular negative membrane potential. The mechanism for this resting membrane potential is as follows: Na^+/K^+ ATPase (sodium pump) transports intracellular Na^+ to the extracellular space in exchange of entry of K^+ into cells. This creates a concentration gradient of Na^+ and K^+ (Figure 1). The resting neuronal cell membrane contains more open K^+ channels than open Na^+ and Cl^- channels or channels for other ions. K^+ flows to the outside of the cell down its concentration gradient, resulting in a negative potential inside the cell.

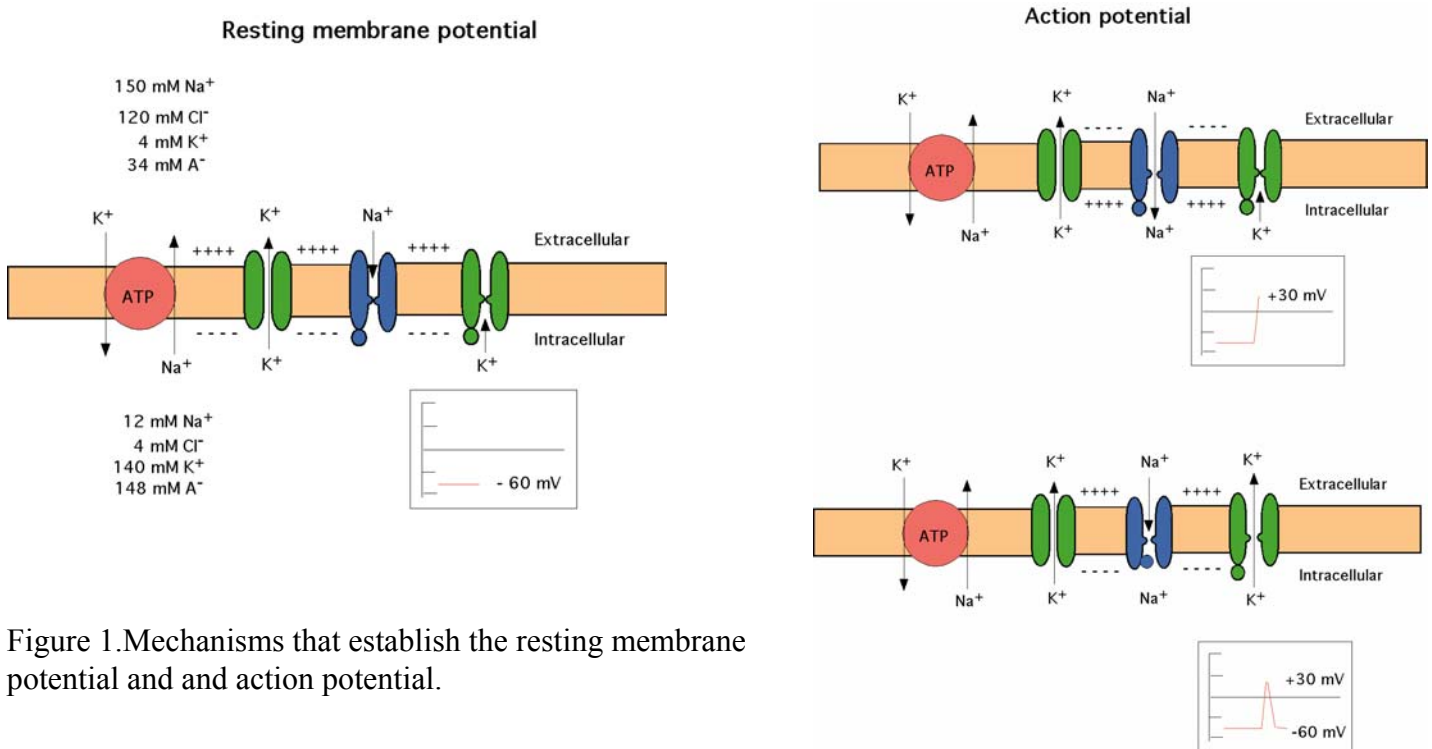


Figure 1. Mechanisms that establish the resting membrane potential and action potential.

