Local Anesthesia

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All LAs are membrane stabilizing drugs; they reversibly decrease the rate of depolarization and repolarization of excitable membranes (like nociceptors) .

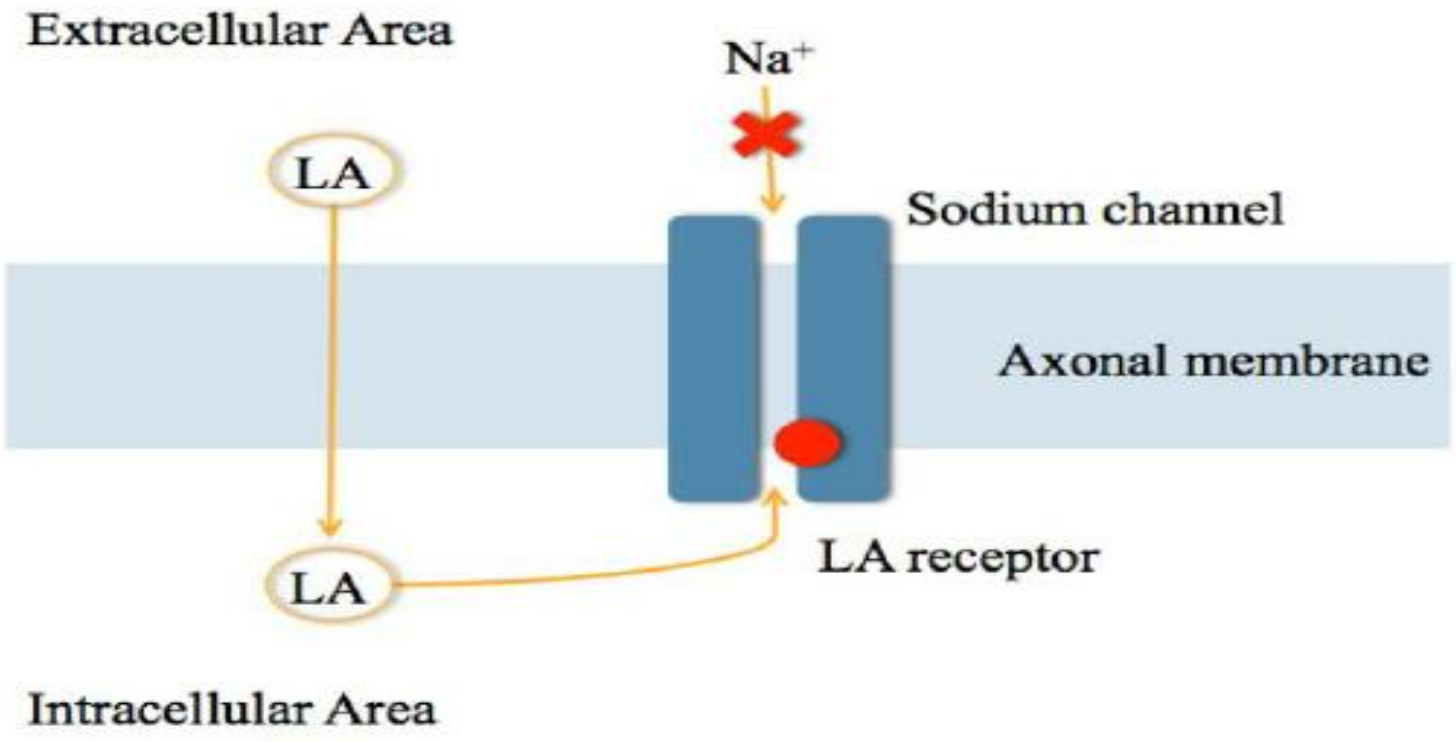
Though many other drugs also have membrane-stabilizing properties, not all are used as LAs (proporanolol for example, though it has LA properties).

