Anesthetics
Synaptic block:
- ↓ presynaptic Ca^{2+} entry
- ↓ transmitter release
- ↑ postsynaptic Cl^{-} entry and ↓ K^{+} outward leakage → inhibition

Conduction block:
- ↓ axonal Na^{+} entry → failure of action potential propagation
Local Anesthetics
Local Anesthetics

Local Anesthesia

- Reversible loss of sensation
- No loss of consciousness
Local Anesthetics

FIGURE 25-1. Mechanisms of action of local anesthetics. (A) The local anesthetic binds to sodium channels and blocks the generation and conduction of action potentials in peripheral neurons. (B) The sodium channel includes four transmembrane domains. The inactivation gate is a short intracellular loop between domains 3 and 4. The local anesthetic binds to amino acid residues located on domain 4. (C) The nonionized form of the local anesthetic (R-NH₂) penetrates the axonal membrane and is then converted to the ionized form (R-NH₂⁺). The ionized form binds to the sodium channel in the open state, and this prolongs the sodium channel inactivation state. Sodium entry is blocked during the inactivation state.
Local Anesthetics

Mechanism of Action

Figure 25–2. Schematic diagram of the sodium channel in an excitable membrane (e.g., an axon) and the pathways by which a local anesthetic molecule (Drug) may reach its receptor. Sodium ions are not able to pass through the channel when the drug is bound to the receptor. The local anesthetic diffuses within the membrane in its uncharged form. In the aqueous extracellular and intracellular spaces, the charged form (Drug\(^+\)) is also present.
Local Anesthetics

Nerve Fibers

(A)

myelin sheath

node of Ranvier

layers of myelin

axon

nucleus

# Local Anesthetics

## Nerve Fibers

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

---

Local Anesthetics - chemistry

**Procaine**

![Chemical structure of Procaine]

*amide linkage present in some anesthetics

**Cocaine**

![Chemical structure of Cocaine]

**Benzocaine**

![Chemical structure of Benzocaine]

**Procaine**

![Chemical structure of Procaine]

**Lidocaine**

![Chemical structure of Lidocaine]
Local Anesthetics

Ester-type drugs
- Benzocaine
- Chloroprocaine
- Cocaine
- Procaine
- Tetracaine

Amide-type drugs
- Bupivacaine
- Etidocaine
- Lidocaine
- Mepivacaine
- Prilocaine
- Ropivacaine
Local Anesthetics

1. Weak bases (pKa=8-9) – ionized / non ionized

2. Hydrophilic / Lipophilic

![Diagram showing tertiary amine and quaternary ammonium cation](image)
Local Anesthetics

Mechanism of Action

- Synaptic cleft
- Axon membrane
- Sodium channel
- Cocaine
- Channel open (hydrophilic pathway)
- Charged species
- Local anaesthetic effect
- Cytoplasm
- Channel closed (hydrophobic pathway)
- Uncharged species
- Local anaesthetic effect

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Local Anesthetics

Rate of onset
pKa dependent

Duration
Metabolism (amide-type) - slow
Hydrolysis by plasma esterases (ester-type)
pKa – trapping within a cell
Local Anesthetics

- Local anesthetics
  - Esters
    - Long duration (tetracaine)
    - Medium duration (cocaine)
    - Short duration (procaine)
  - Amides
    - Surface-active (benzocaine, cocaine)
    - Long duration (bupivacaine)
    - Medium duration (lidocaine)
Local Anesthetics

Therapeutic Indications

• Local Anesthesia – nerve, tissue
• Anesthesia of legs and pelvis – epidural space
• Anesthesia of skin and mucous membranes – lozenges, sprays and creams
Local Anesthetics

Adverse effects

• CNS – convulsions, respiratory depression
Cocaine – euphoria (monoamine uptake inhibition)

• Cardiovascular - ↓BP
  ↓Na\(^+\) - ↓Ca\(^{2+}\)
  ↓contraction, ↓arrhythmias, vasodilatation
Lidocaine – antidysrhythmic drug