When stimulated (electrically or chemically), a depolarization in the neuron (axon) membrane opens voltage-gated Na^+ channels. This leads to a burst of flow of Na^+ into the cell down the concentration gradient, causing a reversal of the membrane potential (from negative inside to positive inside). Eventually, the influx of Na^+ is stopped when the Na^+ concentration gradient is balanced inside and outside the cell (i.e., when the reversal potential is reached). Na^+ channels are closed by the voltage-sensitive regulatory domain and become

temporarily insensitive to depolarization. Subsequently, voltage-gated K^+ channels open, allowing accelerated outflow of K^+ . The membrane potential then returns to the resting state. This process is called the action potential and takes only a few milliseconds to complete. An action potential at one site of the neuron causes partial depolarization of neighboring regions, activating voltage-gated Na^+ channels in the neighboring region and thus causes propagation of the action potential (electrical signals) along the axon to synapses. Local anesthetics bind to and block the function of voltage-gated sodium channels and thus block conduction of action potentials.

Chemistry of local anesthetics:

The most widely used local anesthetics today include lidocaine, bupivacaine, procaine, and tetracaine.


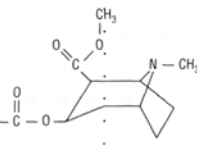
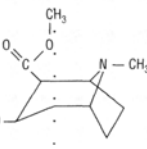
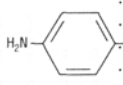
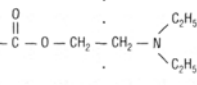

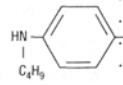
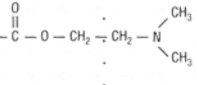

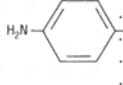
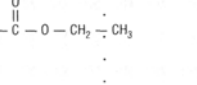
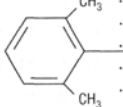
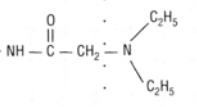
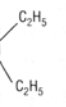
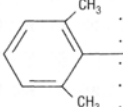
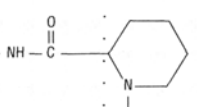
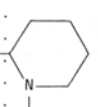
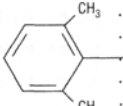
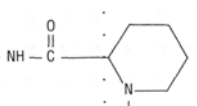
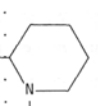
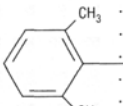
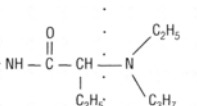
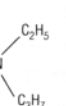
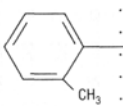
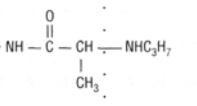
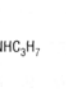
Currently used local anesthetics are structural mimetics of cocaine. Most of the drugs consist of a hydrophobic group (often an aromatic ring) connected by an intermediate chain (containing an ester or amide bond) to an ionizable group (usually a tertiary amine group).

Local anesthetics are weak bases. The pK_a 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 ($\text{Log}(\text{cationic form}/\text{uncharged form}) = pK_a - pH$). 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.

Mechanism of action:

Local anesthetics reversibly bind to voltage-gated sodium 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.

Table 1 Structure and properties of some ester and amide local anesthetics.¹

	Lipophilic Group	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 (Marcaine)				16	Long
Etidocaine (Duranest)				16	Long
Prilocaine (Citanest)				3	Medium

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.

