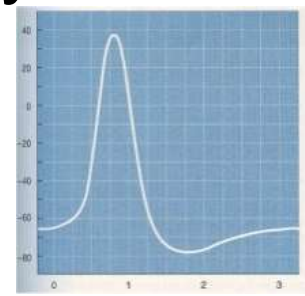
UCL
School of
Pharmacy

Local Anaesthetics 2025

Local anaesthetics

- **Local anaesthetics** are a group of chemical compounds that transiently inhibit electrical excitation-conduction in peripheral nerve fibres by blocking voltage-activated Na^+ channels and so reversibly block the sensation of pain or feeling in specific areas of the body, without the loss of consciousness.



- **They are used clinically** for performing minor surgical operations or procedures *e.g.* **tooth extraction.**

History of local anaesthesia

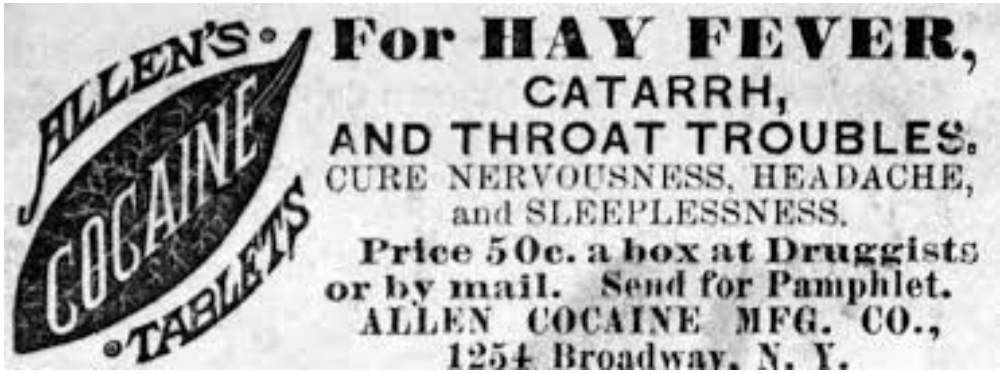
- **The first known local anaesthetic agent was cocaine**
- present in the leaves of the bush ***Erythroxylin coca*** which grows in S. America.

- **Peruvian Indians** chewed on coca leaves to obtain a CNS stimulant effect (unrelated to local anaesthesia). **Cocaine** was first isolated in 1865.

- **In 1884, Carl Koller** first demonstrated the usefulness of **coca leaf extract** as a topical anaesthetic in ophthalmology.

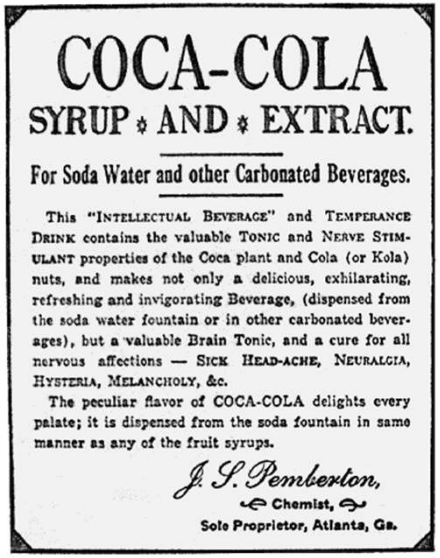
History of local anaesthesia

- **Cocaine tonics/powders/pills** were once very popular in the USA for headaches, fatigue, asthma, impotence. Coca wine was an example, which mixed coca-leaf extract with Bordeaux wine.



History of local anaesthesia

- **Cocaine and *Coca-Cola***. *Coca-Cola* was first created in the USA in 1886 as a non-alcoholic alternative to Coca wine and contained coca-leaf extract (cocaine) along with extract of kola nut (for caffeine) hence the name. It contained cocaine up until 1929 when it was removed, but **the company officially deny cocaine was ever included in their drink.** The modern formula (secret) most likely still contains cocaine-free coca-leaf extract for taste.


COCA-COLA

SYRUP ✦ AND ✦ EXTRACT.

For Soda Water and other Carbonated Beverages.

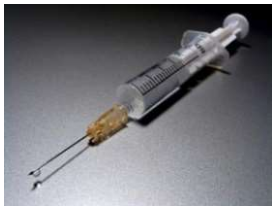
This "INTELLECTUAL BEVERAGE" and TEMPERANCE DRINK contains the valuable TONIC and NERVE STIMULANT properties of the Coca plant and Cola (or Kola) nuts, and makes not only a delicious, exhilarating, refreshing and invigorating Beverage, (dispensed from the soda water fountain or in other carbonated beverages), but a valuable Brain Tonic, and a cure for all nervous affections — SICK HEAD-ACHE, NEURALGIA, HYSTERIA, MELANCHOLY, &c.

The peculiar flavor of COCA-COLA delights every palate; it is dispensed from the soda fountain in same manner as any of the fruit syrups.

J. S. Pemberton,
Chemist,
Sole Proprietor, Atlanta, Ga.

History of local anaesthesia

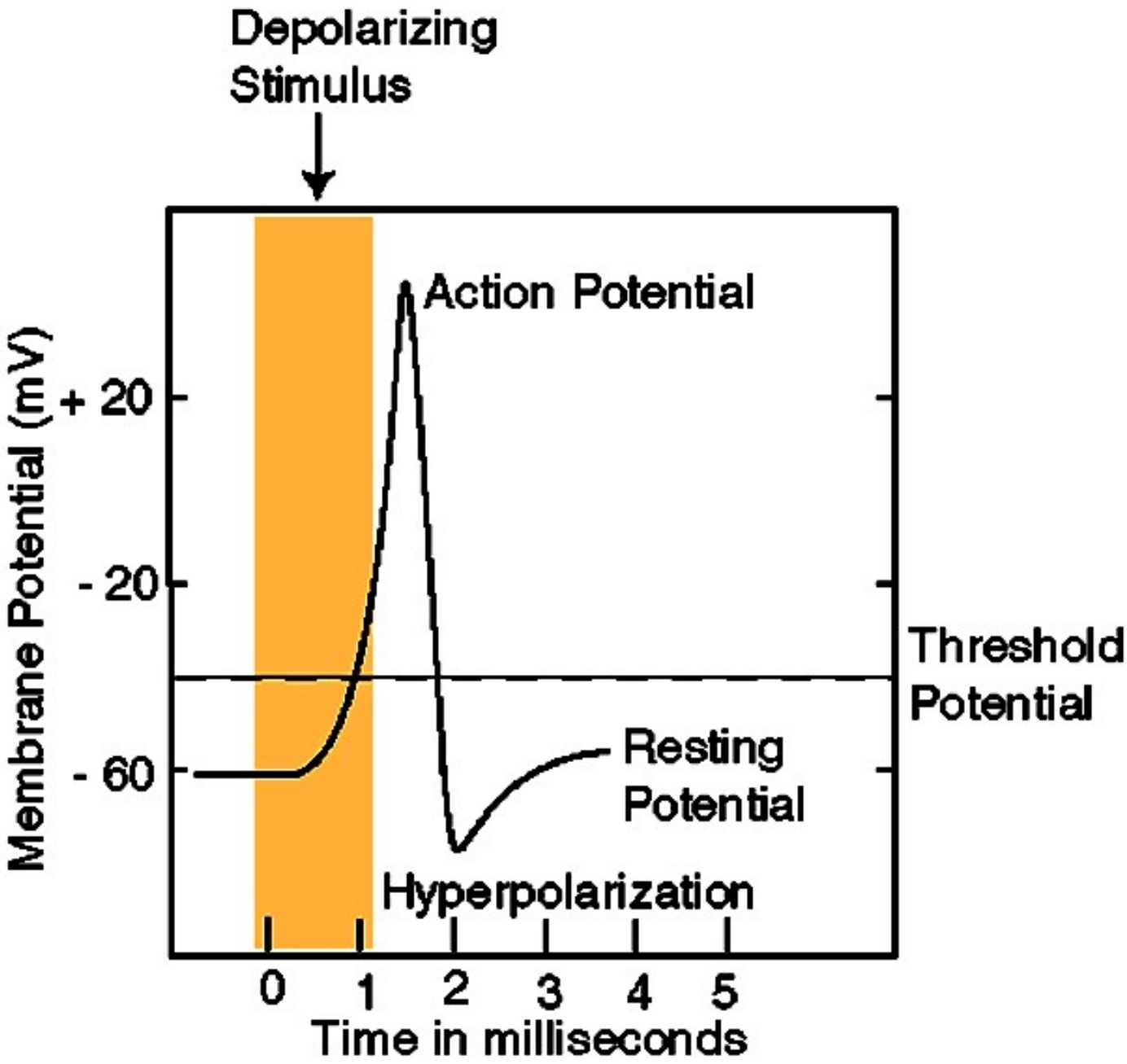
- **Procaine** (*Novocaine*) was the first derivative of cocaine, synthesized in 1905 – fewer side effects - no CNS stimulant effects. No longer used in the UK.



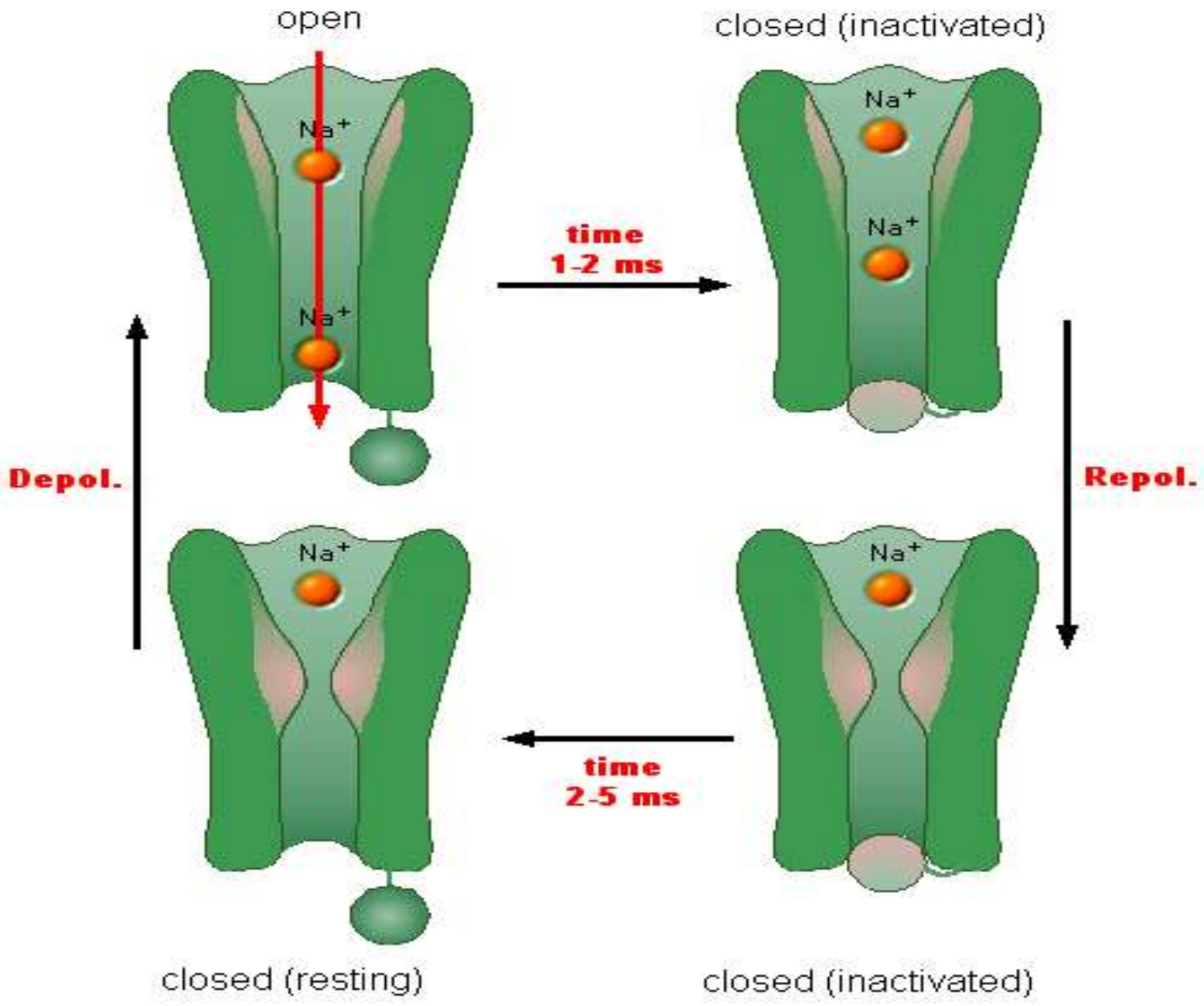
- **Lidocaine** (*Lignocaine: Xylocaine*) was synthesized in 1943 as a new amide class of local anaesthetiic – fewer allergic responses – faster onset of action.

