Pharmacology of Local Anesthetics

Outline

- History
- Chemistry and Structure-Activity Relationships
- Mechanism of Action
- Pharmacological effects and toxicities
- Clinical aspects
Albert Niemann isolated crystals from the coca shrub – and called it “cocaine” – he found that it reversibly numbed his tongue!

Sigmund Freud became aware of the mood altering properties of cocaine, and thought it might be useful in curing morphine addiction. Freud obtained a supply of cocaine (from Merck) and shared it with his friend Carl Koller, a junior intern in ophthalmology at the University of Vienna.

Following preliminary experiments using conjunctival sacs of various animals species, Koller did first eye surgery in humans using cocaine as local anesthetic.

German chemist Alfred Einhorn produced the first synthetic ester-type local anesthetic - novocaine (procaine) - retained the nerve blocking properties, but lacked the powerful CNS actions of cocaine.

Swedish chemist Nils Löfgren synthesized the first amide-type local anesthetic - marketed under the name of xylocaine (lidocaine).
Pharmacology of Local Anesthetics

Outline

• History

• Chemistry and Structure-Activity Relationships

• Mechanism of Action

• Pharmacological effects and toxicities

• Clinical aspects
Pharmacology of Local Anesthetics - Chemistry

Structure-Activity Relationships

All local anesthetics contain 3 structural components:

- an aromatic ring (usually substituted)
- a connecting group which is either an ester (e.g., novocaine) or an amide (e.g., lidocaine)
- an ionizable amino group
Chemical structures of prototypical ester- and amide-type local anesthetics – comparison with cocaine (note 3 structural components of procaine)
Pharmacology of Local Anesthetics – Chemistry

Structure-Activity Relationships:

Two **important** chemical properties of local anesthetic molecule that determine activity:

**Lipid solubility:** increases with extent of substitution (# of carbons) on aromatic ring and/or amino group

**Ionization constant** (**pK**) – determines proportion of ionized and non-ionized forms of anesthetic
**Pharmacology of Local Anesthetics** – **Chemistry**

**Lipid solubility**: determines, potency, plasma protein binding and duration of action of local anesthetics

<table>
<thead>
<tr>
<th></th>
<th>Lipid solubility</th>
<th>Relative potency</th>
<th>Plasma protein binding (%)</th>
<th>Duration (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>procaine</strong></td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>60-90</td>
</tr>
<tr>
<td><strong>lidocaine</strong></td>
<td>4</td>
<td>2</td>
<td>65</td>
<td>90-200</td>
</tr>
<tr>
<td><strong>tetracaine</strong></td>
<td>80</td>
<td>8</td>
<td>80</td>
<td>180-600</td>
</tr>
</tbody>
</table>
Local anesthetics are weak bases – proportion of free base (R-NH₂) and salt (R-NH₃⁺) forms depends on pH and pK of amino group.

\[
\text{pH} = \text{pK} + \log \left[ \frac{\text{base}}{\text{salt}} \right]
\]

(\text{Henderson-Hasselbalch equation})

**Example:** Calculate the proportions of free base and salt forms of tetracaine (pK = 8.5) at pH (7.5).

\[
7.5 = 8.5 + \log \left[ \frac{\text{base}}{\text{salt}} \right]
\]

\[
\log \left[ \frac{\text{base}}{\text{salt}} \right] = -1
\]

\[
\left[ \frac{\text{base}}{\text{salt}} \right] = 10^{-1} = 1/10
\]

∴ there is 10x more drug in the ionized than in the non-ionized form at physiological pH.
Both free base and ionized forms of local anesthetic are necessary for activity:

Local anesthetic enters nerve fibre as neutral free base and the cationic form blocks conduction by interacting at inner surface of the Na⁺ channel.
Local anesthetics with lower pK have a more rapid onset of action (more uncharged form more rapid diffusion to cytoplasmic side of Na\(^+\) channel)

<table>
<thead>
<tr>
<th>Local Anesthetic</th>
<th>pK</th>
<th>% free base at pH 7.4</th>
<th>Onset of anesthesia (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>lidocaine</td>
<td>7.9</td>
<td>25</td>
<td>2-4</td>
</tr>
<tr>
<td>bupivacaine</td>
<td>8.1</td>
<td>18</td>
<td>5-8</td>
</tr>
<tr>
<td>procaine</td>
<td>9.1</td>
<td>2</td>
<td>14-18</td>
</tr>
</tbody>
</table>
Pharmacology of Local Anesthetics

Outline

• History

• Chemistry and Structure-Activity Relationships

• Mechanism of Action

• Pharmacological effects and toxicities

• Clinical aspects
Mechanism of Action

- conduction of nerve impulses is mediated by action potential (AP) generation along axon

- Cationic form of anesthetic binds at inner surface of Na⁺ channel – preventing Na⁺ influx (rising phase of membrane potential) which initiates AP → blockade of nerve impulses (e.g., those mediating pain)
Mechanism of Action

- **Na⁺ channel (resting)**
- **Na⁺ channel (open)**
- **depolarization**
- **action potential**

- **Na⁺ channel (resting)**
- **Na⁺ channel (open)**
- **II**
- **no depolarization**

- **rapid**

- **local anesthetic**
- **Na⁺ channel - local anesthetic complex (inactive)**

- **slow**
Mechanism of Action

- Local anesthetics bind to the open form of the Na\(^+\) channel from the cytoplasmic side of the neuronal membrane.