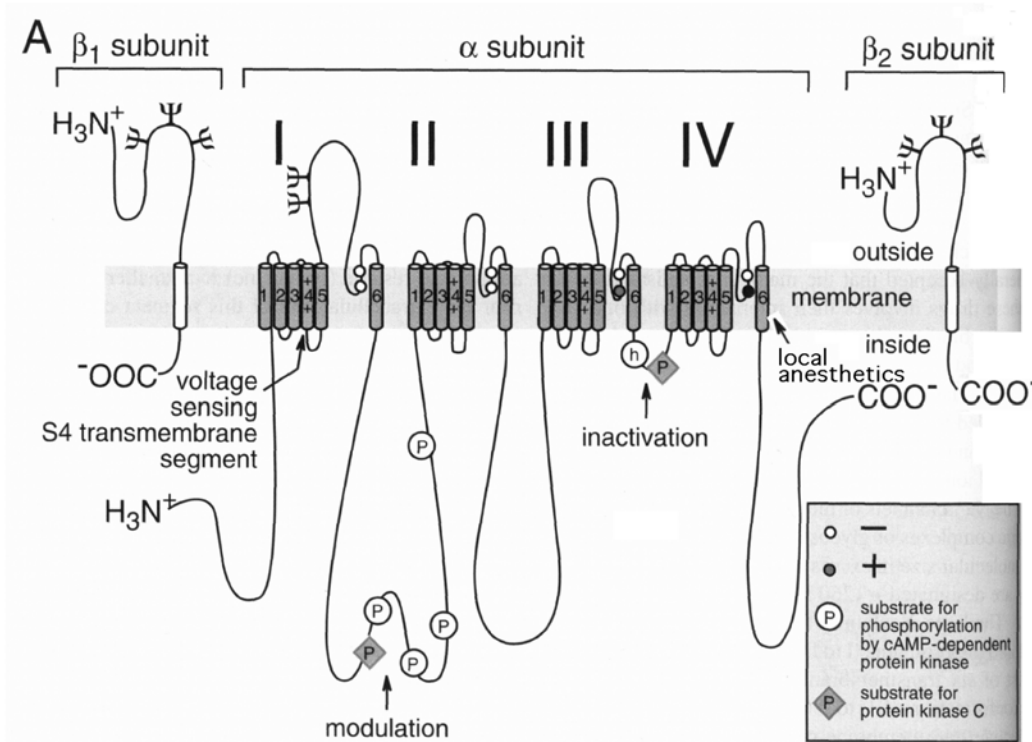


Figure 2. Schematic of the voltage-dependent sodium channel.

Characteristics of local anesthetic action:

1. Local anesthetics preferentially block small nerve fibers. This is because the distance of passive propagation of impulses in the small fibers is shorter. In general, small unmyelinated C fibers (pain signal) and small myelinated Aδ fibers (pain and temperature) are blocked before larger myelinated Aγ, Aβ and Aα fibers (postural, touch, pressure and motor signals) (Table 1).
2. Nerves with higher firing frequency and more positive membrane potential are more sensitive to local anesthetic block (use-dependent block). This is because the charged local anesthetic molecules are more likely to access to the binding sites in the open Na⁺ channel, and less likely to dissociate from its binding sites in the open or inactivated channels in comparison with the resting Na⁺ channels. Sensory fibers, especially pain fibers, have a high firing rate and relatively longer action potential duration than motor fibers, and thus are more sensitive to lower concentrations of local anesthetics. Frequency- and voltage-dependence is also the mechanism of anti-arrhythmic effects of local anesthetics on cardiac cells.
3. In nerve bundles, fibers that are located circumferentially are affected first by local anesthetics. In large nerve trunks, motor nerves are usually located circumferentially and may be affected before the sensory fibers. In the extremities, proximal sensory fibers are located more circumferentially than distal sensory fibers. Thus, loss of sense may spread from proximal to distal part of the limb.

4. Effectiveness of local anesthetics is affected by the pH of the application site. As mentioned above, the uncharged form of local anesthetics is more likely to penetrate the membrane but the charged form is more active in blocking the Na⁺ channel. At high pH, most local anesthetics are uncharged but also have a lower affinity for the sodium channel. At very low pH, there is a higher percentage of charged molecules which reduces the effects of the drugs as they are less likely to enter cells.

Table 2. Relative size and susceptibility to block of types of nerve fibers.