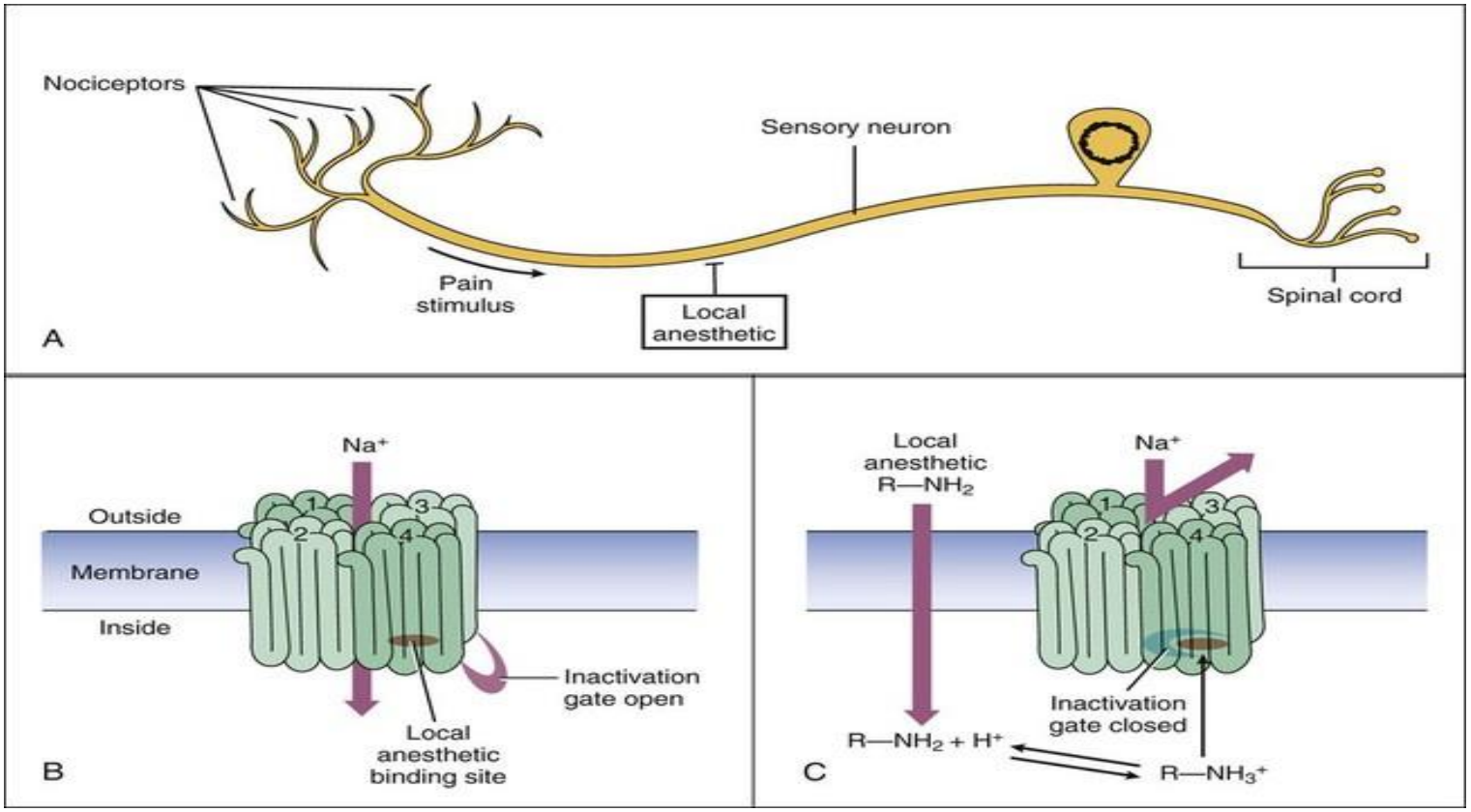
LA drugs act mainly by inhibiting sodium influx through sodium-specific ion channel in the neuronal cell membrane, in particular the so-called voltage-gated sodium channels.

