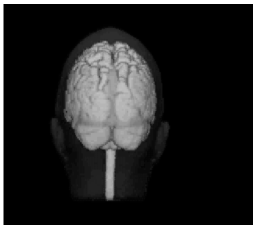
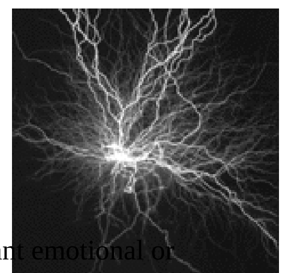
Neurophysiology and Pain



Local anesthetics prevent the generation and the conduction of a nerve impulse

PAIN:

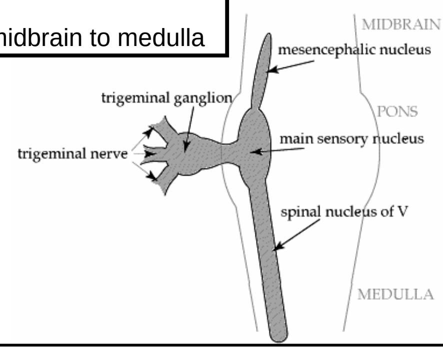


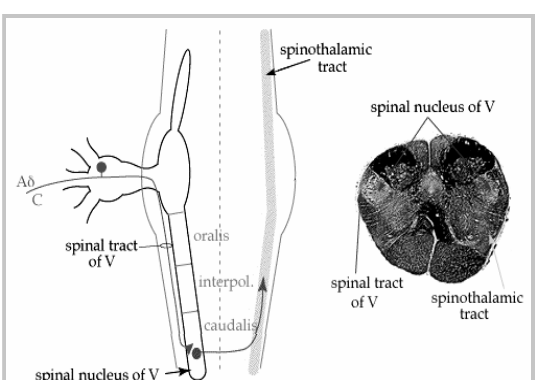
"……an unpleasant emotional or sensory experience associated with actual or potential tissue damage or described in terms of such damage"

International Association for the Study of Pain (IASP, 1973)

Trigeminal Nucleus

from midbrain to medulla

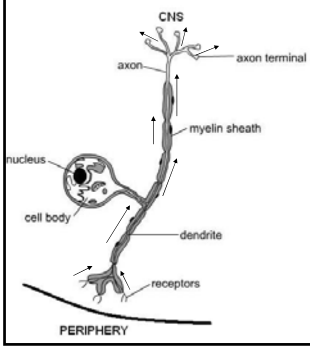




The Neuron:

- Structural unit of the nervous system which allows CNS to communicate with periphery.
- 2 basic types:
  - Sensory (afferent)
  - Motor (efferent)

The Sensory Neuron



- Nociceptive neurons
  - Dendritic zone
    - Arborization of free nerve endings
  - Axon
  - Cell body

- Dendritic zone is the most distal segment and is composed of free nerve endings which respond to stimulation and provokes a stimulus that is propagated along the <u>axon</u>
- The cell body of the sensory neuron is not involved in the process of impulse transmission
- it does provide metabolic support for the neuron

The Axon

- Long cylinder of neural cytoplasm (axoplasm)
- Surrounded by nerve membrane (axolemma)
  - Phospholipid bilayer
  - Embedded lipoglycoprotein channels & Na^+/K^+ pumps

- Most (all but the smallest) nerve fibers are covered by an insulating lipid layer of myelin.
- Myelinated nerve fibers are wrapped in layers of lipoprotein myelin sheaths, specialized forms of Schwann cells.
  - Schwann cell sheath
  - Myelinated (Nodes of Ranvier, saltatory conduction) vs. Unmyelinated (several cells wrapped with single sheath

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Physiology of Peripheral Nerves

- Nerves carry <u>impulses</u> from one part of the body to another
- Brief increases in membrane permeability to Na+ cause depolarizations of the membrane or <u>action potentials</u>
- Once initiated, the amplitude and shape of an impulse remain constant