- Many other amide local anaesthetics are now available: *e.g.* **mepivacaine, prilocaine, bupivacaine, tetracaine.**

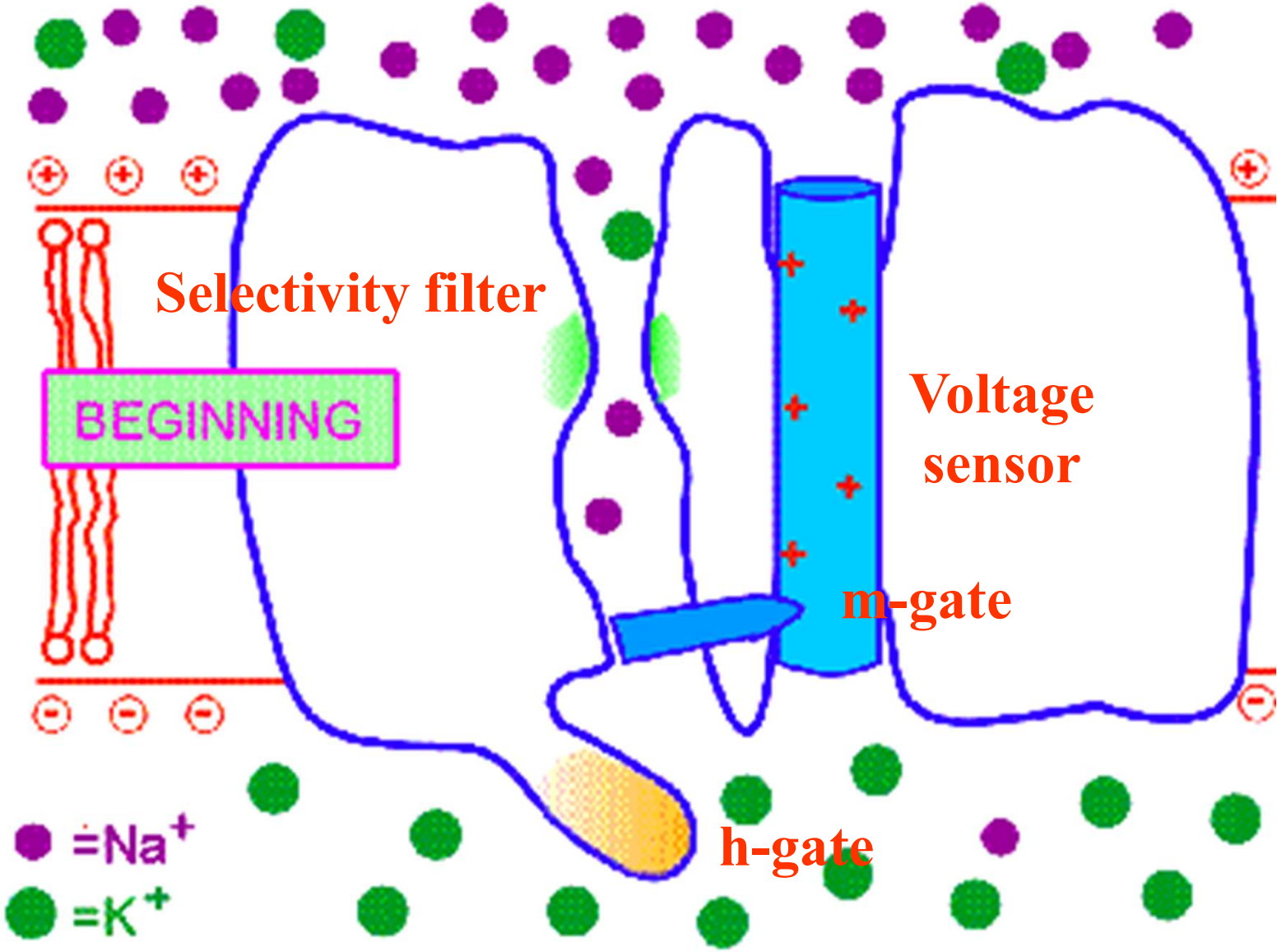
The nerve action potential



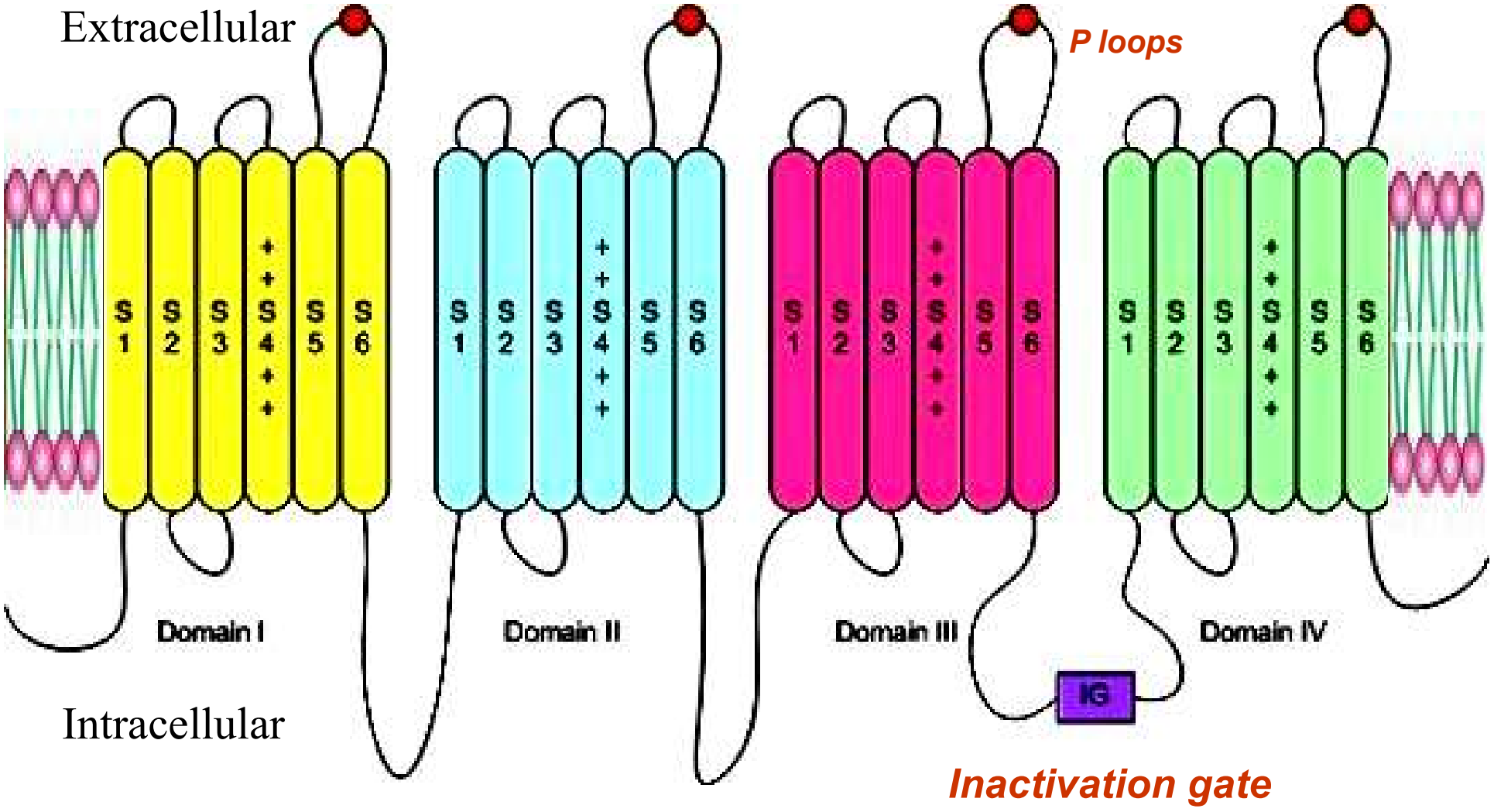
Activation/inactivation of a Na^+ channel