• Hypersensitivity – allergy, anaphylaxis
Ester-type
<table>
<thead>
<tr>
<th>Drug</th>
<th>Induction</th>
<th>Duration</th>
<th>Indication</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>Fast</td>
<td>Moderate</td>
<td>most types of anesthesia</td>
<td>CNS: restlessness, respiration depression, Hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>i.v. - arrhythmias</td>
<td>cardiovascular collapse</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>Slow</td>
<td>Long</td>
<td>surface, infiltration, nerve-block and spinal anesthesia</td>
<td>same</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Slow</td>
<td>Long</td>
<td>epidural anesthesia</td>
<td>same more cardiotoxic Levobupivacaine -less toxic</td>
</tr>
<tr>
<td>Benzocaine</td>
<td>Slow</td>
<td>Long</td>
<td>topic anesthesia cream, spray</td>
<td>systemic toxicity when high concentration and large areas are covered</td>
</tr>
</tbody>
</table>
General Anesthetics
General Anesthetics

Effect of General Anesthetics

- Analgesia
- Amnesia
- Loss of consciousness
- Inhibition of sensory and autonomic reflexes
- Skeletal muscle relaxation
General Anesthetics

A Good General Anesthetic gives:

Controllable and Reversible Anesthesia

Rapid Anesthesia

Rapid Recovery

Level of Anesthesia
General Anesthetics

Pharmacology

I. LOSS OF PAIN SENSATION

II. COMBATIVELY BEHAVIOR

III. SURGICAL ANESTHESIA

IV. MEDULLARY PARALYSIS AND DEATH
General Anesthetics
Pharmacology

No similar structure

Potency ~ lipid solubility

1. **Lipid theory**: Cell membrane

2. **Protein theory**: Hydrophobic binding sites on proteins - ion channels (GABA)
### General Anesthetics

**Pharmacology – Protein Theory**

<table>
<thead>
<tr>
<th>Transmitter</th>
<th>Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate</td>
<td>NMDA, Non-NMDA</td>
</tr>
<tr>
<td>GABA</td>
<td>GABA&lt;sub&gt;A&lt;/sub&gt;, GABA&lt;sub&gt;B&lt;/sub&gt;</td>
</tr>
<tr>
<td>Glycine</td>
<td>Glycine (strychnine sensitive)</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Nicotinic, muscarinic</td>
</tr>
<tr>
<td>5-HT</td>
<td>5-HT&lt;sub&gt;1a&lt;/sub&gt;–&lt;sub&gt;d&lt;/sub&gt;, 5-HT&lt;sub&gt;2&lt;/sub&gt;–&lt;sub&gt;7&lt;/sub&gt;</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>α&lt;sub&gt;1&lt;/sub&gt;, α&lt;sub&gt;2&lt;/sub&gt;, β&lt;sub&gt;1&lt;/sub&gt;–&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>Dopamine</td>
<td>D&lt;sub&gt;1&lt;/sub&gt;–&lt;sub&gt;5&lt;/sub&gt;</td>
</tr>
<tr>
<td>Cholecystokinin</td>
<td>CCK&lt;sub&gt;A&lt;/sub&gt;, CCK&lt;sub&gt;B&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

**Anesthetics**

<table>
<thead>
<tr>
<th>R effect</th>
<th>Anesthetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑pain</td>
<td>-</td>
</tr>
<tr>
<td>↓pain</td>
<td>+</td>
</tr>
<tr>
<td>↑pain</td>
<td>-</td>
</tr>
</tbody>
</table>
General Anesthetics

- **Inhalation**
  - N₂O
  - Nonflammable Halogenated hydrocarbons
  - Ethers

- **Intravenous**
  - Water-soluble
  - Aqueous propylene glycol solutions
  - Emulsions

Usually a mix is given: IV for fast onset, Inhalation for prolonged, deep anesthesia.
General Anesthetics

Partition Coefficients

Oil:gas
Solubility in oil
• High – ↑potency
  hangover

Blood:gas
Solubility in blood
• Low - ↑ induction
  ↑ recovery
• High - ↓ induction
  ↓ recovery
General Anesthetics
Partition Coefficients (inhaled)
**General Anesthetics**

