Local anaesthesia

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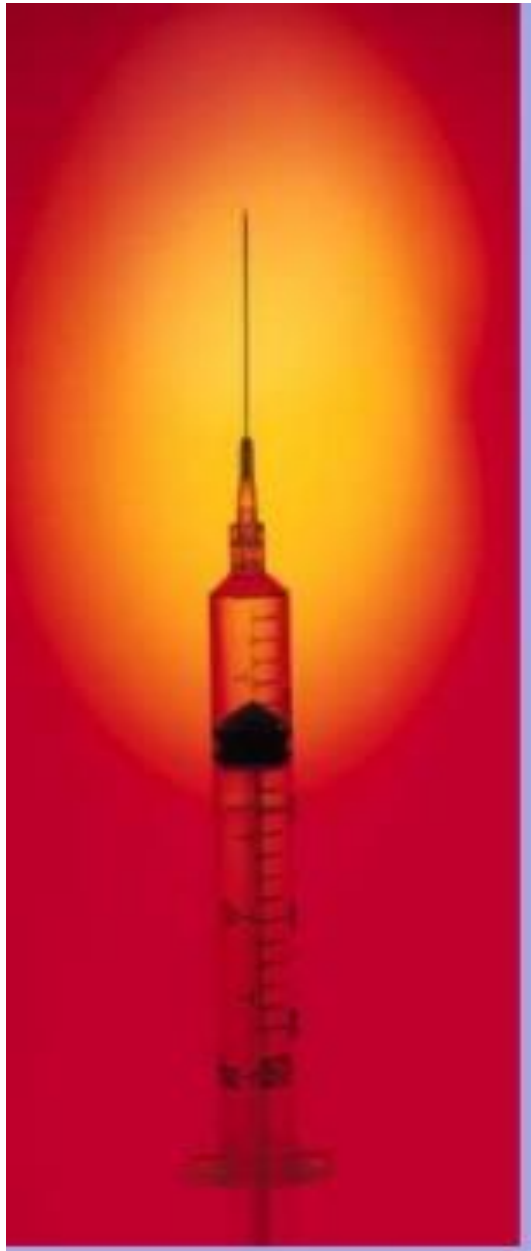
OMFS, KHMH



COMERCIALLY PREPARED LOCAL ANESTHESIA CONSISTS OF:

- Local anesthetic agent (xylocaine, lignocaine 2%)
- Vasoconstrictor (adrenaline 1: 80,000)
- Reducing agent (sodium metabisulphite)
- Preservative (methylparaben,capryl hydrocuprienotoxin)
- Fungicide (thymol)
- Vehicle (distillde water,NaCl)

Pharmacology of Local Anesthetics - Chemistry

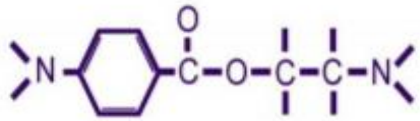
Structure-Activity Relationships

All local anesthetics contain 3 **structural components**:

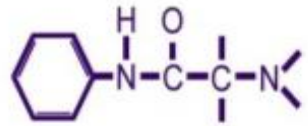
- **an aromatic ring (usually substituted)**
- **a connecting group which is either an ester (e.g., novocaine) or an amide (e.g. lidocaine)**
- **an ionizable amino group**