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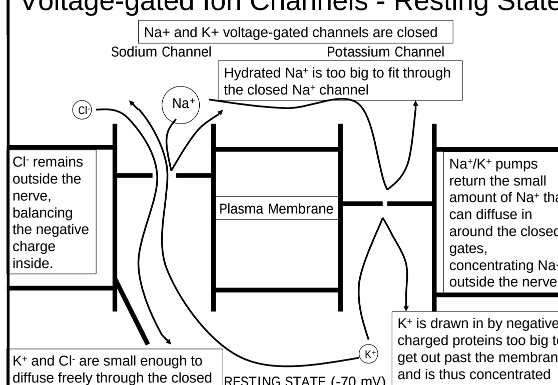
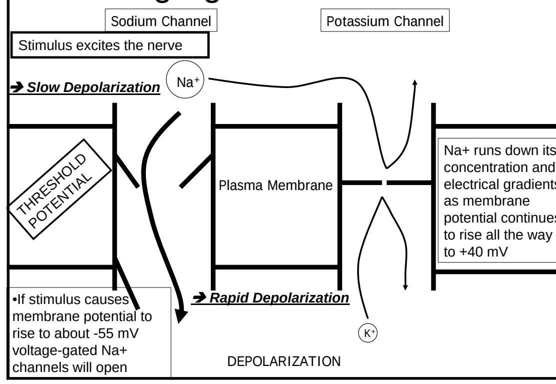
Voltage-gated Ion Channels - Resting State

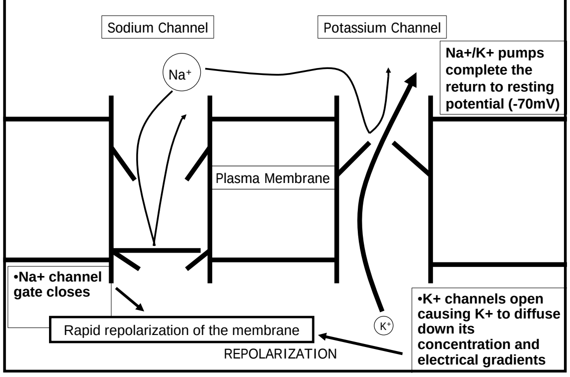


- In its resting state the nerve membrane is
  - Slightly permeable to Na^+
  - Freely permeable to K^+
  - Freely permeable to C^-

Voltage-gated Ion Channels



Voltage-gated Ion Channels



Electrochemistry of Nerve Conduction

- The preceding sequence of events depend on two important factors:
  - Electrolyte concentration in the axoplasm and extracellular fluids
  - Permeability of the nerve membrane to sodium and potassium ions

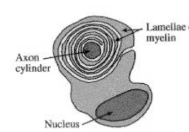
Refractory period

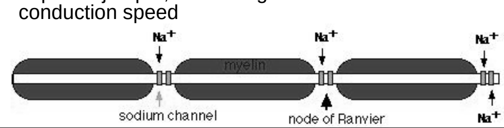
- **Absolute** refractory period ➔ no way Na^+ can possibly rush in
- **Relative** refractory period ➔ depolarization can be initiated, but requires a stronger than normal stimulus

- Retrograde movement of the impulse is prevented by the unexcitable refractory segment

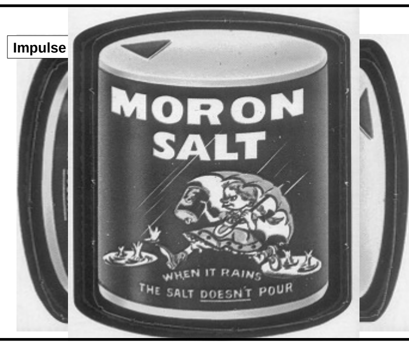
Myelinated vs. Nonmyelinated Nerves

- High lipid content = ion (electrical) and pharmalogical insulator
- In myelinated axons, ion exchange (and channel density) is confined to discrete areas
- Impulse "jumps", increasing conduction speed





Saltitory Conduction



- Saltitory conduction usually progresses from one node to the next.
- If a node is blocked and if the current flow at the next node is high enough to reach the firing threshold, the current will skip over the blocked node and continue depolarization.
- A minimum of ~ 8-10mm of nerve must be covered by anesthetic solution to ensure blockade.