Activation/inactivation of a Na^+ channel

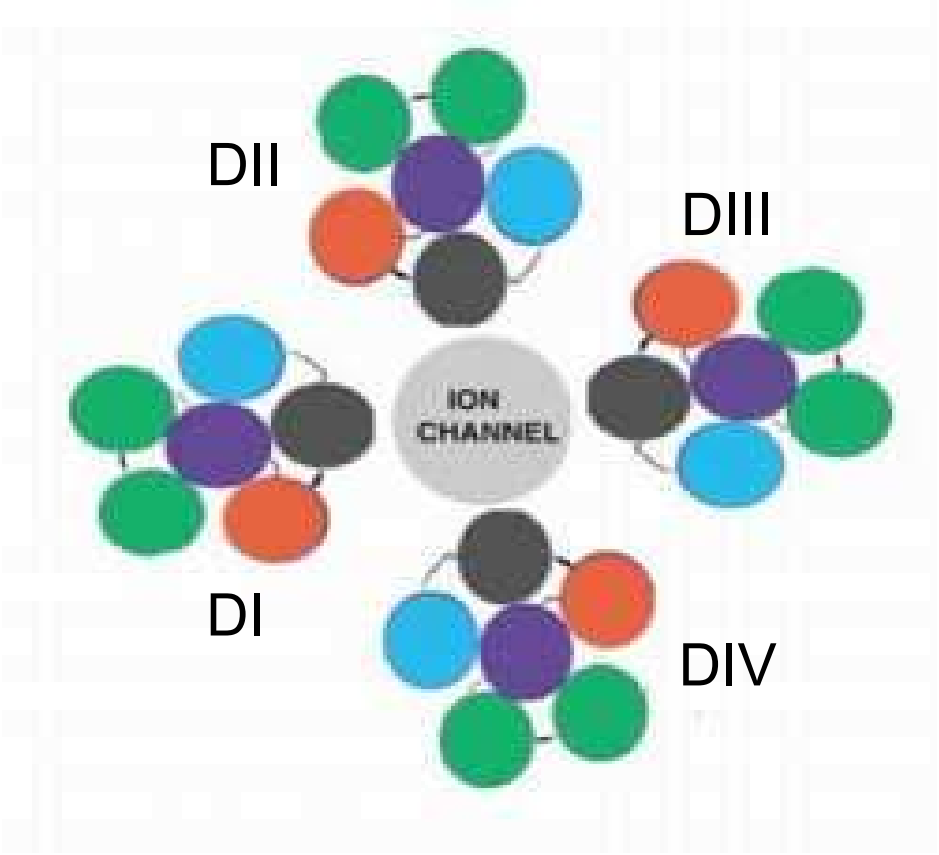


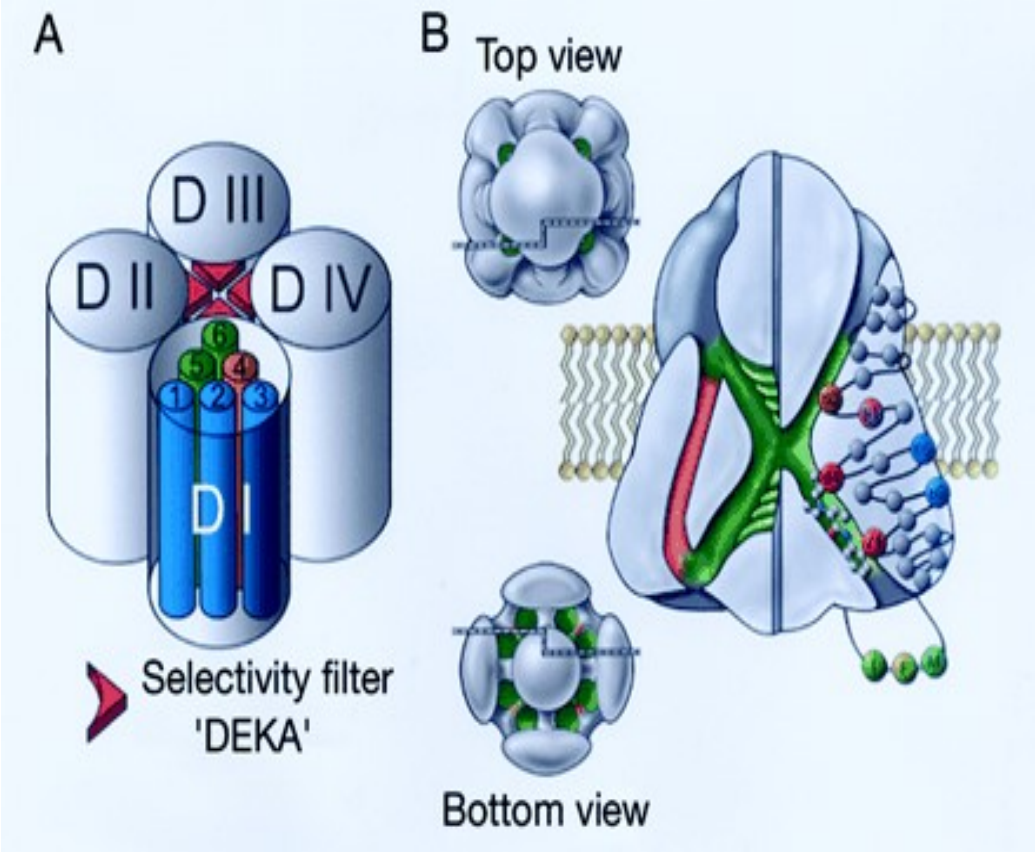
Basic structure of voltage-gated Na^+ channel



α-subunit: 260 kDa

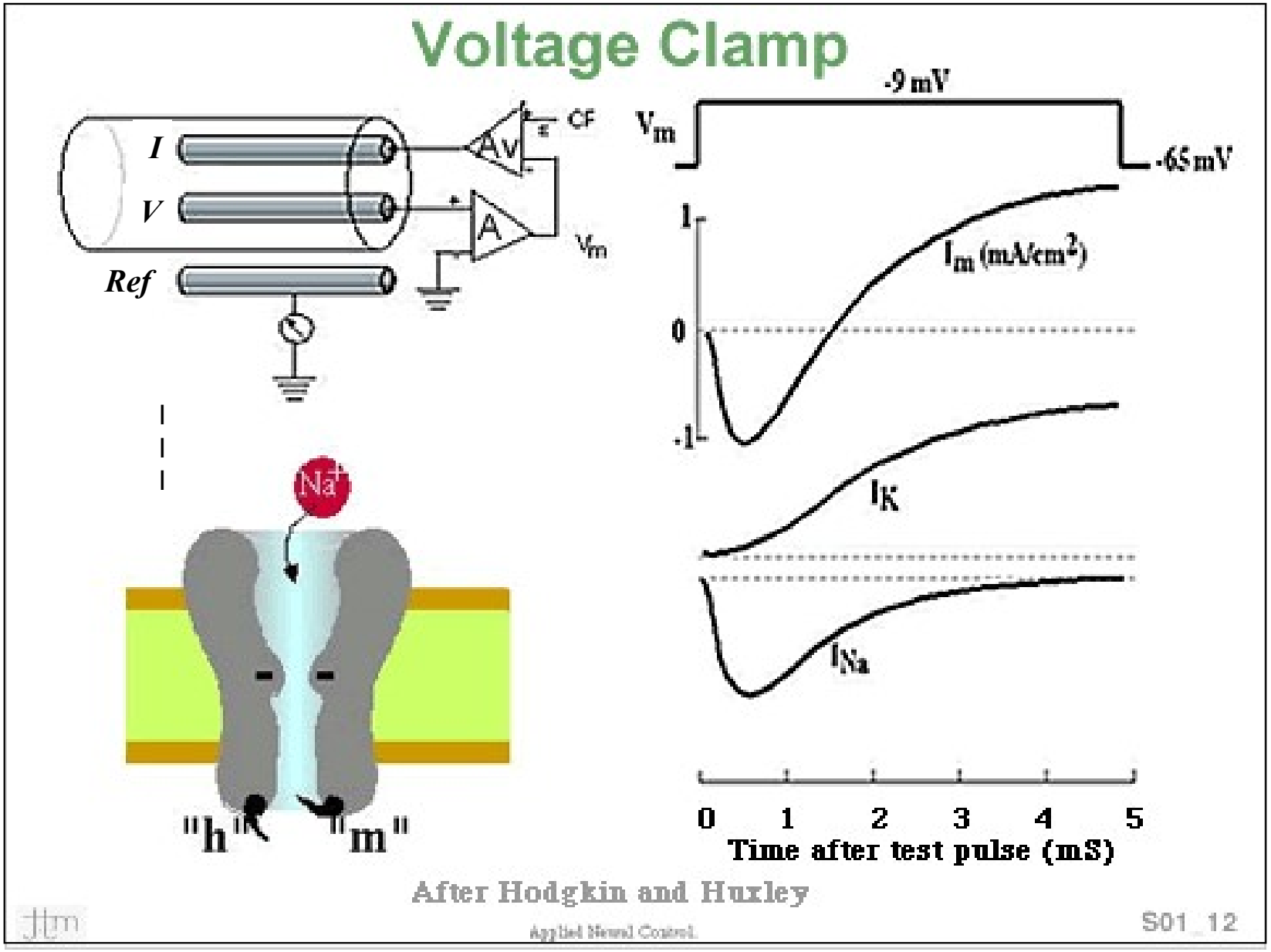
Basic structure of voltage-gated Na^+ channel



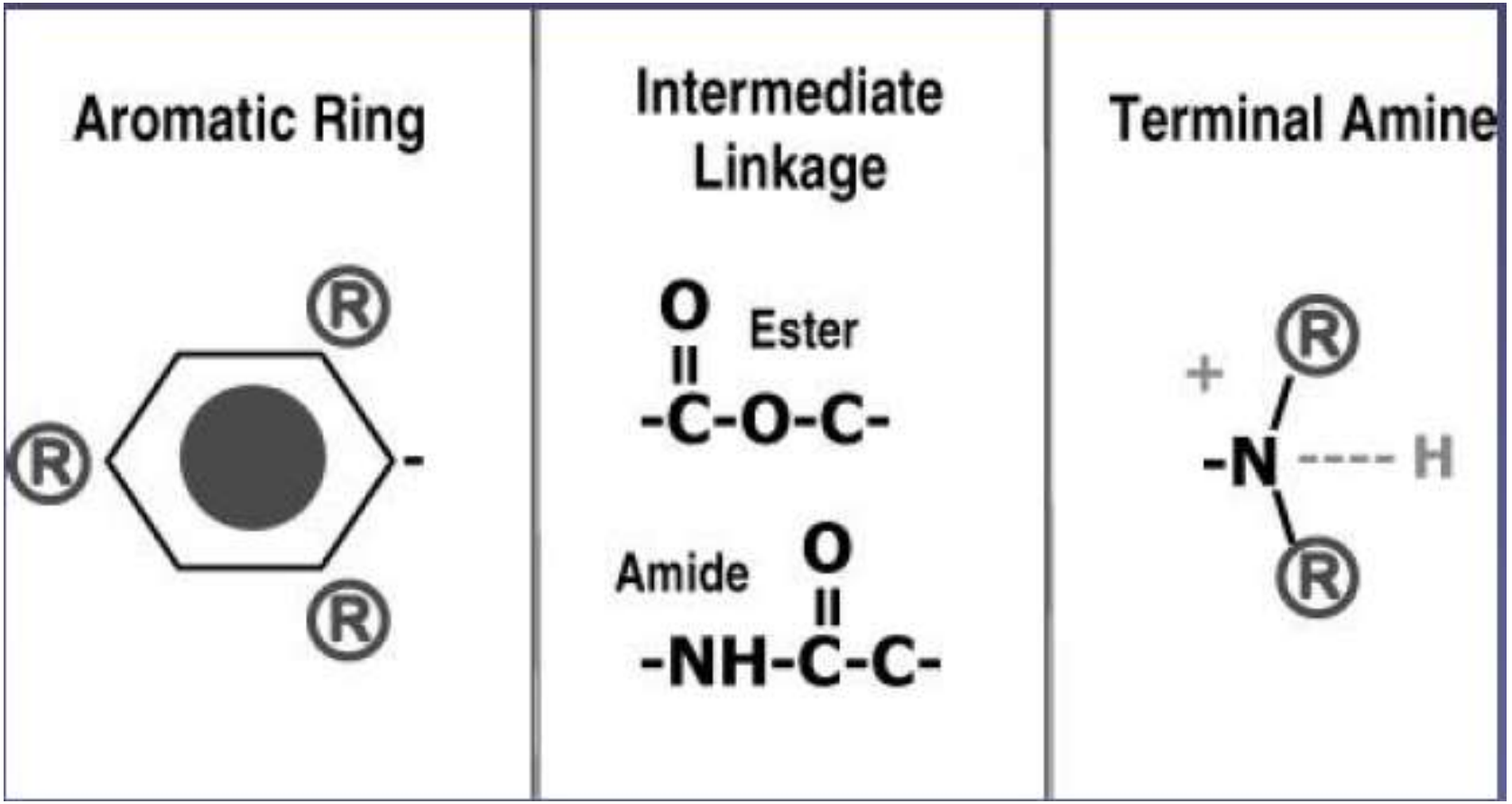


Arrangement of transmembrane segment domains to form a *central ion channel pore*.

