Local Anesthetics
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lipophilic ester or amide linkage hydrophilic

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \quad \text{C} \quad \text{O} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{N} \\
\text{CH}_2 & \quad \text{CH}_3
\end{align*}
\]
lipophilic ester or amide linkage

H₂N─C─O─CH₂─CH₂─N─CH₂─CH₃

hydrophilic

duration of action

g potency

metabolism

c hemical stability

hypersensitivity
Local anesthetics block action potential without affecting resting potential.
Local Anesthetic Sites of Action

- **Extracellular fluid**
- **Membrane**
- **Axoplasm**

**Representative agent(s):**
- Tetrodotoxin, saxitoxin
- Benzocaine
- Quaternary ammonium compounds
- Amide and ester local anesthetics (e.g., lignocaine, procaine)

**Membrane site:**
1. Receptor at external surface
2. Expansion of axonal membrane
3. Receptor at internal surface
4. Combination of (3) and (4)
Local Anesthetic Sites of Action

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Representative agents:
- Tetrodotoxin, saxitoxin
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Chemical structure:
\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \\
\text{C} & \quad \text{O} \quad \text{C}_2\text{H}_5
\end{align*}
\]
Local Anesthetic Sites of Action

1. Receptor at external surface
2. Expansion of axonal membrane
3. Receptor at internal surface
4. Combination of (2) and (3)

Representative agents:
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Local Anesthetic Sites of Action

Conduction blockade occurs after

- Diffusion of the base form across nerve sheath and membrane
- Re-equilibration between base and cationic forms in the axoplasm
- Penetration of cation into and attachment to receptor at site within the sodium channel
• Blockade of sodium channel
• Inhibition of sodium conductance
• Decrease in rate and degree of depolarization phase of the action potential
• Failure to achieve threshold potential
• Lack of development of a propagated action potential
• Conduction blockade

\[
\log \frac{[H^+LA]}{[LA]} = pK_a - pH
\]

Henderson-Hasselbach equation
Local anesthetics act in a frequency-dependent manner

Local anesthetics bind with greater affinity to the inactivated state of the sodium channel. Hence, rapidly firing neurons are blocked more rapidly.
Local Anesthetics: Effect of Fiber Diameter

- Small diameter fibers blocked first
- Myelinated nerves blocked before unmyelinated (of the same diameter)

Order of Susceptibility to Local Anesthetics

autonomic
pain
temperature
pressure
proprioception
motor
In general, local anesthetics are very safe if used correctly.

Toxicity results from bad technique.
Major cause of systemic toxicity is high blood concentration

- Use least volume of the most dilute solution
- Include a vasoconstrictor
- Topical use is not necessarily safe

Plasma levels of tetracaine after several routes of administration
cocaine

- Esteratic linkage
- Recreational drug
- Blocks reuptake of catecholamines
- Topical use
- Corneal damage

short-acting local anesthetics

- procaine - esteratic linkage, metabolized to PABA
- chloroprocaine - esteratic linkage, extremely short duration of action
- articaine - amide linkage, rapid onset of action
### Intermediate-Acting Local Anesthetics

- **Lidocaine** - amide linkage, rapid onset of action, high intrinsic activity to vasodilate, very widely used
- **Mepivacaine** - amide linkage, very rapid onset of action
- **Prilocaine** - amide linkage, methemoglobinemia

### Long-Acting Local Anesthetics

- **Tetracaine** - esteratic linkage, slow onset of action
- **Etidocaine** - amide linkage, rapid onset of action
- **Bupivacaine** - amide linkage; available as S-enantiomer, levobupivacaine (Chirocaine®)
- **Ropivacaine** - amide linkage, marketed as S-enantiomer
- **Dibucaine** - amide linkage, potent, toxic, and long-acting
ropivacaine

- long-acting
- amide linkage
- marketed as the S-enantiomer
- less cardiotoxicity
- greater separation between sensory and motor blockade

EMLA
Eutectic Mixture of Local Anesthetics

- lidocaine and prilocaine
- used topically prior to painful procedures
Spinal Anesthesia

- Injected into subarachnoid space
- Potential for hypotension and respiratory arrest
- Neurological complications
- Less potential for physiological perturbations
- Low probability of systemic toxicity
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Epidural Anesthesia

- Injected into epidural space
- Requires injection of large amounts of drug
- Higher probability of systemic toxicity
- Lower occurrence of headaches
A healthy 39 year old pharmacology professor has received a subarachnoid injection of local anesthetic in preparation for Caesarean section. Her blood pressure falls to 60/40 mmHg. The **MOST** plausible explanation for this is:

A. Vasodilatory action of epinephrine included in the local anesthetic solution.
B. Direct action of the local anesthetic on the peripheral vasculature.
C. Hypersensitivity response to the local anesthetic.
D. High systemic levels of the local anesthetic.
E. Local anesthetic-induced sympathetic denervation.