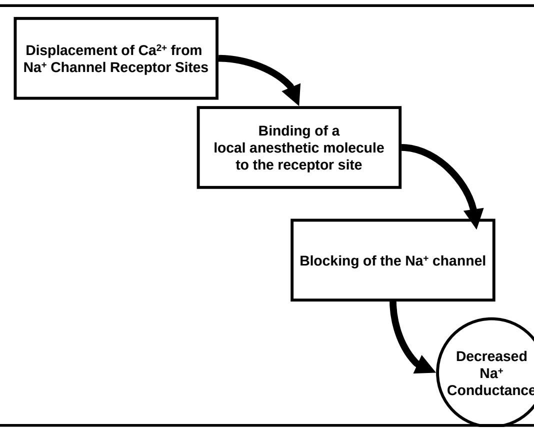
Mode of Action of Local Anesthetics

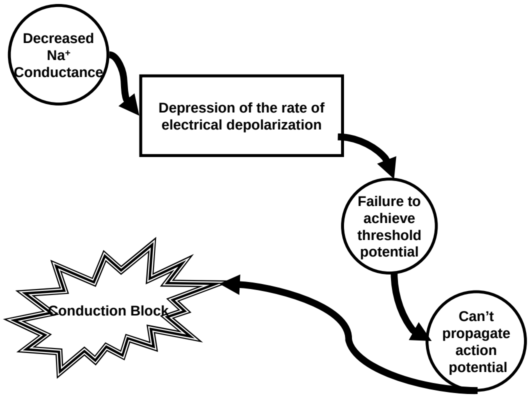
- Local anesthetic agents may:
  - Alter the basic resting potential of the nerve membrane
  - Alter the threshold potential
  - Decrease the rate of depolarization
  - Prolong the rate of repolarization

Local Anesthetics Work at the Nerve Membrane

2 acceptable theories:

- Membrane Expansion Theory
  - Molecules of LA disturb the membrane structure, expanding certain regions ➔ preventing Na^+ permeability increase
- Specific Receptor Theory
  - LA's bind to specific receptors on the Na channel ➔ direct action → once bound to the receptor, Na^+ permeability is decreased, stopping nerve conduction

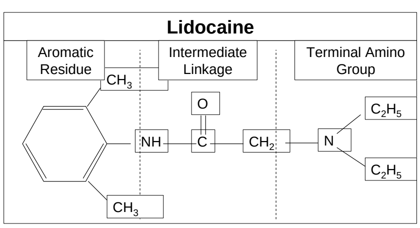


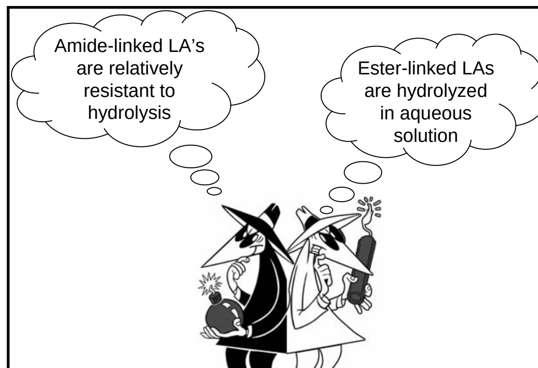


Active forms of Local Anesthetics

- (Most) injectable LAs are tertiary amines
- Injectable LAs are amphipathic (possess both lipophilic an hydrophylic characteristics
  - The hydrophilic part is an amino derivative of ethyl alcohol or acetic acid
    - w/o a hydrophilic part, may be a good topical, but can't be injected (benzocaine)

- There are three components to most local anesthetics
  - A lipophilic aromatic residue
  - And intermediate amide or ester linkage
  - A terminal hydrophilic amino group





Amide vs. Esters

Active forms of Local Anesthetics

- LAs are basic compounds, poorly soluble in water and unstable.
- Their pKa values range from 7.5 to 10
- They must be combined with acid to form salts which are soluble in water and comparatively stable