Chemical structure of local anesthetics

Aromatic lipophilic portion - Intermediate chain - Amine hydrophilic portion



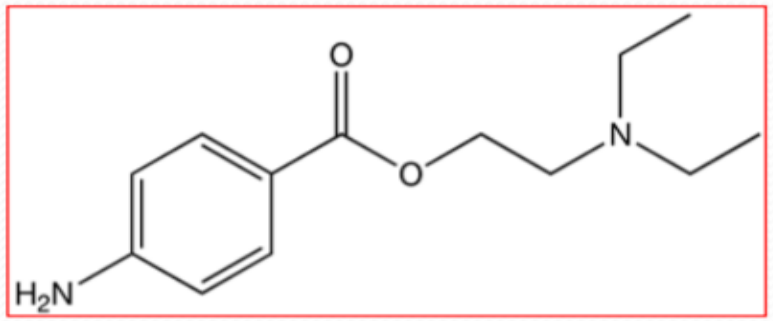
AMINO ESTERS



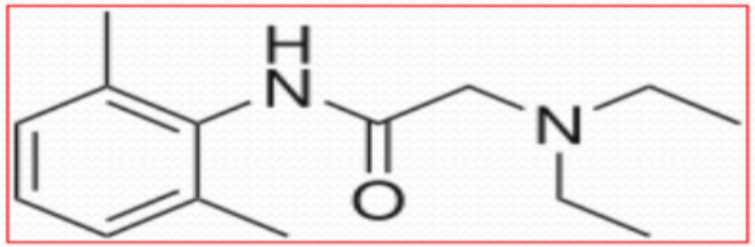
AMINO AMIDES

Pharmacology of Local Anesthetics – Chemistry

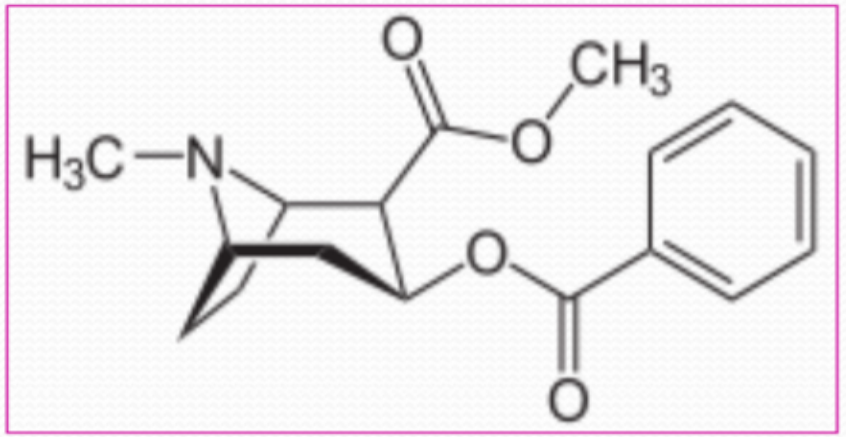
Chemical structures of prototypical ester- and amide-type local anesthetics – comparison with cocaine (note 3 structural components of procaine)



procaine/novocaine



lidocaine/xylocaine



cocaine

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

	Lipid solubility	Relative potency	Plasma protein binding (%)	Duration (minutes)
procaine	1	1	6	60-90
lidocaine	4	2	65	90-200
tetracaine	80	8	80	180-600

Pharmacology of Local Anesthetics – Chemistry

Local anesthetics are weak bases – proportion of free base ($R\text{-}NH_2$) and salt ($R\text{-}NH_3^+$) forms depends on pH and pK of amino group

$$pH = pK + \log [base]/[salt]$$

(Henderson-Hasselbalch equation)

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

$$7.5 = 8.5 + \log [base]/[salt]$$

$$\log [base]/[salt] = -1$$

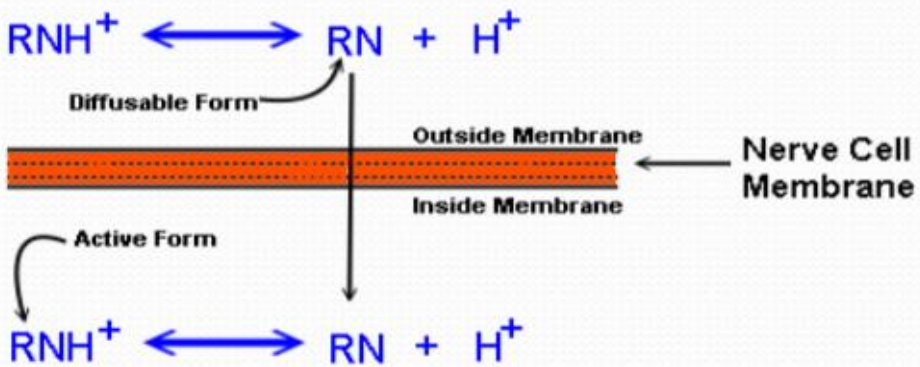
$$[base]/[salt] = 10^{-1} = 1/10$$

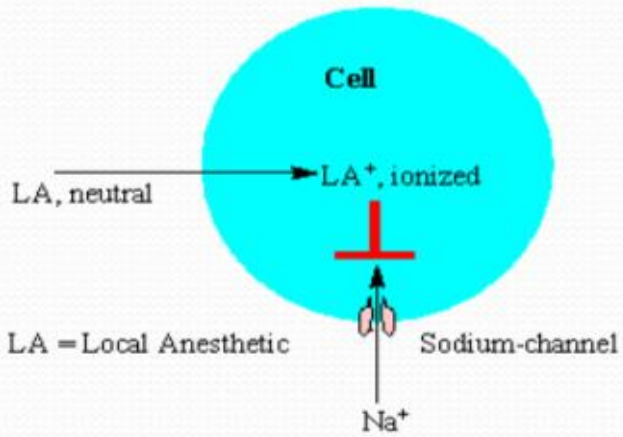
∴ there is 10x more drug in the ionized than in the non-ionized form at physiological pH