- In contrast, a number of highly polar toxins (e.g., tetrodotoxin and saxitoxin) block the Na\(^+\) channel from the outer surface of the neuronal membrane.

Schematic representation of a Na\(^+\) channel showing binding sites for tetrodotoxin (TTX) and saxitoxin (ScTX).
Mechanism of Action

Structures of two naturally occurring highly polar substances with powerful local anesthetic activity causing fatal paralysis – **tetrodotoxin** (puffer fish) and **saxitoxin** (shell fish)

![Tetrodotoxin Structure](image)

![Saxitoxin Structure](image)

tetrodotoxin  \hspace{2cm} saxitoxin
Pharmacology of Local Anesthetics

Outline

• History

• Chemistry and Structure-Activity Relationships

• Mechanism of Action

• Pharmacological effects and toxicities

• Clinical aspects
Pharmacological effects and toxicities

Functional consequences of Na$^+$ channel blockade by local anesthetics:

- **nerves**: decrease or abolition of conduction
- **vascular smooth muscle**: vasodilatation
- **heart**: decreased excitability (reduced pacemaker activity, prolongation of effective refractory period)
- **central nervous system**: increased excitability, followed by generalized depression
Pharmacological effects and toxicities

Effects of local anesthetics on nerve conduction

- **Na\(^+\) channels** are present in all nerves and local anesthetics, at sufficient concentrations, can completely block action potential generation and conduction.

- “**differential nerve blockade**” – nerve fibres differ markedly in their susceptibility to conduction blockage by local anesthetics (this is the basis of their clinical use).
  
  e.g., **small, non-myelinated neurons** mediating pain are much more susceptible than **large, myelinated fibres** mediating motor functions.
Pharmacological effects and toxicities

Relative size and myelination and susceptibility to blockage by local anesthetics

<table>
<thead>
<tr>
<th>Fibre type</th>
<th>function</th>
<th>diameter (µm)</th>
<th>myelination</th>
<th>susceptibility to LA block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A</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>+</td>
</tr>
<tr>
<td>beta</td>
<td>touch, pressure</td>
<td>5-12</td>
<td>heavy</td>
<td>++</td>
</tr>
<tr>
<td>gamma</td>
<td>muscle spindles</td>
<td>3-6</td>
<td>heavy</td>
<td>++</td>
</tr>
<tr>
<td>delta</td>
<td>pain, temperature</td>
<td>2-5</td>
<td>heavy</td>
<td>+++</td>
</tr>
<tr>
<td>Type B</td>
<td>preganglionic</td>
<td>&lt;3</td>
<td>light</td>
<td>++++</td>
</tr>
<tr>
<td>Type C</td>
<td>dorsal root</td>
<td>0.4-1.2</td>
<td>none</td>
<td>++++</td>
</tr>
</tbody>
</table>
Pharmacological effects and toxicities

Differential susceptibility of nerves to local anesthetics

1. In neuronal conduction, depolarizing current moves along nodes of Ranvier – 2-3 successive nodes must be blocked to completely impair neuronal conduction.

small fibres have smaller internodal distances - ∴ a shorter length of nerve fibre needs to be blocked to impair conduction as compared to larger nerve fibres.
Pharmacological effects and toxicities

Differential susceptibility of nerves to local anesthetics (cont’d)

2. Anesthetic blockade of Na\(^+\) channels exhibits “use-dependence” - increased frequency of stimulation increased level of blockade

Illustration of use-dependent local anesthetic neuronal blockade – as stimulation frequency increases from 1 to 25, the downward Na\(^+\) current spike is progressively reduced.

- neurons with high rates of firing (e.g., pain fibres) or ectopic pacemakers in the myocardium will be highly susceptible to blockade by local anesthetics
Pharmacological effects and toxicities

Differential susceptibility of nerves to local anesthetics (cont’d)

3. In excitable tissues with long action potentials, probability of Na⁺ channels being in (susceptible) “open” form is increased enhanced susceptibility to blockade by local anesthetics

e.g., pain fibres have long action potentials (3 millisecond) versus motor fibres (0.5 millisecond)

cardiac muscle has prolonged action potentials relative to other excitable tissues - myocardium highly susceptible to local anesthetics (clinically important)
Pharmacological effects and toxicities

Effects of local anesthetics on vascular smooth muscle

Blockade of Na\(^+\) channels in vascular smooth muscle by local anesthetics \(\rightarrow\) vasodilatation

consequences of vasodilatation:

- **enhanced rate of removal** of anesthetic from site of administration *(decreased duration of anesthetic action and increased risk of toxicity)*
- **hypotension** *(may be intensified by anesthetic-induced cardiodepression)*
Pharmacological effects and toxicities

Effects of local anesthetics on vascular smooth muscle

Anesthetic-induced vasodilatation can be counteracted by the concomitant administration of a vasoconstrictor.