Membrane Na^+ currents under voltage clamp



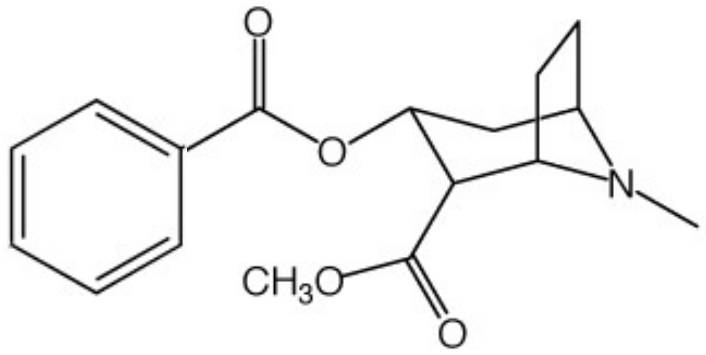
Structure of local anaesthetics



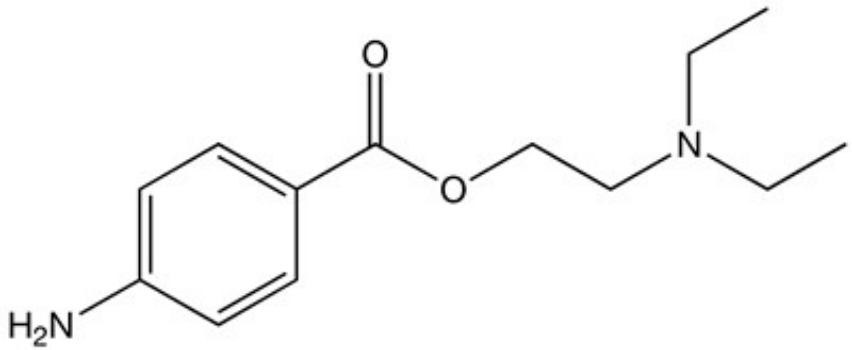
Local anaesthetics usually consist of a lipophilic aromatic ring and a hydrophilic terminal amine group separated by an intermediate ester (COO) or amide (NHCO) linkage chain.

Structure of local anaesthetics

Esters

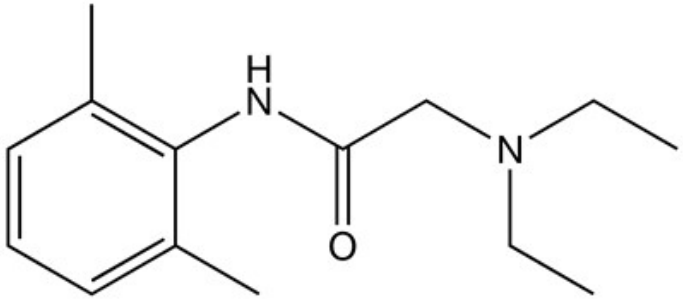


Cocaine

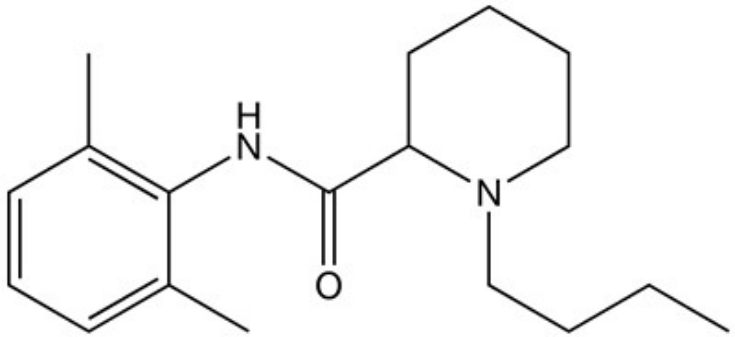


Procaine

Amides



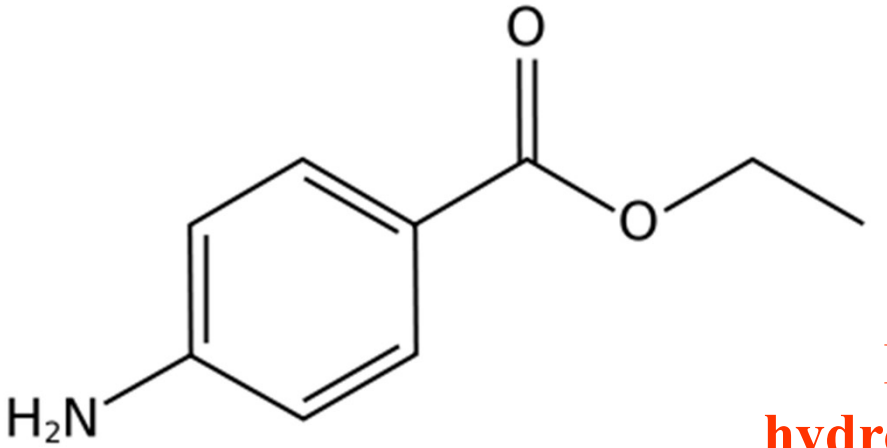
Lidocaine



Bupivacaine

Structure of local anaesthetics

Non-typical ester



Lacks terminal hydrophilic amine group

Benzocaine

Physiochemical properties

The potency of local anaesthetics also depends on:

- **their relative lipid solubility** (octanol: water partition coefficient) – **the higher the lipid solubility the higher the potency.**

- **the degree of protein binding *in vivo*** – poorly bound drugs will have shorter duration of action and *vice versa*.

- **their pKa value** – the lower the pKa →lower degree of ionization →better cell penetration → faster onset rate → longer duration of action.

The Henderson–Hasselbach equation:

The pKa equals the pH where the ionized and non-ionized forms are at equilibrium *i.e.* 50% of each form is present.

$$pH = pK_a + log \frac{[base]}{[acid]}$$

Potency, pK_a, Lipophilicity

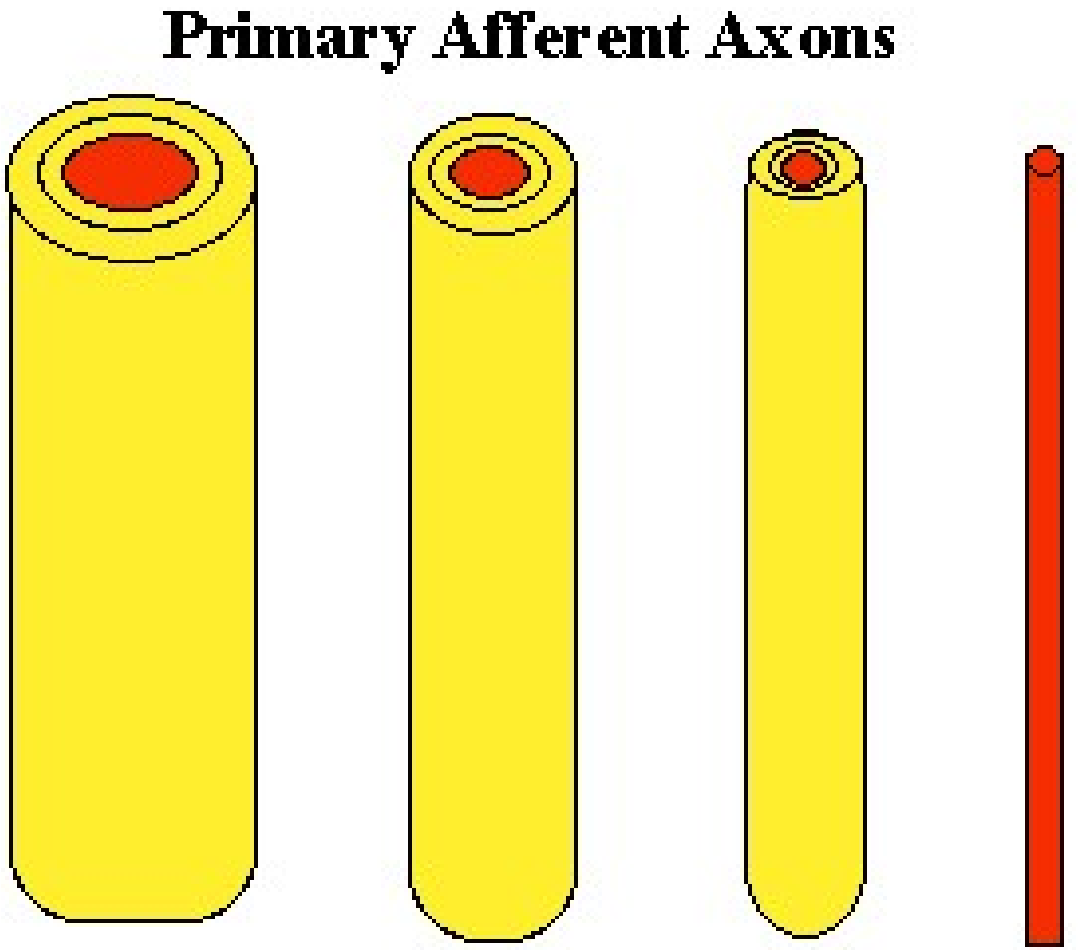
Drug	pK_a	Octanol/H_2O
Low Potency		
Procaine	8.9	100
Intermediate potency		
Mepivacaine	7.7	130
Prilocaine	8.0	129
Lidocaine	7.8	366
High potency		
Amethocaine	8.5	5800
Tetracaine	8.4	5822
Bupivacaine	8.1	3420
Etidocaine	7.9	7320
Levobupivacaine	8.1	3420

Influence of pH

The potency of local anaesthetics is strongly influenced by pH

- **All local anaesthetics are weak bases** and have a pKa of ~7.6 – 8.9; so at pH 7.4, the ionized cationic form will predominate.
- **At alkaline pH,** the proportion of ionized molecules is low, so an increase in proportion of permeable neutral base will occur →rate of onset of action increased →effect duration prolonged.
- **Inflamed tissues are acidic,** so onset of local anaesthesia is slowed and effect duration is decreased.