- Acidification of tissue decreases local anestheic effectiveness
- Inadequate anesthesia results when local anesthetics are injected into infected or inflamed areas.
- The inflammatory process produces acidic products: the pH of normal tissue is 7.4; the pH of an inflamed area is 5 to 6
- Local Anesthetics containing epi or other vasopressors are acidified to inhibit the oxidation of the vasopressor
  - The pH of solutions w/o epi is about 5.5; with epi ~3.3
  - Clinically, the lower pH is more likely to produce a burning sensation on injection as well as a slightly slower onset of action

- Increased pH (alkalinization) of a local anesthetic solution speeds the onset of its action, increases it s clinical effectiveness, and makes its injection more comfortable, but it is unstable and precipitates out of alkalinized solution.

Dissociation

- Weak acid/base salts in solution exist simultaneously as
- Uncharged molecules or base (RN)
- Positively charged molecules or cation (RNH^+)

$$RNH^+ \rightleftharpoons RN + H^+$$

- The relative proportion of each ionic form <u>varies with the pH</u> of the solution or surrounding tissues.
- In a low pH environment [high H^+]:

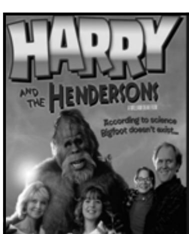
$$\underline{RNH^+} \leftleftharpoons RN + H^+$$

- In a high pH environment [low H^+]:

$$\underline{RNH^+} \rightleftharpoons RN + H^+$$

Dissociation Constant (pKa)

- The relative proportion of ionic forms also depends on the pKa (a measure of a molecule's affinity for hydrogen ions)
- When the solution's pH = the anesthetic's pKa, RNH^+/RN = 50/50
- The % in either form can be determined from the Henderson-Hasselbalch equation



Henderson-Hasselbalch Equation

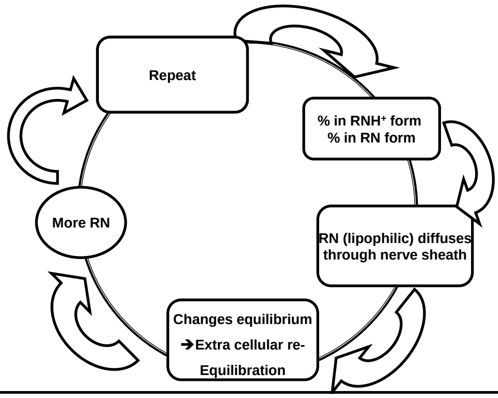
$$pH = pKa + \log\frac{Base}{Acid}$$

-OR-

$$\log\frac{Base}{Acid} = pH - pKa$$

Action on Nerve Membranes

- 2 factors involved in the action of local anesthetic
  - **<u>Diffusion of the drug through the nerve sheath</u>**
  - Binding at the receptor site in the ion channel



Dissociation Constants (pKa) of Local Anesthetics

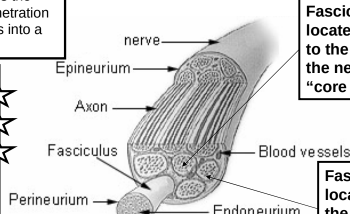
Agent	pKa	% Base at pH 7.4	~ onset of action (min)
Benzocaine	3.5	100	-
Mepivicaine	7.7	33	2-4
Lidocaine	7.8	29	2-4
Articaine	7.8	29	2-4
Prilocaine	7.9	25	2-4
Ropivicaine	8.1	17	2-4
Bupivicaine	8.1	17	5-8
Cocaine	8.6	7	-
Propoxycaine	8.9	4	9-14
Procaine	9.1	2	14-18

Peripheral Nerve Organization

The thicker the perineurium, the slower the rate of local anesthetic diffusion across it.