Consequences of including vasoconstrictor:

- Prolongation of anesthetic action
- Decreased risk of toxicity
- Decrease in bleeding from surgical manipulations
Pharmacological effects and toxicities

Effects of vasoconstrictors on local anesthetic duration

**Adrenaline** is the conventional vasoconstrictor included in commercial local anesthetic preparations.

The **concentration** of adrenaline in these preparations can vary and is expressed as **grams/ml** (e.g. 1:100,000 = 1 gram/100,000 ml).

<table>
<thead>
<tr>
<th>local anesthetic</th>
<th>adrenaline</th>
<th>duration of anesthesia (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>lidocaine (2%)</td>
<td>-</td>
<td>5-10</td>
</tr>
<tr>
<td>lidocaine (2%)</td>
<td>1:100,000</td>
<td>60</td>
</tr>
<tr>
<td>lidocaine (2%)</td>
<td>1:50,000</td>
<td>60</td>
</tr>
</tbody>
</table>
Pharmacological effects and toxicities

Effects of local anesthetics on heart

- Local anesthetics can reduce **myocardial excitability** and **pacemaker activity** and also prolong the **refractory period** of myocardial tissue – this is the basis of the **antiarrhythmic** effects of local anesthetics.

- Local anesthetic-induced **myocardial depression** (compounded by anesthetic-induced **hypotension**)) can also be a manifestation of toxicity and can lead to **cardiovascular collapse** and even **death**!
As is the case with CNS depressants generally (e.g., alcohol) local anesthetics (at toxic doses) produce a biphasic pattern of excitation followed by depression.

The excitatory phase likely reflects the preferential blockade of inhibitory neurons and effects can range from mild hyperactivity to convulsions.

The subsequent depressive phase can progress to cardiovascular collapse and even death if unmanaged.
Pharmacology of Local Anesthetics

Outline

• History
• Chemistry and Structure-Activity Relationships
• Mechanism of Action
• Pharmacological effects and toxicities
• Clinical aspects
Clinical aspects

Applications of local anesthesia:

- **nerve block**: injected locally to produce regional anesthesia (e.g., dental and other minor surgical procedures)
- **topical application**: to skin for analgesia (e.g., benzocaine) or mucous membranes (for diagnostic procedures)
- **spinal anesthesia**: injection into CSF to produce anesthesia for major surgery (e.g., abdomen) or childbirth
- **local injection**: at end of surgery to produce long-lasting post-surgical analgesia (reduces need for narcotics)
- **i.v. infusion**: for control of cardiac arrhythmias (e.g., lidocaine for ventricular arrhythmias)
Clinical aspects

Nerve block by local anesthetics

- most **common** use of local anesthetics (e.g., dental)
- **order of blockade**: pain > temperature > touch and pressure > motor function - **recovery** is reverse (i.e., sensation of pain returns last)
- **recall**: onset of anesthesia determined by pK, duration increases with **lipophilicity** of the anesthetic molecule
- **recall**: concommitant use of vasoconstrictor → **prolongation of anesthesia** and **reduction in toxicity**
- inflammation → **reduced** susceptibility to anesthesia (lowered local pH increases proportion of anesthetic in charged form that cannot permeate nerve membrane)
Clinical aspects

local anesthetic toxicity

most **common** causes:

- inadvertent **intravascular injection** while inducing nerve block (important to always **aspirate** before injecting!)
- **rapid** absorption following **spraying of mucous membranes** (e.g., respiratory tract) with local anesthetic prior to diagnostic or clinical procedures

**manifestations of local anesthetic toxicity**: allergic reactions, cardiovascular and CNS effects
Clinical aspects

local anesthetic toxicity (cont’d)

- **allergic reactions**: restricted to esters – metabolized to allergenic p-amino benzoic acid (PABA) (∴ amides usually preferred for nerve block)

- **cardiovascular**: may be due to anesthetic (cardiodepression, hypotension) or vasoconstrictor (hypertension, tachycardia) ∴ monitor pulse/blood pressure

- **CNS**: excitability (agitation, increased talkativeness – may → convulsions) followed by CNS depression (∴ care in use of CNS depressants to treat convulsions - may worsen depressive phase – convulsions usually well tolerated if brain oxygenation maintained between seizures)
Thanks for your attention!

- Happy Thanksgiving!!

- Contact: dgodin@mail.ubc.ca