Sensitivity of nerve fibres

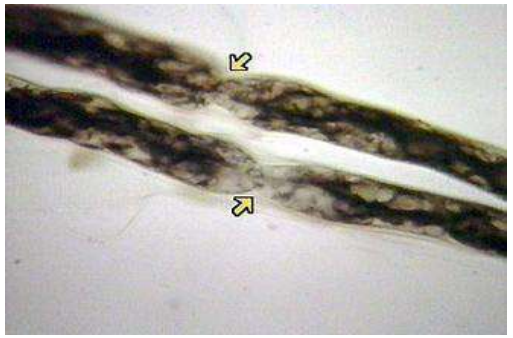


Axon Type	Aα	Aβ	Aδ	C
Diameter (μm)	13-20	6-12	1-5	.2-1.5
Speed (m/s)	80-120	35-75	5-35	.5-2.0

Sensitivity of nerve fibres

- **Local anaesthetics preferentially block smaller diameter nerve fibres in the order:**

Type C (1 μm; dull pain and autonomic postganglionic -unmyelinated)> **Aδ** (2 μm; sharp pain-myelinated) >**Aβ** (5 μm; sensory-myelinated) >**Aα** (12 μm; motor-myelinated)

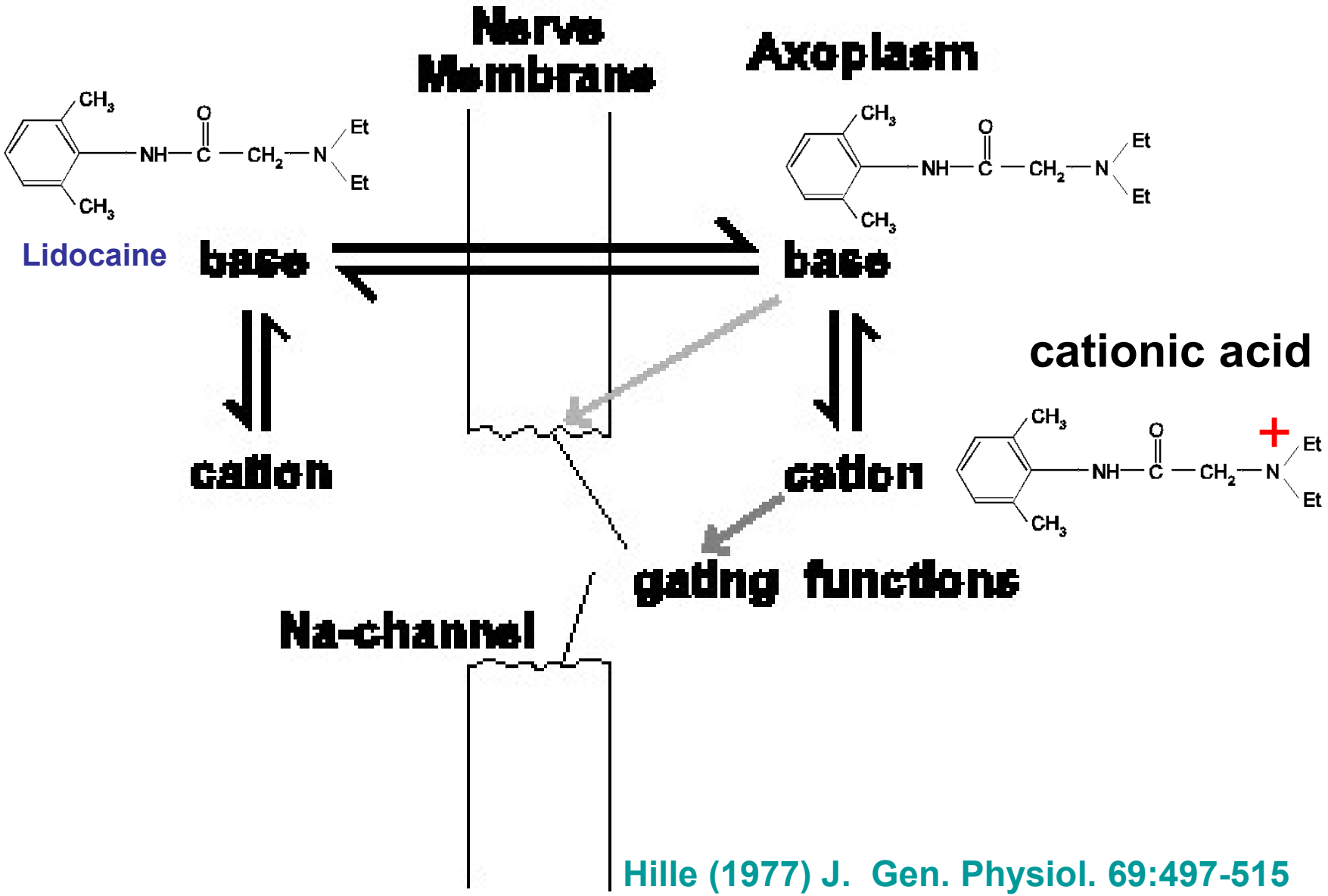


- In myelinated fibres, local anaesthetics can only act at the **Nodes of Ranvier.**

- **The order of nerve sensitivity is:** autonomic>pain>temperature>touch>pressure (proprioception)>skeletal muscle tone.

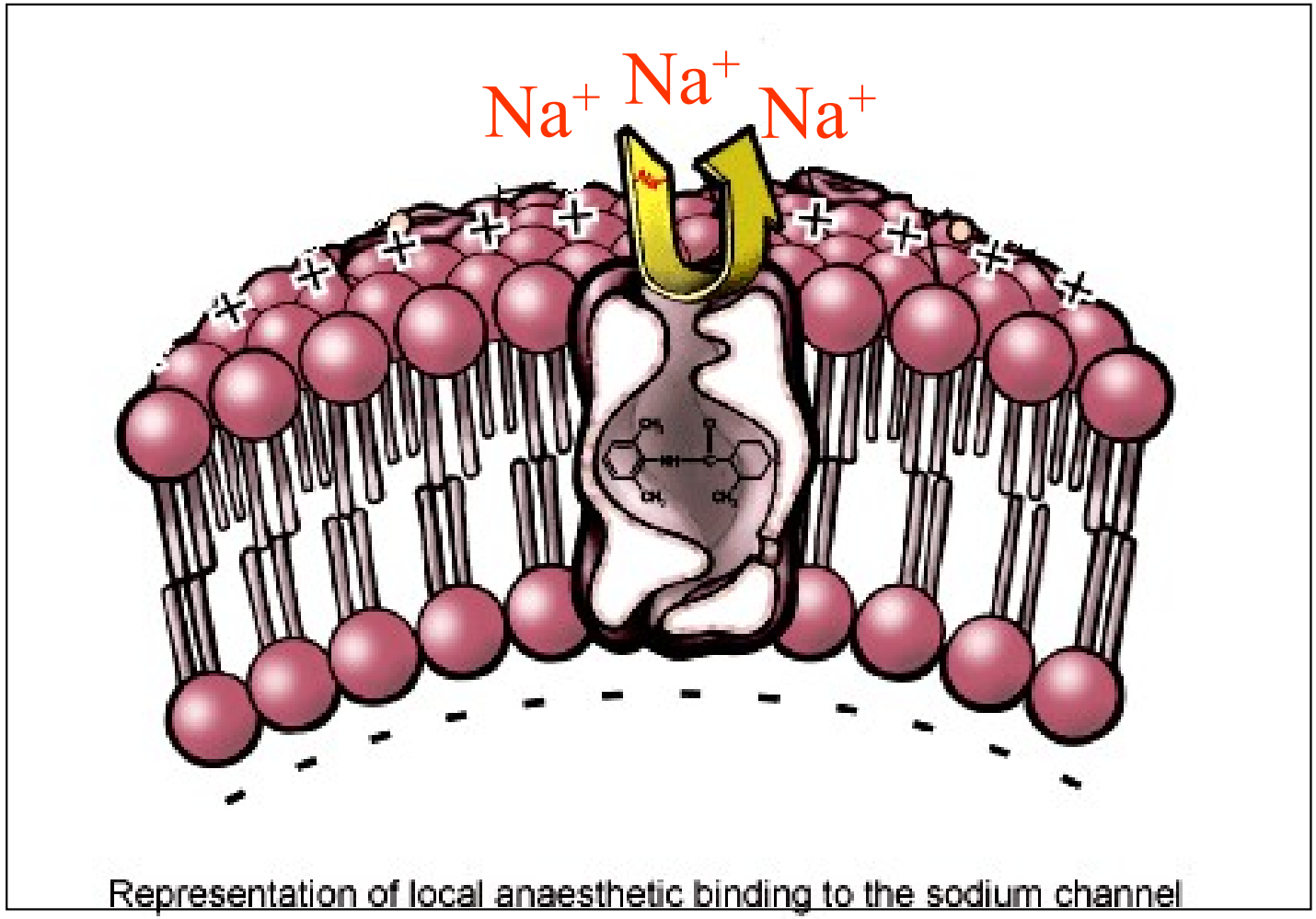
Model for Na^+ channel block by local anaesthetics

Hille model (classic 'hydrophilic' pathway)



Hille (1977) J. Gen. Physiol. 69:497-515

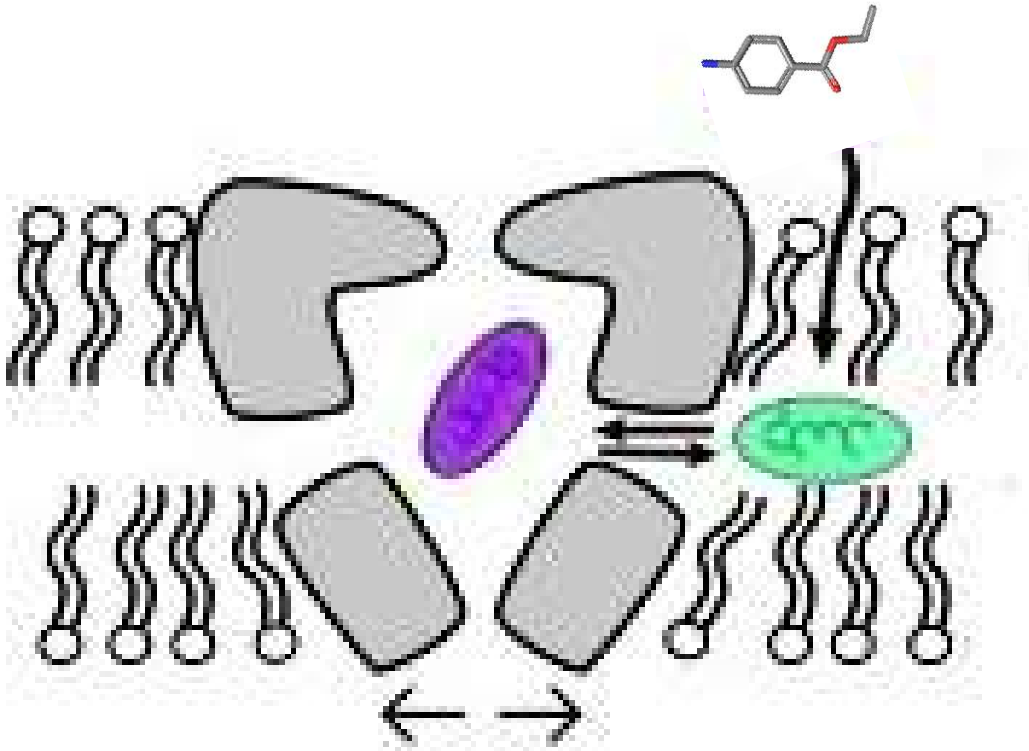
Block of Na^+ channel by local anaesthetics