The **perineurium** is the main barrier to penetration of local anesthetics into a nerve

May explain the clinical situation of inadequate pulpal anesthesia in the presence of subjective symptoms of adequate soft tissue anesthesia



Fasciculi located closer to the core of the nerve are "core bundles"

Fasciculi located near the surface of the nerve are "mantle bundles"

Complete conduction block of all nerve fibers requires an adequate volume and an adequate concentration of local anesthetic

- Induction time➔ the period from deposition of the anesthetic solution to complete conduction blockade
- Diffusion➔ the unhindered migration of molecules or ions through a fluid medium under the influence of the concentration gradient
- Penetration➔ (of an anatomical barrier to diffusion) occurs when a drug passes through a tissue that tends to restrict free molecular movement
- Complete conduction block of all nerve fibers requires an adequate volume and an adequate concentration of local anesthetic

- Lipid solubility is related to LA potency
  - Increased lipid solubility permits the anesthetic to penetrate the nerve membrane more easily
  - Greater lipid solubility ➔ more effective conduction block at lower concentrations
- Protein Binding related to duration of action
  - LA's with greater degree of protein binding (bupivicaine) attach more securely to the protein receptor sites ➔ longer duration of action
- Vasoactivity affects both LA potency and duration of action
  - LA's with greater vasodilating properties (procaine) increase perfusion ➔ increase absorption → shorter duration of anesthesia and decreased potency

Factors Affecting Local Anesthetic Action

Factor	Affected	Description
pKa	Onset	Lower pKa→ More rapid onset of action, more RN molecules present to diffuse through nerve sheath ➔ ↓'d onset time
Lipid Solubility	Potency	↑'d lipid solubility → ↑'d potency
Protein Binding	Duration	↑'d protein binding allows anesthetic cations (RNH^+) to be more firmly attached to proteins located at receptor site ➔ ↑'d duration of action
Nonnervous Tissue Diffusibility	Onset	↑'d diffusibility → ↓'d onset time
Vasodilator Activity	Potency and Duration	↑'d vasodilator activity → ↑'d blood flow to region → rapid removal of anesthetic molecules from injection site ➔ ↓'d potency and ↓'d duration

Recovery

- Follows the same diffusion pattern, but in reverse
- LA stops working when…
  - LA redistributed - Concentration gradient favors the movement of LA from inside to outside
- LA excreted through the GI tract and kidneys, after being processed in the liver
- Recovery is slower than induction because the LA is bound to the receptor site and is released more slowly than it is absorbed

Topicals

- To make topical anesthetics more clinically effective a more concentrated form of the drug is commonly used (5% or 10% lidocaine) than for injection (1% or 2% lidocaine)

Overuse of Skin Numbing Creams Can Cause Death: FDA February 7, 2007

- People who use large amounts of skin-numbing creams and lotions, often in conjunction with cosmetic procedures, are at risk of irregular heartbeats, seizures and even death, U.S. health officials warned on Tuesday.
- The Food and Drug Administration, citing two deaths, said such topical anesthetics can be applied in amounts so large that a lethal dose of the chemicals can enter the bloodstream.
- A 22-year-old woman and a 25-year-old woman who applied numbing creams after laser hair removal on their legs later died, the agency said
- After the procedure, "these women then wrapped their legs in plastic wrap, as they were instructed, to increase the creams' numbing effect.
- **Both women had seizures, fell into comas, and subsequently died from the toxic effects of the anesthetic drugs**," the FDA said.
- Numbing creams and lotions, available both by prescription and over the counter, are approved to soothe burning or itching skin as well as pain before, during and after various procedures. **They contain numbing drugs that can include lidocaine, tetracaine, benzocaine and prilocaine**.
- But the FDA said consumers should be cautious about using them without medical supervision.
- Leaving the creams on the skin for long periods of time or on large portions of their bodies can increase the risk, officials have said. Small children and people with heart or severe liver disease are also at higher risk…"You should also discuss with your doctor whether there are other ways to reduce the pain you may feel during the procedure," it added.

INFECTION

Lower pH reduces number of available unionized ions to diffuse across nerve cell membrane.

Methods of Local Anesthesia

- Mechanical Trauma
- Low Temperature
- Anoxia
- Chemical Irritants
- Neurolytic Agents
  - Alcohol and Phenol
- Local Anesthetics
  - Transient and Completely reversible

Properties of LA

- Non-irritating
- No permanent alteration of nerve structure
- Toxicity should be low
- Effective if injected or topical
- Time of onset short
- Duration of action should be adequate to complete work, but not need extended recovery.