Pharmacology of Local Anesthetics – Chemistry

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



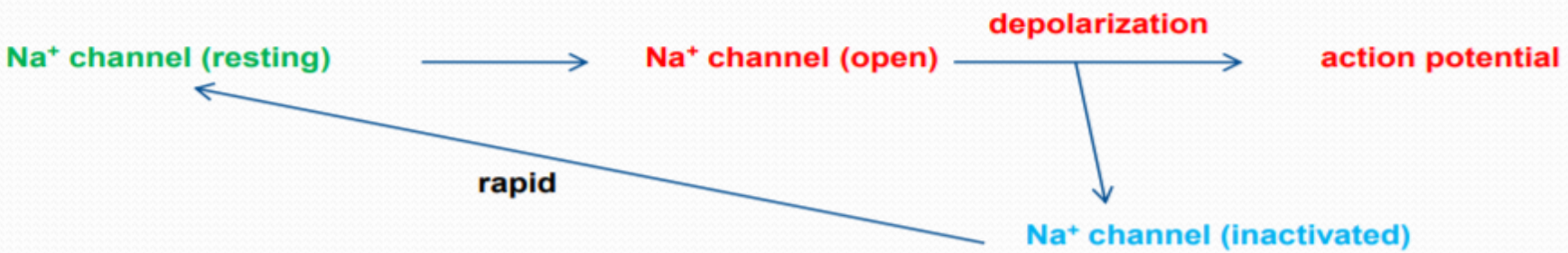


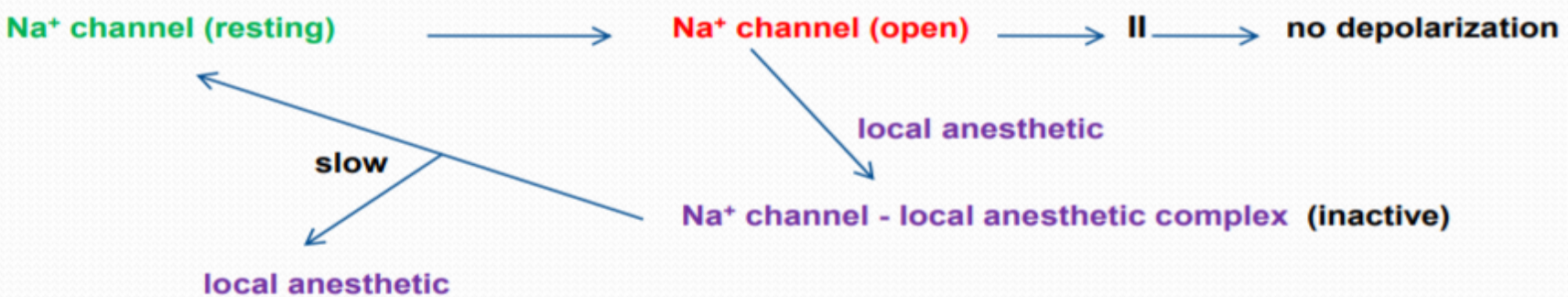
Pharmacology of Local Anesthetics – Chemistry

Local anesthetics with lower pK have a more rapid onset of action (more uncharged form ⟹ more rapid diffusion to cytoplasmic side of Na^+ channel)

	pK	% free base at pH 7.4	Onset of anesthesia (min)
lidocaine	7.9	25	2-4
bupivacaine	8.1	18	5-8
procaine	9.1	2	14-18

Mechanism of Action





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 susceptiblity 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 **that large**, **myelinated fibres** mediating **motor functions**

Pharmacological effects and toxicities

Effects of local anesthetics on vascular smooth muscle

Blockade of Na^+ channels in vascular smooth muscle by local anesthetics → 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)**

local anesthetic	adrenaline	duration of anesthesia (min)
lidocaine (2%)	-	5-10
lidocaine (2%)	1:100,000	60
lidocaine (2%)	1:50,000	60

Pharmacological effects and toxicities

Effects of local anesthetics on CNS

- 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.

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)

THANK YOU