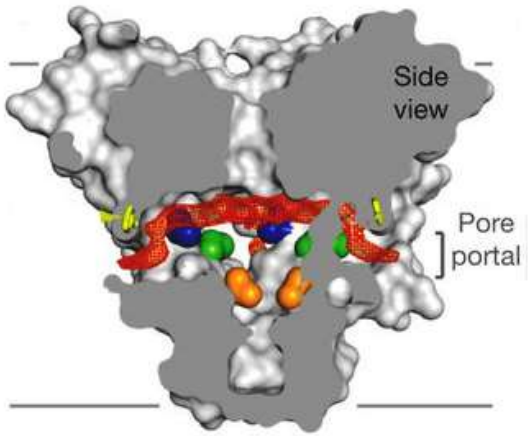


Representation of local anaesthetic binding to the sodium channel

Model for Na^+ channel block by local anaesthetics

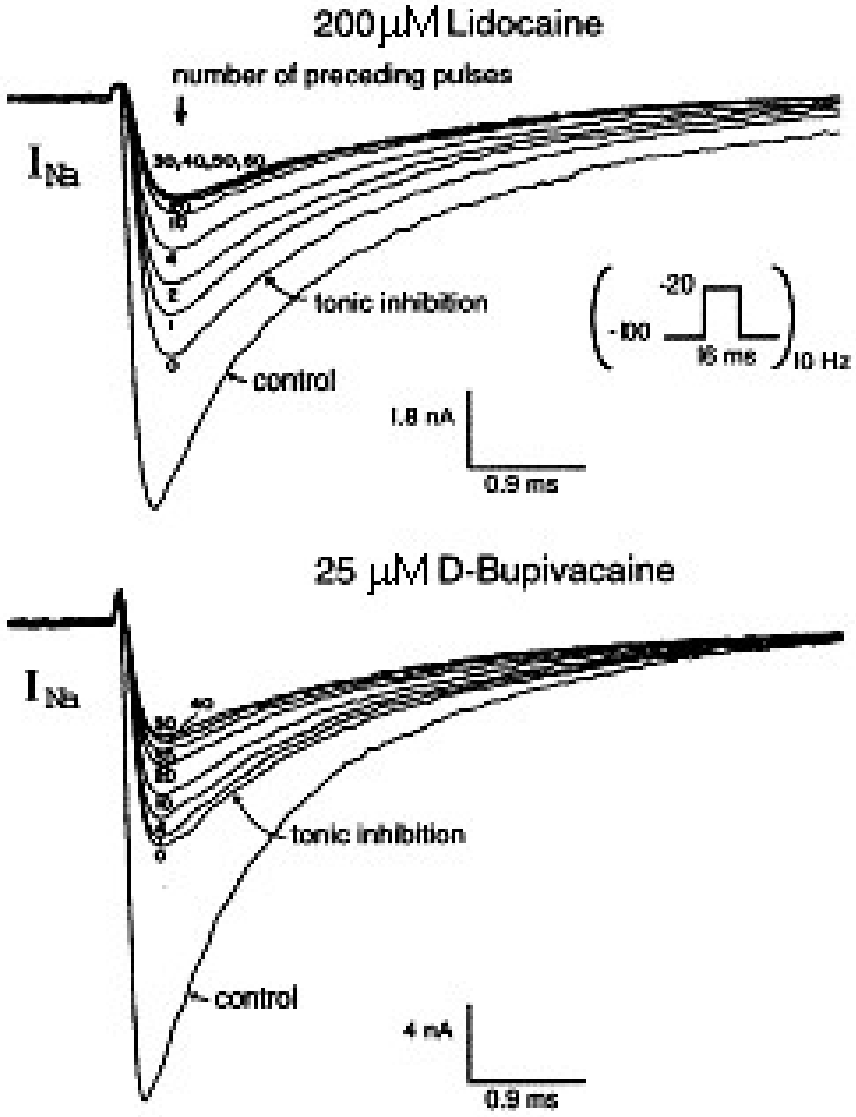
'Hydrophobic' pathway





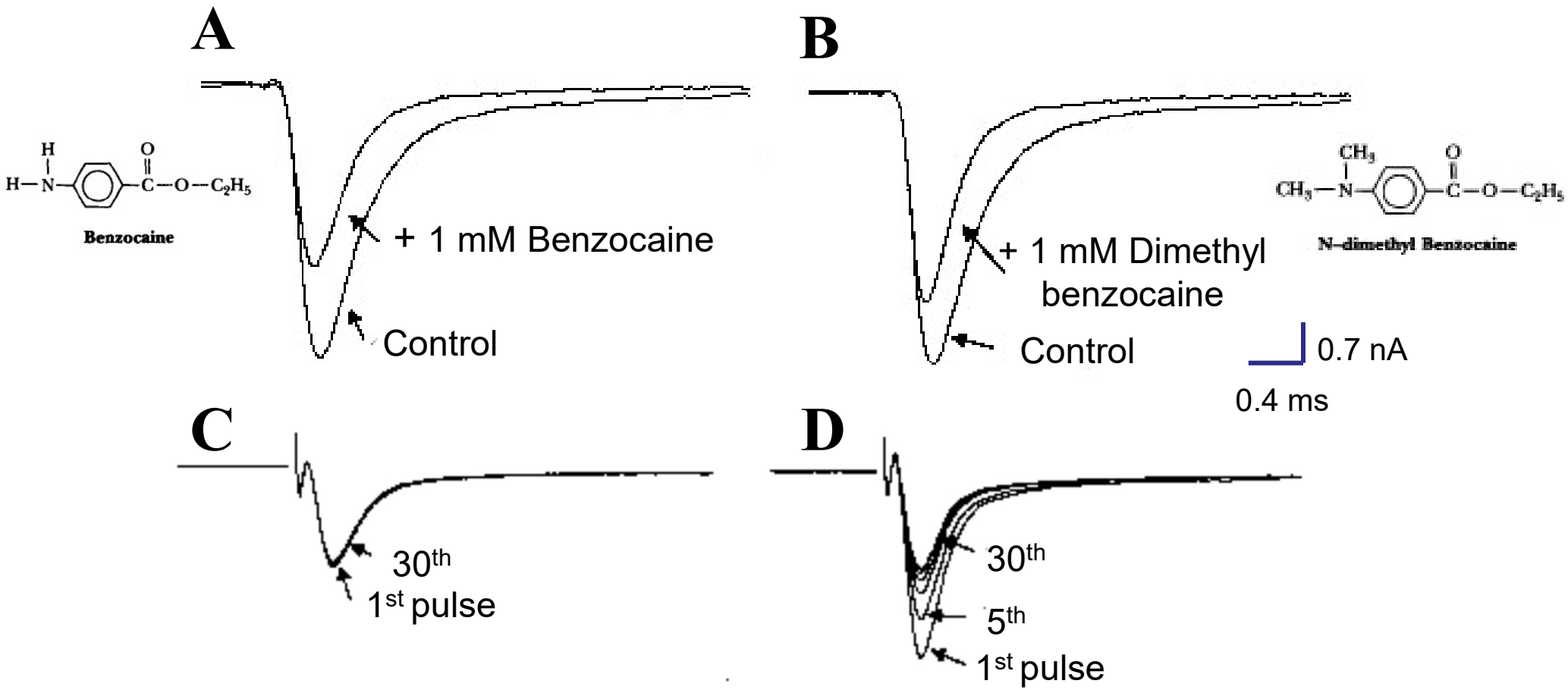
Another 'hydrophobic' pathway, is seen with benzocaine, a permanently uncharged local anaesthetic, primarily used for topical anaesthesia. It reaches the sodium channel directly through the nerve membrane and then lateral movement into the channel (closed), a concept supported by recent crystallographic investigations.

Use-dependent block by local anaesthetics



Local anaesthetics preferentially bind to the Na^+ channel in its open or inactivated states. Repeated stimulation → increasing drug access to the channel binding site → progressive increase in block (*use-dependence*)

Non use-dependent block by Benzocaine

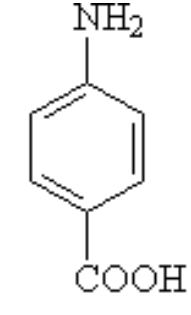


Na^+ channel currents recorded in rat pituitary GH_3 cells activated by a +30 mV depolarizing test pulse from -100 mV, before and after applying 1 mM benzocaine (A) or 1 mM N-dimethyl benzocaine (B). Application of repetitive test pulses (+30 mV; 25 ms; 5 Hz) produced no further block in benzocaine (C) but did in N-dimethyl benzocaine (D).

J. Gen. Physiol. 103: 501-518.

Metabolism

- **Amides**
  - Primarily hepatic
  - Plasma concentration may accumulate with repeated doses
  - Toxicity is dose-related, and may be delayed by minutes or even hours from time of dose.
- **Esters**
  - Ester hydrolysis in the plasma by pseudocholinesterase
  - Little potential for accumulation
  - Metabolites may induce allergic reactions due to formation of PABA-like compounds

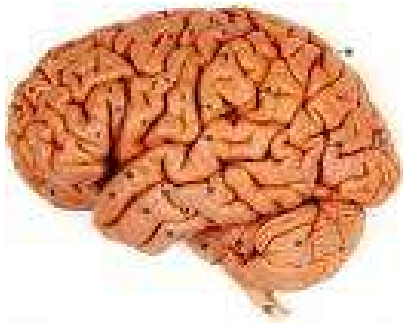


para-aminobenzoic acid (PABA)

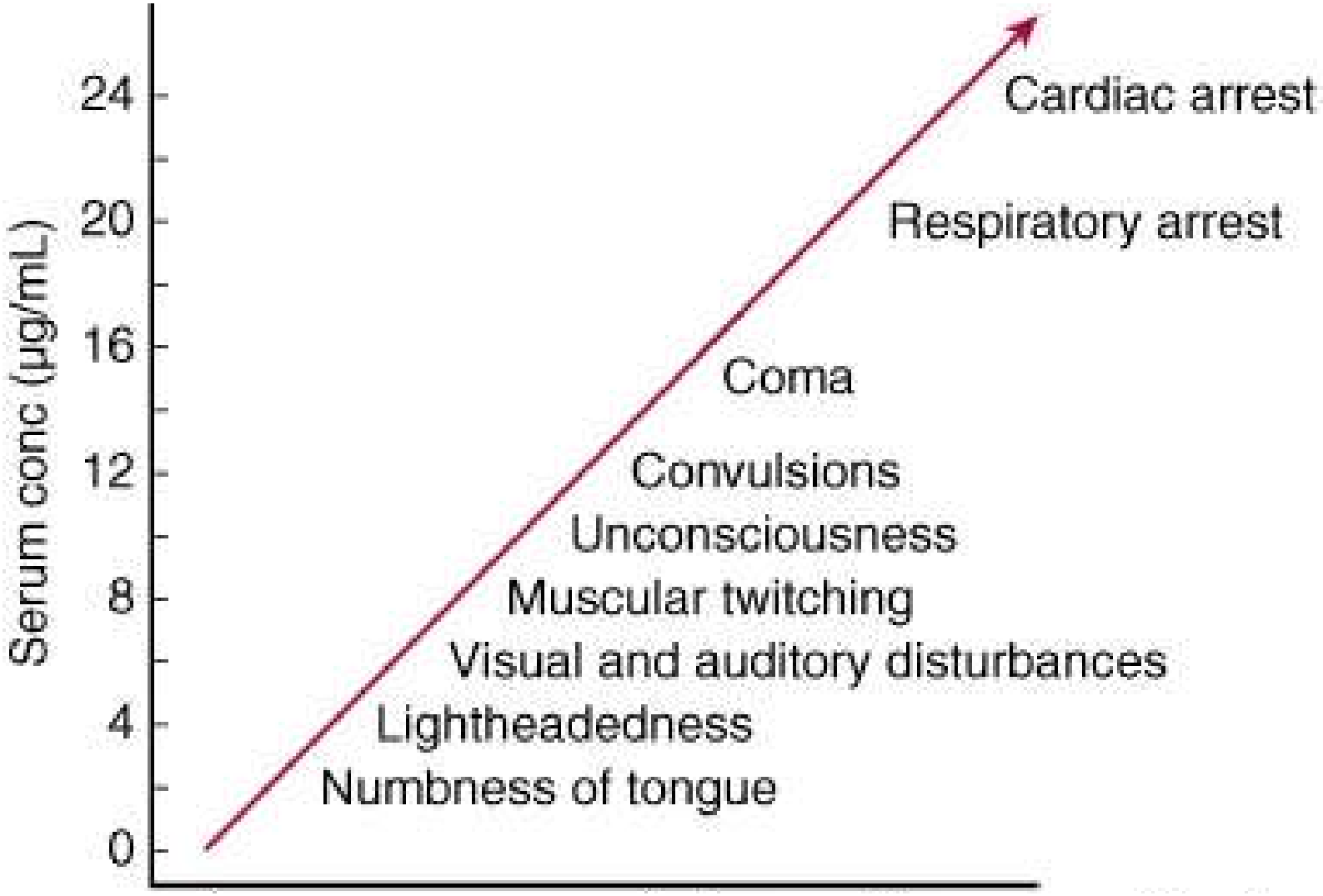
Toxicity

Although rare, local anaesthetics can also produce toxic effects if enough is absorbed systemically or after accidental i/v injection (Local Anaesthetic Systemic Toxicity: LAST)

- **CNS effects:** tinnitus, perioral tingling (parasthaesia), tongue numbness, slurred speech, agitation, anxiety, confusion, dizziness, restlessness, a metallic taste, drowsiness, blurred vision, tremor, muscle twitching, generalized seizures; respiratory depression→ arrest; coma.



