



Local anesthetics

BY

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▶ **What is a local anesthetic?:**

- ▶ A drug that interrupt pain impulses in a specific region of the body **without loss of patient consciousness.**
 - ▶ Local anesthetic produces transient reversible analgesia **in a circumscribed region of the body.**
 - ▶ Used in minor operations
 - ▶ Cocaine was the first local anesthetic
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Nerve fibers affected by local anesthetics

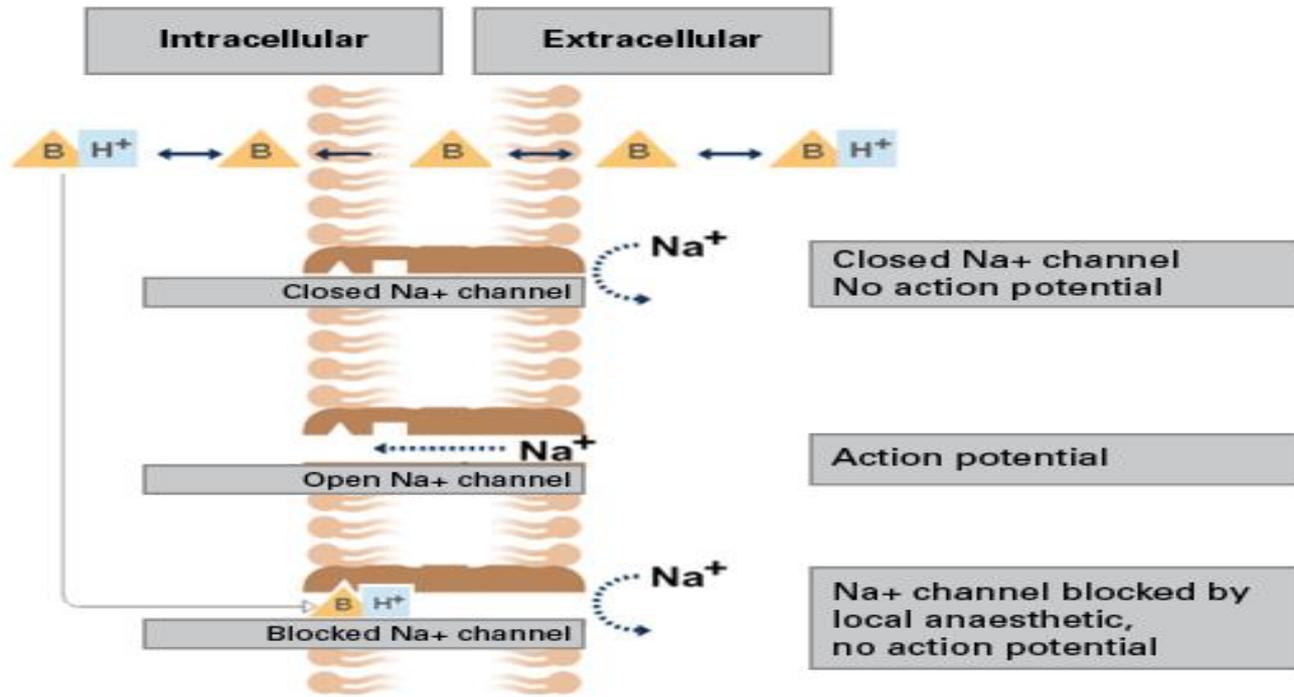
- ▶ Non-myelinated and Smaller myelinated fibers are easier to block than larger fibers.
- ▶ Smaller non-myelinated C fibers (pain)
- ▶ large myelinated ($A\alpha$ and $A\beta$: preganglionic sympathetic) fibers
- ▶ small myelinated axons ($A\gamma$ motor and $A\delta$ sensory fibers)