Inhalation anesthetics

simple lipophilic molecules

<table>
<thead>
<tr>
<th>Nitrous oxide</th>
<th>$\text{N}_2\text{O}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>$\text{CF}_3-\text{CHBrCl}$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Molecular Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desflurane</td>
<td>$\text{CHF}_2-\text{O}-\text{CF}_3$</td>
</tr>
<tr>
<td>Diethyl ether</td>
<td>$\text{CH}_3-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_3$</td>
</tr>
<tr>
<td>Enflurane</td>
<td>$\text{CHFCl}-\text{CF}_2-\text{O}-\text{CHF}_2$</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>$\text{CF}_3-\text{CHCl}-\text{O}-\text{CHF}_2$</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>$\text{CHCl}_2-\text{CF}_2-\text{O}-\text{CH}_3$</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>$\text{CH}_2\text{F}-\text{O}-\text{CH(CF}_3)_2$</td>
</tr>
</tbody>
</table>
General Anesthetics

Inhalation anesthetics & adjunction therapy

Some functions of adjuncts to anesthesia

- Relieve anxiety (benzodiazepine)
- Relax muscles (muscle relaxant)
- Prevent secretion of fluids into the respiratory tract (anticholinergic drug)
- Rapid induction of anesthesia (short-acting barbiturate)
- Prevent postsurgical nausea and vomiting (antiemetic drug)
**General Anesthetics**

**Intravenous anesthetics**

Used mostly to induce drowsiness and relaxation before the procedure.

<table>
<thead>
<tr>
<th>Water soluble (short-acting)</th>
<th>Aqueous propylene glycol solutions</th>
<th>Emulsions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td>Imidazole</td>
<td>Dialkyphenol</td>
</tr>
<tr>
<td><em>Thiopental, Methohexital, Thiamylal</em></td>
<td><em>Etomidate</em></td>
<td><em>Propofol</em></td>
</tr>
<tr>
<td>Cyclohexylamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Ketamine (given I.M.)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Diazepam, Midazolam</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butyrophenones</td>
<td>Compatible with pre-anesthetics</td>
<td>Non-compatible with pre-anesthetics</td>
</tr>
<tr>
<td><em>Droperidol</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid Analgesics</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Morphine, fentanyl</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
General Anesthetics

Intravenous anesthetics

- Thiopental Sodium
- Ketamine
- Etomidate
- Fentanyl
- Propofol
- Midazolam
**General Anesthetics**

**Side Effects**

**All** - Cardiovascular and respiratory depression, convulsions

**Halothane** - Hypotension, Arrhythmias, Malignant hyperthermia

**Methoxyflurane** - Nephrotoxicity

**Ketamine** *(dissociative anesthesia)* - **Post-operative**: nausea, vomiting, hallucinations in adults
<table>
<thead>
<tr>
<th><strong>Drug</strong></th>
<th>induction /recovery</th>
<th><strong>Indication</strong></th>
<th><strong>Side-effects</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N₂O</strong></td>
<td>Fast</td>
<td>Low potency - Combined with other inhalation agents</td>
<td>Anemia with prolonged use</td>
</tr>
<tr>
<td><strong>Halothane</strong></td>
<td>Medium</td>
<td>common use newer agents preferable</td>
<td>Hypotension Arrhythmias Malignant hyperthermia Hepatotoxicity (repeated use)</td>
</tr>
<tr>
<td><strong>Enflurane</strong></td>
<td>Medium</td>
<td>widely used</td>
<td>Convulsions Malignant hyperthermia</td>
</tr>
<tr>
<td><strong>Isoflurane</strong></td>
<td>Medium</td>
<td>widely used as alternative to halothane</td>
<td></td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td>induction /recovery</td>
<td><strong>Indication</strong></td>
<td><strong>Side-effects</strong></td>
</tr>
<tr>
<td>------------</td>
<td>---------------------</td>
<td>-----------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Thipenthal</td>
<td>Fast induction</td>
<td>widely used as induction agent</td>
<td>Cardiovascular and respiratory depression</td>
</tr>
<tr>
<td></td>
<td>Slow recovery, hangover</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>Fast</td>
<td>widely used day-case surgery</td>
<td>Cardiovascular and respiratory depression</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Slow</td>
<td>minor procedures in children dissociative anesthesia</td>
<td>Post-operative: nausea, vomiting hallucinations in adults</td>
</tr>
</tbody>
</table>