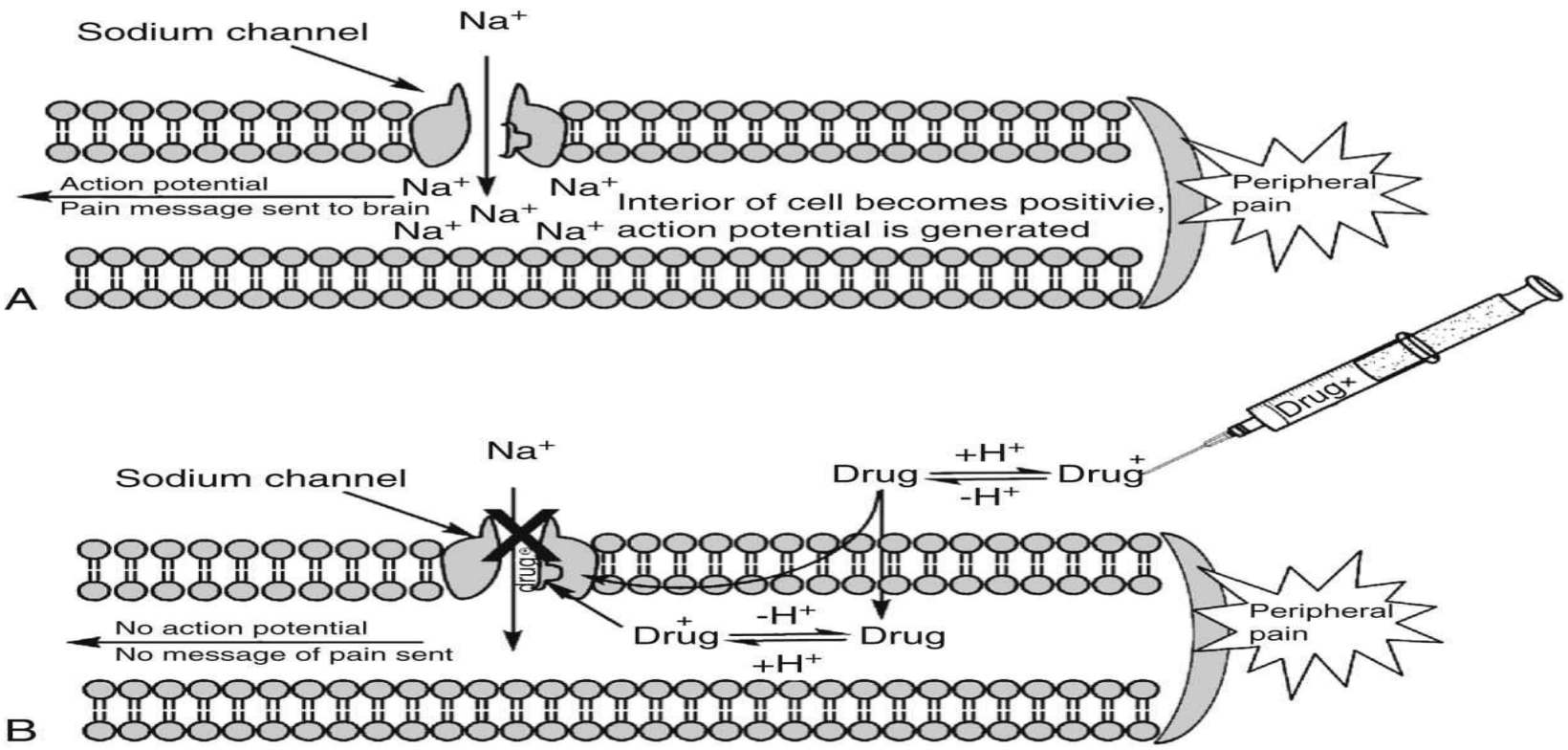
When the influx of sodium is interrupted, an action potential cannot arise and signal conduction is inhibited.

The receptor site is thought to be located at the cytoplasmic (inner) portion of the sodium channel.

Local anesthetic drugs bind more readily to sodium channels in an activated state, thus onset of neuronal blockade is faster in rapidly firing neurons. This is referred to as state-dependent blockade


Extracellular Area
Na+
LA
Sodium channel
Axonal membrane
LA
LA receptor
Intracellular Area


Nociceptors
Sensory neuron
Pain stimulus
Local anesthetic
Spinal cord
A
Na+
Outside
Membrane
Inside
1
2
3
4
Inactivation gate open
Local anesthetic binding site
B
Local anesthetic R—NH2
Na+
Inactivation gate closed
R—NH2 + H+
R—NH3+
C


Sodium channel
Na+
Action potential
Pain message sent to brain
Na+
Na+
Na+
Na+
Na+
Interior of cell becomes positivie,
action potential is generated
Peripheral pain
A
Drug+
Na+
Sodium channel
Drug
+H+
-H+
Drug+
drug
No action potential
No message of pain sent
Drug+
-H+
Drug
+H+
Peripheral pain
B

Local anesthetic consist of

Lipophilic group > aromatic benzene ring

Hydrophilic group > tertiary amine

Separated by intermediate chain that determines whether it is

(ESTERS AND AMIDES)

Local anesthetic are weak bases that is positively charged .

Amides and esters

Bupivacaine

Etidocaine

Lidocaine

Mepivacaine

Prilocaine

Ropivacaine

Chloroprocaine

Cocaine

Procaine

Tetracaine

SENSITIVITY

Nerve fiber sensitivity to inhibition by local depend on

Axonal diameter and myelination

POTENCY

related to Lipid Solubility

Ex. Lidocaine is less lipid soluble , fast onset but less potent

Bupivacaine is high lipid soluble , slow onset but more potent

Block of nerve fibers are affected by

Fiber size	PH
Fiber Type	frequency of depolarization
Myelination	electrolyte

*Hypokalemia and hypercalcemia antagonise the block

Onset of action :

.Lipid solubility

.Relative concentration of nonionized lipid form (B) and ionized water soluble form (BH+)

Onset can be increased by adding Bicarbonate that will lead to increase in PH .