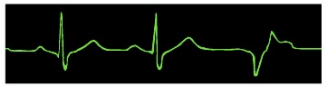
Toxicity

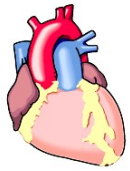


Lidocaine Toxicity by Concentration

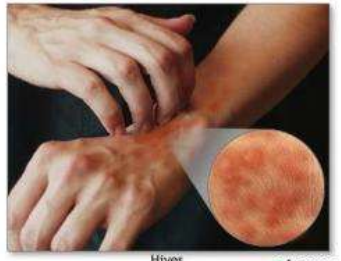
Toxicity

- **Cardiovascular effects:** hypotension (due to direct vasodilation) → possible cardiovascular collapse→coma; cardiac depression → bradycardia, arrhythmias, →possible ventricular fibrillation and cardiac arrest.





- **Allergic reactions:** more common with ester-type local anaesthetics →dermatitis, bronchospasm, hives – due to generation of PABA derivatives on ester hydrolysis. Allergic reactions to amide anaesthetics are rare.



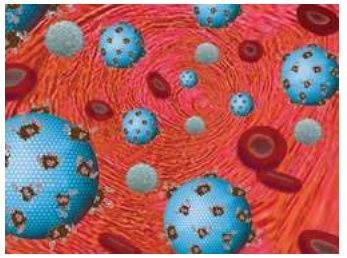
Toxicity

CENTRAL NERVOUS SYSTEM	CARDIOVASCULAR SYSTEM
Initial phase	**Initial phase**
Circumoral paresthesia	Hypertension
Tinnitus	Tachycardia during CNS excitatory phase
Confusion	
Excitatory phase	**Intermediary phase**
Convulsions	Myocardial depression
	Decreased cardiac output
	Hypotension
Depressive phase	**Terminal phase**
Loss of consciousness	Peripheral vasodilatation
Coma	Severe hypotension
Respiratory depression	Sinus bradycardia
	Conduction defects
	Dysrhythmias

Lipid rescue

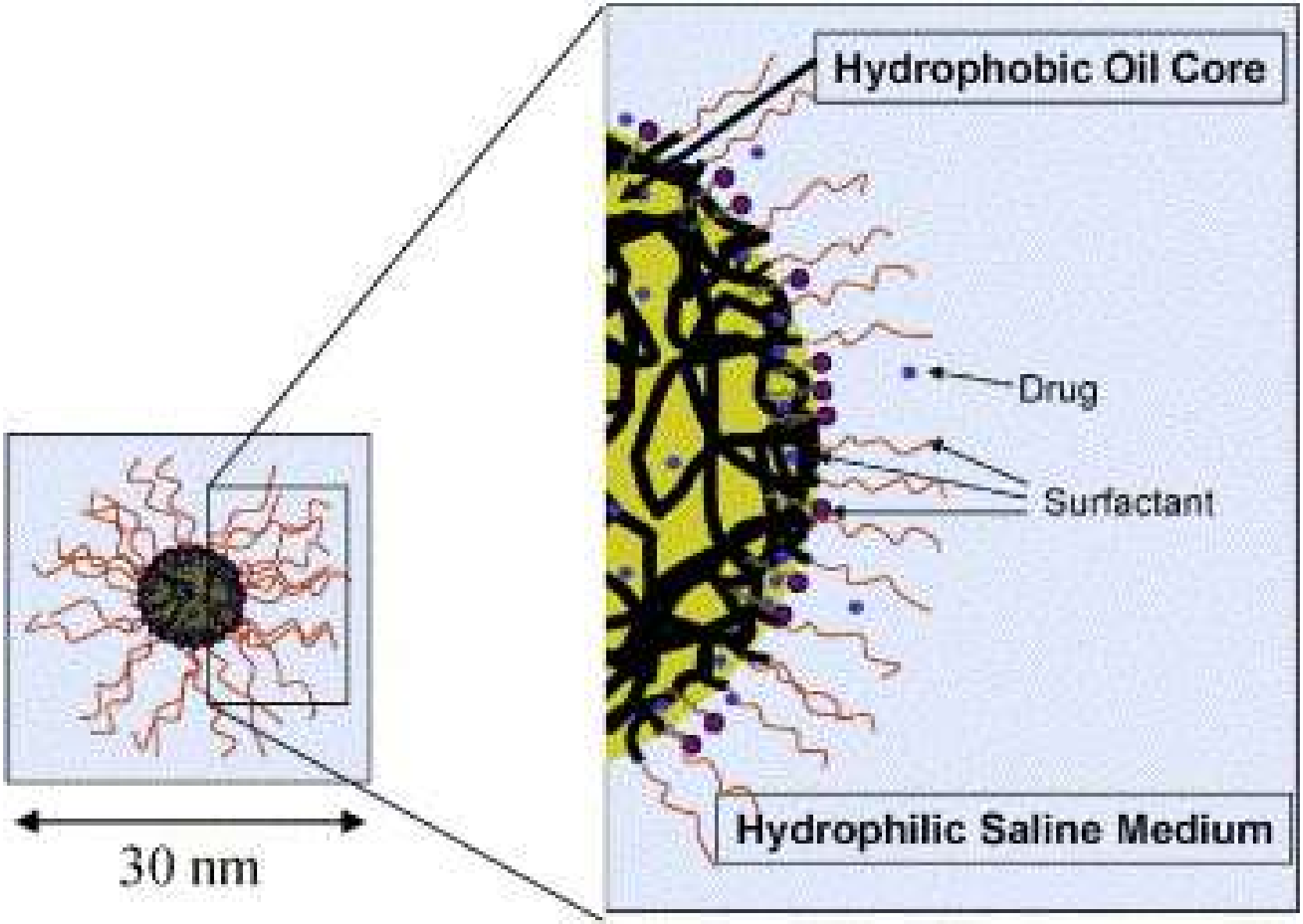
This concept was introduced recently to counteract severe local anaesthetic toxicity

- **An aqueous i/v infusion of very fine lipid droplet suspensions (nanoparticles) (Intralipid®: 20%)** is used to scavenge uncharged local anaesthetic molecules (and any lipophilic toxic metabolites) from the plasma and affected tissues, thereby preventing entry into nerve membranes and interaction with Na^+ channels



- Also being advocated for treatment of poisoning by other lipophilic drugs

Nanoparticles

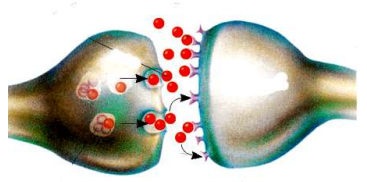


Combination with vasoconstrictors

- **Cocaine** produces local vasoconstriction by inhibiting noradrenaline uptake into sympathetic nerve terminals
- Most other local anaesthetics like lidocaine have **a direct vasodilator activity**→ increased chance of systemic absorption→ possible toxic side effects.

- **Adrenaline 1:50,000** is included in injected solutions of some local anaesthetics to constrict local blood vessels, and therefore localize and lengthen the duration of anesthesia at the injection site. ***It is not advisable to include adrenaline with a local anaesthetic injection in digits or appendages because of the risk of ischaemic necrosis (gangrene)***.

Phentolamine mesylate (a nonselective α-adrenergic blocker), can be used for the reversal of soft-tissue anaesthesia following intraoral submucosal injection of a local anaesthetic containing a vasoconstrictor.



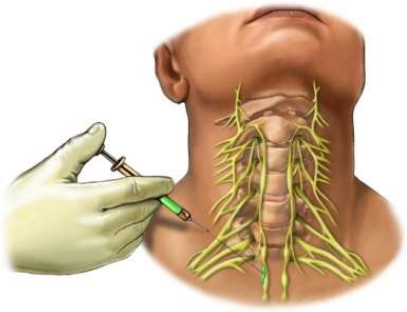
Clinical uses

- **Topical or surface anaesthesia:** Direct application of topical agents used for surface anaesthesia of mucous membranes in nose, mouth, trachea or genitourinary tract; also, cornea of the eye or skin *e.g.* **lidocaine, tetracaine** and **benzocaine** (not in ophthalmology).

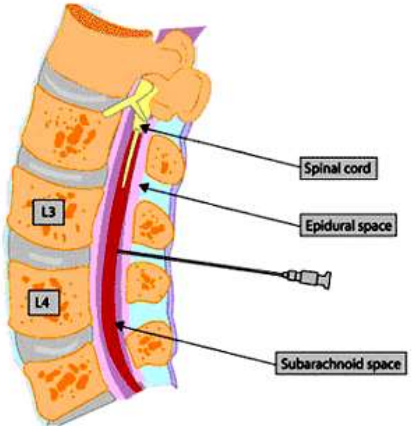
- **Infiltration anaesthesia:** Drug is injected directly into tissue *e.g.* skin, gums, to produce local numbness for carrying out minor surgery. Adrenaline is included in solutions to produce local vasoconstriction.

Clinical uses

- **Regional nerve block anaesthesia:** Drug injected near a peripheral nerve trunk (*e.g.* dental nerves) or nerve plexus to produce regional anaesthesia for dentistry or surgery. Vasoconstrictor may be included.