Order of loss of sensations

- ▶ Pain
- ▶ Cold
- ▶ Heat
- ▶ Touch
- ▶ Deep pressure

- ▶ Order in nerve fibers:
 - ▶ Autonomic
 - ▶ Sensory
 - ▶ Motor

Mechanism of action ■ local anesthetics



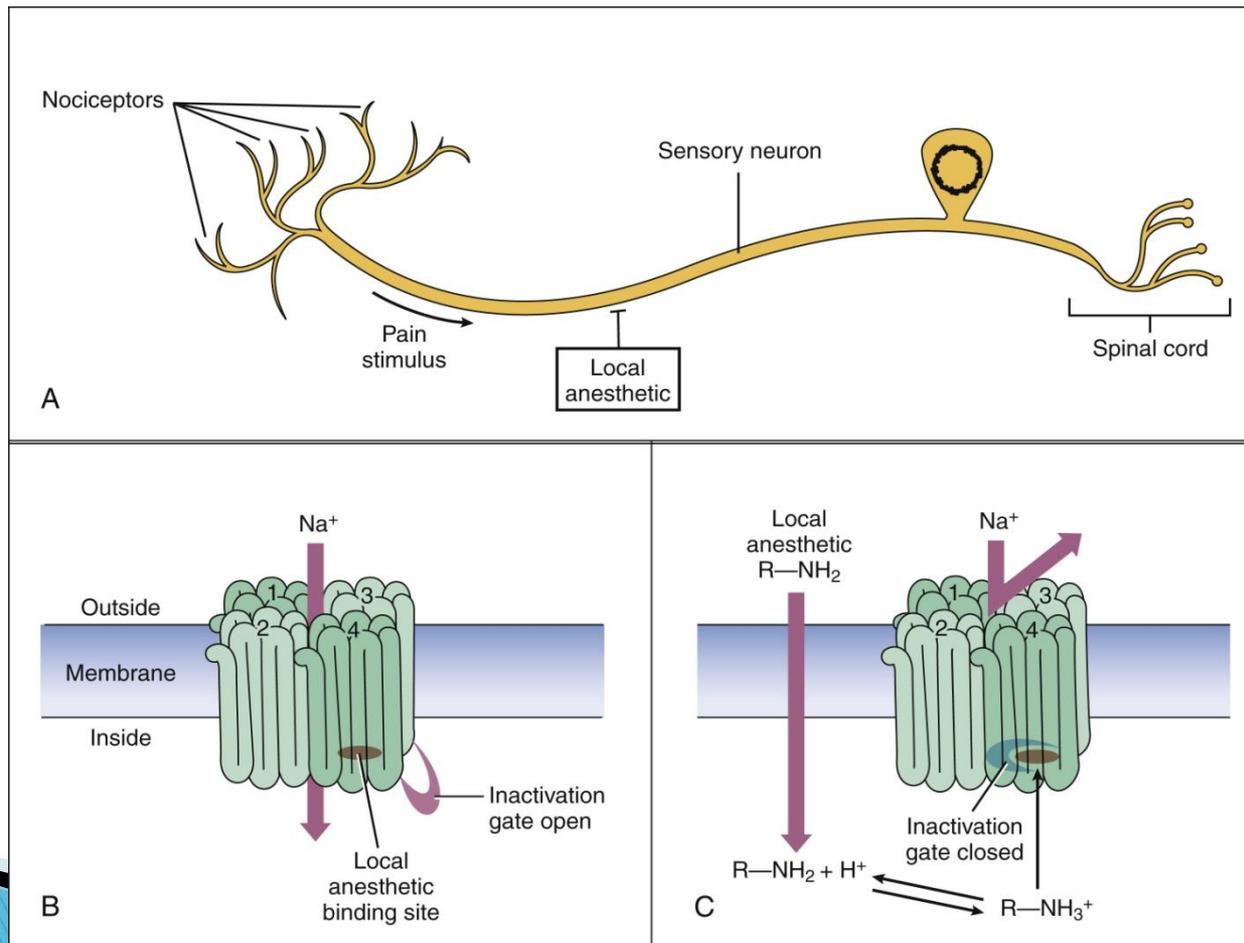
CHANGE PAIN®

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Local anesthetic binds to the inner membrane in a cationic form and physically plugging Na channel

N.B. inside of the neuron is slightly acidic

They bind to afferent nerve fibers which carry pain signals



▶ **They block nerve conduction:**

1. By interacting directly with specific receptors on neuronal Na^+ channels (inactive Na channels), inhibiting Na^+ ion influx.
2. By impairing both generation and propagation of the action potential in the axons

Deadlier
than cyanide,
the toxins in
a single

PUFFER FISH

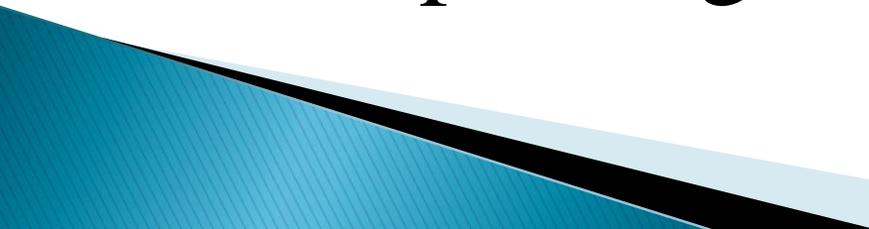
are enough
to kill around
300 humans.