Fiber Type	Function	Diameter (μm)	Myelination	Conduction Velocity (m/s)	Sensitivity to Block
Type A					
Alpha	Proprioception, motor	12–20	Heavy	70–120	+
Beta	Touch, pressure	5–12	Heavy	30–70	++
Gamma	Muscle spindles	3–6	Heavy	15–30	++
Delta	Pain, temperature	2–5	Heavy	12–30	+++
Type B	Preganglionic autonomic	<3	Light	3–15	++++
Type C					
Dorsal root	Pain	0.4–1.2	None	0.5–2.3	++++
Sympathetic	Postganglionic	0.3–1.3	None	0.7–2.3	++++

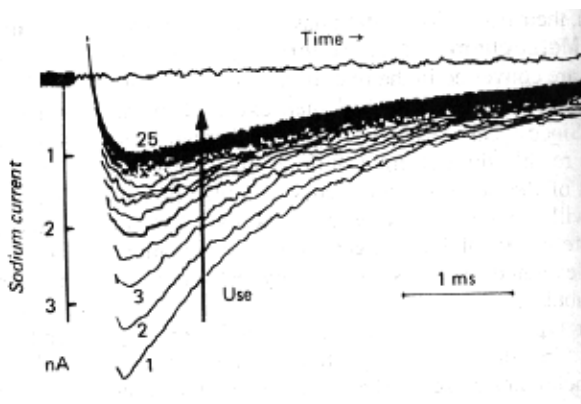


Figure 3. Frequency-dependent block of sodium current by local anesthetics. A series of 25 pulses was applied to a myelinated axon in the presence of a lidocaine derivative. Sodium current was then measured. Note the progressively decreased sodium current.

Pharmacokinetics

Following injection into the area of nerve fibers to be blocked, local anesthetics are absorbed into the blood. Ester-linked local anesthetics are quickly hydrolyzed by butyrylcholinesterase in the blood. Amide-linked local anesthetics can be widely distributed via the circulation. Amide-linked local anesthetics are hydrolyzed by liver microsomal enzymes. Thus, the half life of these drugs is significantly longer and toxicity is more likely to occur in patients with impaired liver function.

Absorption of local anesthetics is affected by the following factors: dosage, site of injection, drug-tissue-binding, and presence of vasoconstricting drugs. Presence of vasoconstricting drugs such as epinephrine significantly reduces absorption of local anesthetics, thus enhancing the local drug concentration, prolonging the local anesthetic effect, and reducing blood anesthetic levels. Epinephrine is included in most clinical preparations of local anesthetics.

Clinical use of local anesthetics:

Examples of local anesthetic use include: infiltration anesthesia, field block anesthesia, nerve block anesthesia, intravenous regional anesthesia, spinal anesthesia and epidural anesthesia.

Some local anesthetics such as lidocaine are also used to treat cardiac arrhythmias. The mechanism of this use is the firing frequency- and potential-dependent block of Na⁺ channels.

Toxicity:

Toxicity of local anesthetics is mostly related to their inhibitory effects on excitable cells such as neurons, cardiac muscle, smooth muscle and skeletal muscle cells.

Central nervous system:

Following absorption, local anesthetics cause stimulation of the CNS, producing restlessness and tremors that may proceed to convulsion. Stimulation is caused by inhibition of inhibitory neuronal activity. At high blood concentrations, local anesthetics cause depression and even respiratory failure. Cocaine is addictive.

Peripheral nervous system:

Local anesthetics affect transmission at the neuromuscular junction and ganglionic synapse.

Cardiovascular system:

1. Decrease electrical excitability, conduction rate, and force of contraction in the myocardium.
2. Cause arteriolar dilation.
3. Cocaine differs from the other local anesthetics: it blocks norepinephrine reuptake, resulting in vasoconstriction and hypertension, even cardiac arrhythmias.
4. Bupivacaine is more cardiotoxic than other local anesthetics and may cause cardiovascular collapse and ventricular tachycardia.

Smooth muscles:

Depress contractions of intestine, vascular, and bronchial smooth muscle.

Allergic reaction:

Ester-linked local anesthetics may cause allergic reaction in a small population of patients.