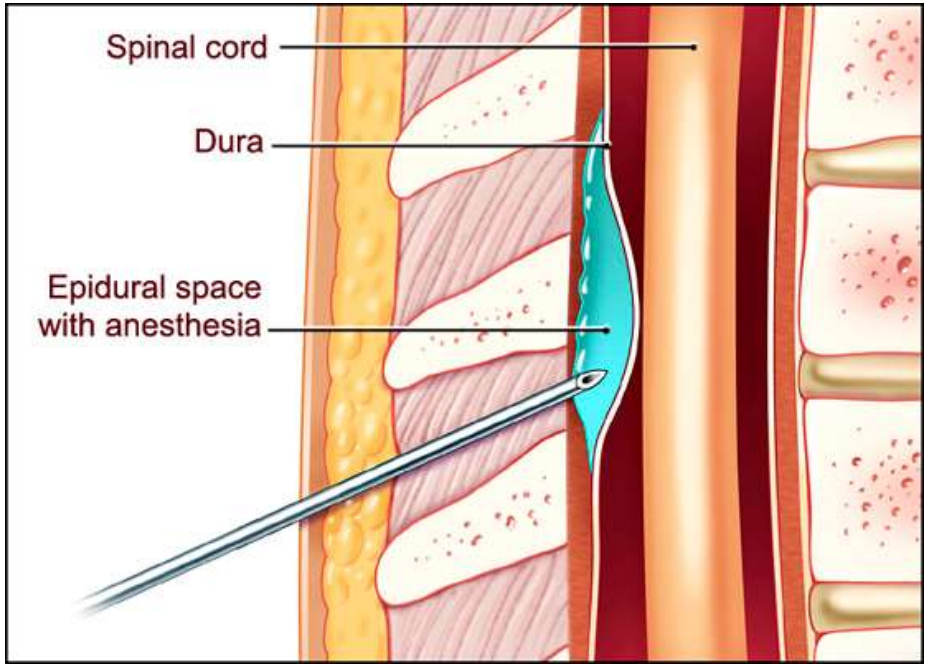


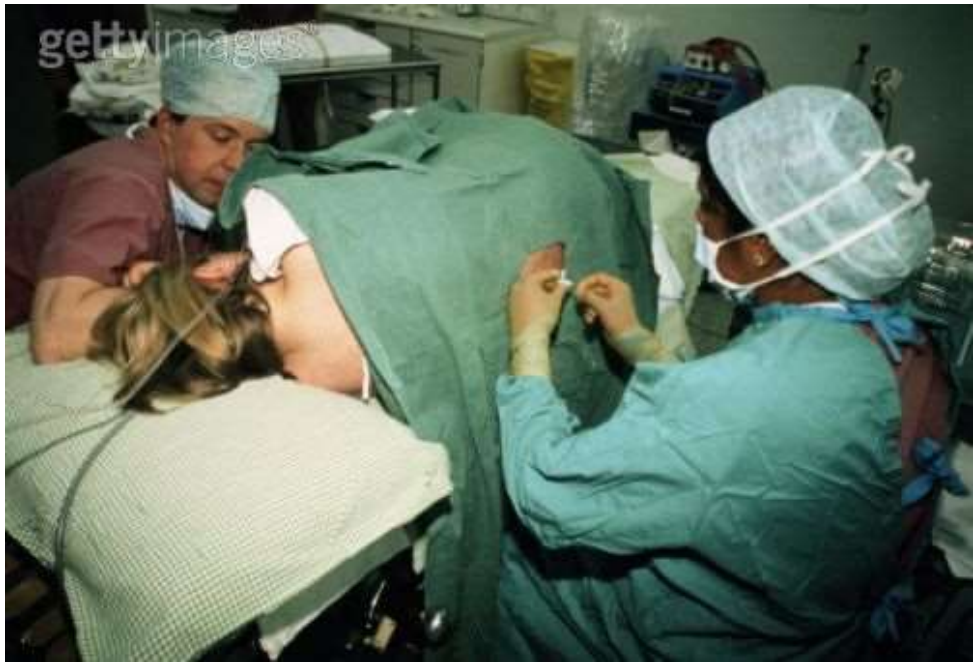
- **Spinal anaesthesia:** Drug injected directly into the lumbar subarachnoid space into the CSF below terminal end of the spinal cord (L2 vertebra) to anaesthetize spinal roots or spinal cord, for abdominal and lower body surgery.



Clinical uses

- **Epidural anaesthesia:** Drug injected into the epidural space (the area between the dura mater and the vertebral wall), at any level of the spinal column to block spinal roots and produce spinal anaesthesia of the thorax, abdomen and lower extremities; also used in ‘painless’ childbirth.



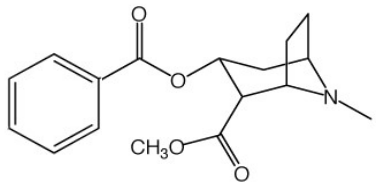


Properties of some local anaesthetics

Cocaine: is a benzoic acid ester: in addition to its local anaesthetic actions and well known CNS stimulant effects, it also blocks nerve terminal noradrenaline reuptake, so produces an intense local vasoconstriction.

Was once used as a topical anaesthetic (4-10% HCl solution) for nasotrachael intubation and in ophthalmology. No longer used.

Systemic side effects: → hypertension, tachycardia, hyperthermia, mydriasis, euphoria. It is more slowly metabolized than other ester local anaesthetics, so more chance of toxicity.

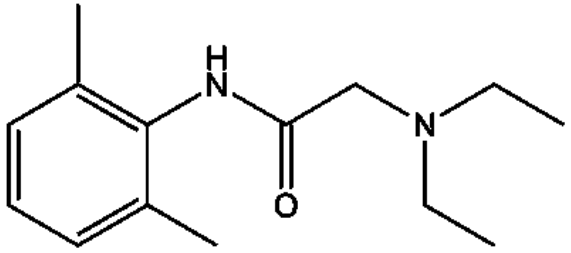


Cocaine

Properties of some local anaesthetics

Lidocaine (*Lignocaine, Xylocaine*): **is a tertiary amide derivative:** Widely used for infiltration and regional local anaesthesia, and in dentistry + adrenaline; also as a 2-4% solution or in ointment (5%) for surface anaesthesia; relatively rapid onset; moderate duration of action (several hours); low allergenic potential. Also given i/v to treat arrhythmias.

Side effects: →hypotension and bradycardia; CNS: confusion, respiratory depression, convulsions.



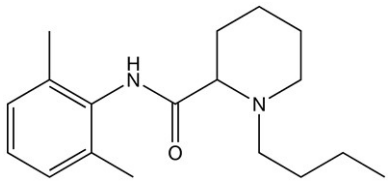
Lidocaine

Properties of some local anaesthetics

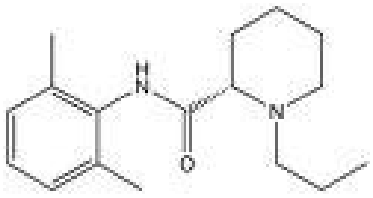
Bupivacaine (*Marcain*): **is an amide derivative:** It has a moderate rate of onset and relatively prolonged duration of action. Used for local infiltration, peripheral nerve block and epidural block in labour (0.25-0.5 % solution). Not given i/v.

Side effects: similar to those of lidocaine, but can be relatively more toxic, especially on the heart.

Ropivacaine (*Naropin*): (a pure S- isomer) is a similar long-acting amide anaesthetic with a better toxicity profile, also used for obstetric anaesthesia, but less potent.



Bupivacaine

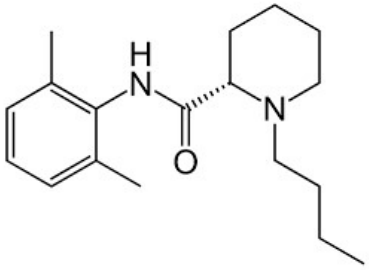


Ropivacaine

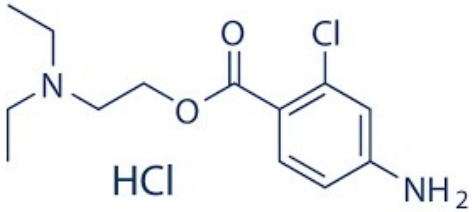
Properties of some local anaesthetics

Levobupivacaine (*Chirocaine*): is an isomer of bupivacaine, with anaesthetic and analgesic properties similar to bupivacaine, but with fewer adverse effects. It is used for local infiltration, peripheral nerve block, lumbar epidural, and intrathecal anaesthesia.

Chloroprocaine (*Ampres*): is **a para-aminobenzoic acid ester,** used for spinal intrathecal anaesthesia in adults where the planned procedure should not exceed 40 minutes.



Levobupivacaine

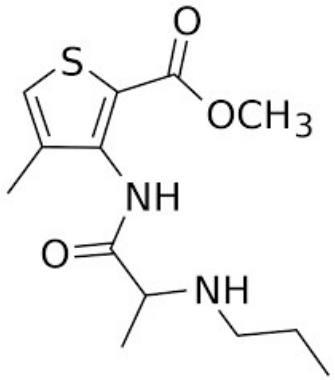


Chloroprocaine

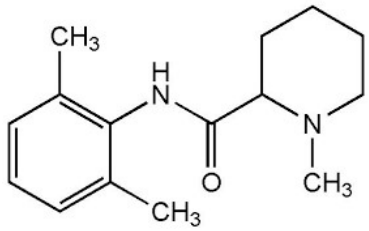
Properties of some local anaesthetics

Articaine (*Septanest*): **is an amide derivative with a thiophene ring:** used widely in combination with adrenaline (1/200,000) for infiltration anaesthesia in dentistry.

Mepivacaine (*Scandonest*): **is also an amide derivative** used for infiltration, nerve block and epidural anaesthesia.



Articaine

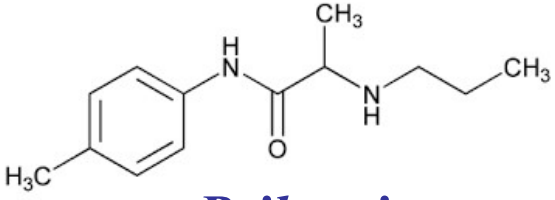


Mepivacaine

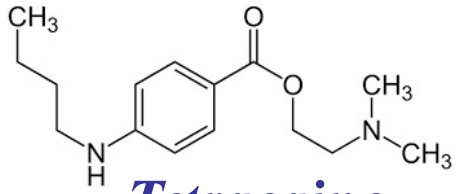
Properties of some local anaesthetics

Prilocaine (*Citanest*) is a local anaesthetic of low toxicity which is similar to lidocaine used for infiltration anaesthesia and nerve block. It is combined with *Felypressin* (0.03 IU/ml) (related to vasopressin) as a vasoconstrictor instead of adrenaline.

Tetracaine (*Ametop*): is **a para-aminobenzoic acid ester**, used for topical application - 4% gel for anaesthesia before venepuncture or venous cannulation. It is rapidly absorbed from mucous membranes and should not be applied to inflamed, infected, traumatised, or highly vascular surfaces, or used for bronchoscopy or cystoscopy.



Prilocaine

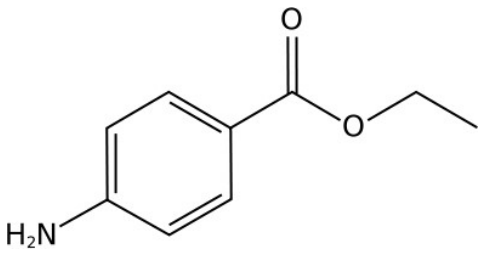


Tetracaine

Properties of some local anaesthetics

Benzocaine: is an ester derivative that lacks the usual terminal amino group.

It is water insoluble and has a low potency and toxicity; it is used exclusively for topical anaesthesia – available in creams and throat lozenges for treating minor ailments. Long-term exposure in topical preparations can lead to contact dermatitis. Use in spray preparations may also cause ***methaemoglobinaemia*** (cyanosis), a condition of elevated methaemoglobin in the blood causing decreased oxygen-carrying capacity.



Benzocaine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