Buzzle.com

TTX: tetrodotoxin???

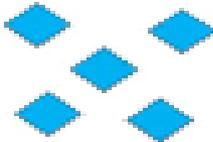
Factors affecting onset, intensity, and duration of local anesthesia action:

1. Lipid solubility: a lipophilic local anesthetic is more potent because it is easier to cross nerve membranes
 2. Protein binding: local anesthetics with a higher degree of protein binding have a prolonged duration of action
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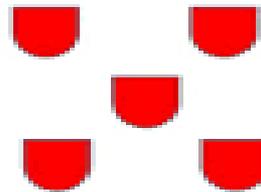
pKa of local anesthetics

pKa

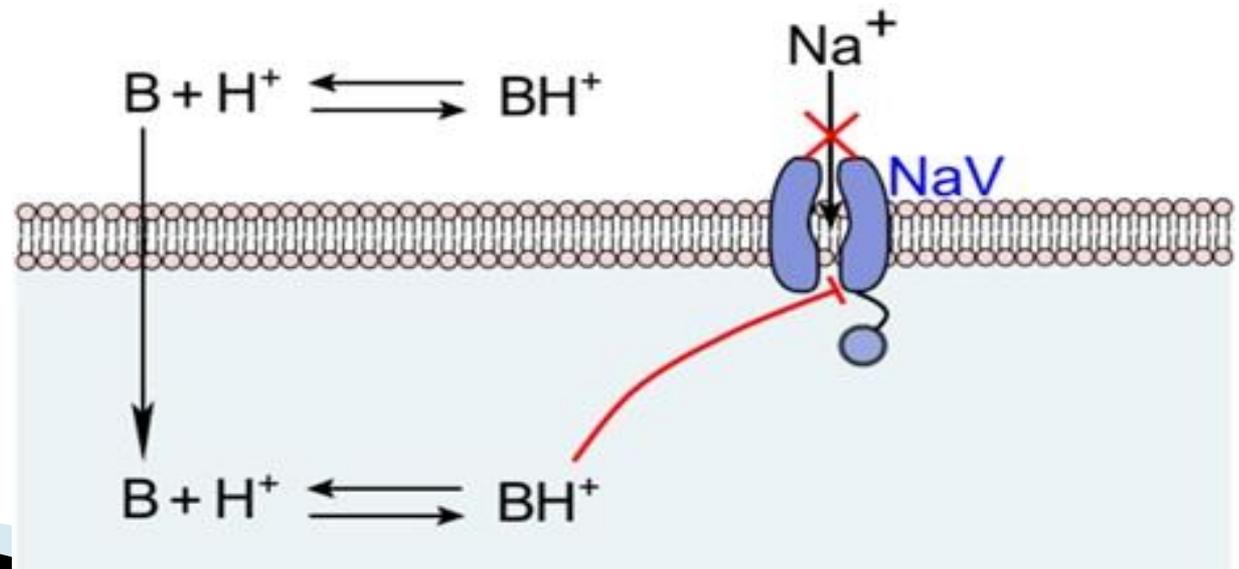
Non-ionized Form



Ionized Form



pKa = pH at which ionized and non-ionized forms of local anesthetics are equal.



3. The pKa:

-The pKa is the pH at which 50% of the local anesthetic is in the ionized form and 50% is in the unionized form.

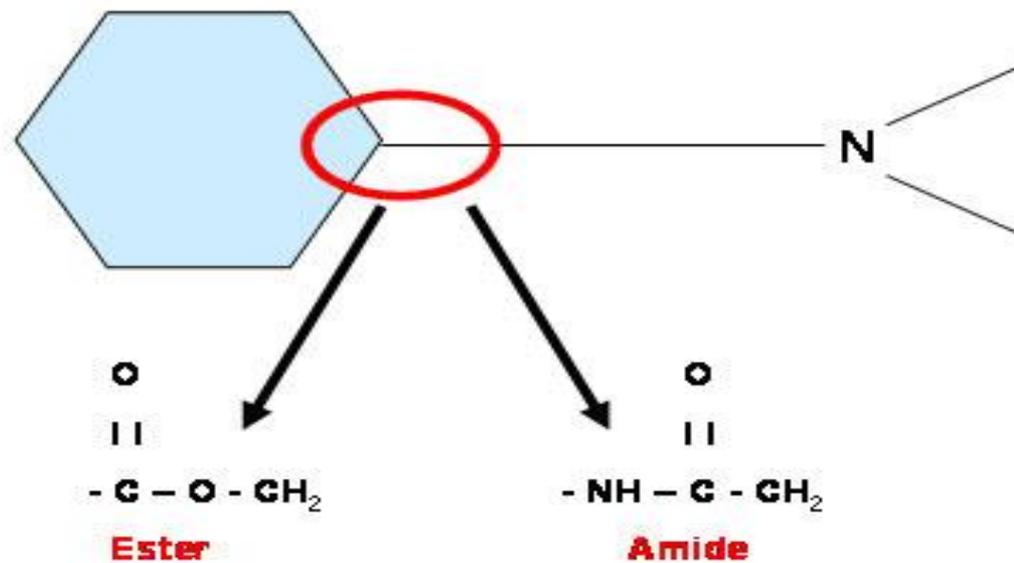
All local anesthetics are weak bases with $pK_a = 8-9$:

- Local anesthetics with pK_a close to physiologic pH are associated with a greater fraction of the molecules existing in the unionized form = more penetration across nerve membranes = faster onset. (Small gap between pH and pK_a)

- Local infection (acidosis) increases the ionized drug fraction which means less drug will be available to penetrate across membranes and bind to intracellular local anesthetic receptors on Na^+ channels = slower onset. (Increased gap between pH and pK_a)

4. Dose: Increasing dose of the anesthetic will increase the duration of the block.

Chemistry



	Esters	Amides
Chemistry	Have an ester (-COO-) link between the aromatic group and the amino terminal	Has an amide (-NHCO-) link between the aromatic group and the amino terminal.
Examples	<p>Procaine: short acting: many side effects</p> <p>Tetracaine: long acting</p> <p>Benzocaine: Topical gel or ointment.</p>	<p>Lidocaine: has fast onset (topical, injection & spray). LIGNOCAINE?? Antiarrhythmic?? Commonly used: good tissue penetration- rapid- moderate duration</p> <p>Mepivacaine : moderate duration, not active topically</p> <p>Etidocaine: fast onset, long duration, muscle relaxation.</p> <p>Bupivacaine: long duration : long procedures dissociate slowly from cardiac Na⁺Channels → ↑risk of cardiotoxicity.</p>
t _{1/2}	Few minutes	Few hours
Metabolism	By plasma pseudocholinesterase. P-aminobenzoic acid is a metabolite & a common cause allergy.	By the liver.
Incidence of allergic	High (cross allergy between esters is also high).	Rare

Clinical uses

Types of local anesthesia

Topical local (surface) anesthesia: for eye, ear, nose, and throat procedures and for cosmetic surgery

Infiltration anesthesia: local injection around the region to be operated.

Conduction anesthesia: local injection around the peripheral nerve trunk

Epidural anesthesia: local injection into the epidural space

Subarachnoid anesthesia or Spinal anesthesia: local injection into the cerebrospinal fluid in subarachnoid cavity

Routes of administration

- ▶ ID
 - ▶ SC
 - ▶ Intrathecal
- 

Side effects

▶ Local:

- ▶ Irritation and inflammation at the site of administration
- ▶ Vasodilatation but local ischemia may arise from a co-administered vasoconstrictor, therefore this should be avoided in the extremities such as the digits. (except cocaine)
- ▶ Cocaine, which blocks noradrenaline reuptake by noradrenergic neurons (uptake 1), produces intense vasoconstriction and has a longer duration of action. Cocaine is restricted to topical use in otolaryngeal procedures, to produce vasoconstriction and reduce mucosal bleeding. (**never used by injection**)

systemic

- ▶ Cardiovascular collapse owing to systemic vasodilatation and a negative inotropic effect. **CHECK BLOOD PRESSURE**
- ▶ Cardiotoxicity with serious arrhythmias is a particular problem with bupivacaine.
- ▶ In the central nervous system (CNS), local anesthetics can produce dizziness, then sedation and loss of consciousness. Severe reactions can be accompanied by convulsions. Metabolites of lidocaine can cause generalised excitation and convulsions.
- ▶ True allergy is rare, but can occur with procaine and tetracaine, related to their metabolism to para-amino-benzoic acid

References

- ▶ **Goodman & Gilman, 13th edition**
 - ▶ **Lippincott® Illustrated Reviews: Pharmacology Seventh Edition**
 - ▶ **Rang and Dale, 6th edition, 2014**
 - ▶ **Flashcards Pharmacology RANG & DALE'S Flash Cards Updated Edition 2014**
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