Duration

Related to potency and lipid soluble

High potent>high lipid soluble >long duration>slow onset

Less potent>less lipid soluble>short duration>fast onset

clinical use of local anesthetics

Topically

Local infiltration

Regional >> intravenous

Peripheral nerve block

Central (Spinal/Epidural

)

Clinical pharmacology

Absorption :

Depend on BLOOD FLOW which depends on

..Site of injection :

IV>Tracheal>Intercostal>paracervical>Epidural>Brachial>sciatic> Subcutaneous

..Presence of vasoconstrictors . Ex epinephrine

enhance block, prolong duration, decrease toxic side effect

..Local anesthetic agent

Biotransformation and excretion

Esters

Metabolized by Pseudocholinesterase

Ester hydrolysis is very rapid and the water metabolites excreted in urine

* Procaine and Benzocaine metabolized to PABA which lead to allergic or anaphylactic reaction

Amides

N-dealkylation and hydroxylation by microsomal P-450 in liver
It is generally slower than esters hydrolysis

Prilocaine :
Metabolized to O-toludine > methemoglobinemia

Benzocaine :
Present in topical anesthesia > methemoglobinemia

Additives to increase Local anesthetic activity :

Epinephrine

Alkalinization of local anesthetic solution

Opioid

Alpha 2 adrenergic agonist

Steroid

Effect on organ systems

Central nervous system

First sign is circumoral numbness and tongue parasthesia.

light-headedness, dizziness, tinnitus, confusion and drowsiness. Patients often will not volunteer information about these symptoms unless asked.

Severe toxicity: tonic-clonic convulsion leading to progressive loss of consciousness, coma, respiratory depression, and respiratory arrest.

Cardiovascular toxicity

Early or mild toxicity:

local Anesthesia with adrenaline causes tachycardia with Hypertension

if no adrenaline : badycardia with hypotension

Severe toxicity: Usually about 4 - 7 times the convulsant dose needs to be injected before CV collapse occurs.

Collapse is due to the depressant effect of the LA acting directly on the myocardium (e.g. Bupivacaine)

Severe and intractable arrhythmias can occur with accidental iv injection.

Table 6:2 Classification of nerve fiber

Fiber Type	Diameter/µm/	Conduction speed m/s	Function
A α (alpha)	12- 20	70 -120	proprioception, somatic nerve
A β (beta)	5- 12	30 -70	touch, pressure
A γ (gamma)	3 – 6	15 – 30	motor to muscle spindle
A δ (delta)	2 – 5	12 – 30	pain, temperature, touch
B	< 3	3 – 15	preganglionic, autonomic
C	.3 -1.3	.5 - 2.3	Pain, reflexes, post ganglionic sympathetic

TABLE 16–3 Clinical use of local anesthetic agents.

Agent	Techniques	Concentrations Available	Maximum Dose (mg/kg)	Typical Duration of Nerve Blocks[1]
Esters				
Benzocaine	Topical[2]	20%	NA[3]	NA
Chloroprocaine	Epidural, infiltration, peripheral nerve block, spinal[4]	1%, 2%, 3%	12	Short
Cocaine	Topical	4%, 10%	3	NA
Procaine	Spinal, local infiltration	1%, 2%, 10%	12	Short
Tetracaine (amethocaine)	Spinal, topical (eye)	0.2%, 0.3%, 0.5%, 1%, 2%	3	Long
Amides				
Bupivacaine	Epidural, spinal, infiltration, peripheral nerve block	0.25%, 0.5%, 0.75%	3	Long
Lidocaine (lignocaine)	Epidural, spinal, infiltration, peripheral nerve block, intravenous regional, topical	0.5%, 1%, 1.5%, 2%, 4%, 5%	4.5 7 (with epinephrine)	Medium
Mepivacaine	Epidural, infiltration, peripheral nerve block, spinal	1%, 1.5%, 2%, 3%	4.5 7 (with epinephrine)	Medium
Prilocaine	EMLA (topical), epidural, intravenous regional (outside North America)	0.5%, 2%, 3%, 4%	8	Medium
Ropivacaine	Epidural, spinal, infiltration, peripheral nerve block	0.2%, 0.5%, 0.75%, 1%	3	Long