



## Lidocaine: a Common Local Anaesthetic

### How does it work and how could it be made?

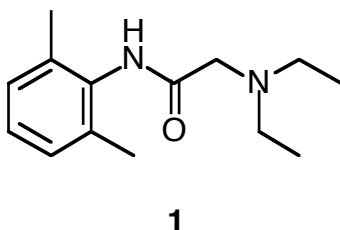
- **Local Anaesthetics: What are they and how do they work?**

Anaesthesia itself is defined as the loss of sensation with or without the loss of consciousness.

The use of local anaesthetics is an all too common experience, a visit to the dentist (don't you just love it), an epidural during surgery or childbirth being typical examples. A local anaesthetic is a drug that, when injected or given topically (on the skin), produces a state of local anaesthesia by reversibly blocking the nerve conductances that transmit the feeling of pain from the point of administration to the brain. They are designed not to distribute widely in the body. They are easily broken down (chemically) by the body's defence mechanisms that exist to allow excretion of xenobiotics (foreign molecules). This means that the duration of action is limited and so feeling returns not too long after your medical ordeal is over.

It is sometimes interesting to reflect on the joy of dental fillings without anaesthetic when contemplating the value of Chemistry to society.

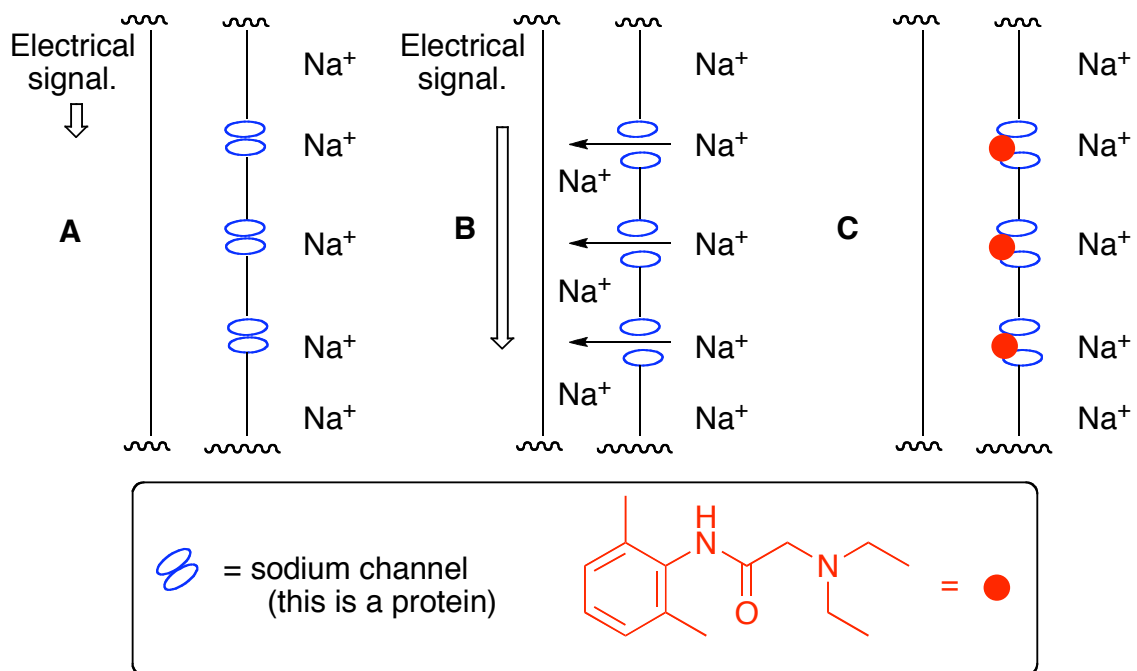
There is a group of modern local anaesthetics, with similar chemical structures, that work by inhibiting the movement of sodium ions into a nerve cell. Lidocaine **1** is one of these and its structure is shown in Figure 1.



*Figure 1:* The structure of lidocaine.

What we have to do is to understand why the arrest of sodium movement reduces pain and how the lidocaine molecule achieves this. When we understand these points we will be in a position to analyse how the particular properties of **1** allow it to achieve an interesting, apparently impossible, balancing act to achieve this blocking of sodium ion movement.

First let's look at a section through a nerve cell (specifically the axon) (Figure 2). As an electrical signal reaches a threshold voltage level and so propagates along its length (**A**) it opens 'sodium channels' (**B**) to allow an influx of sodium ions. These 'sodium channels' are proteins (poly-amino acids) that sit across the membrane that forms the surface of the nerve.



*Figure 2:* Lidocaine interacting with a 'sodium channel'.

This protein folds into a cylindrical shape with a central channel that can be opened and closed in response to voltage signals from the nerve cell. The local anaesthetic works by moving to the inside of the cell then binding to the 'sodium channel' and so blocking the influx of sodium ions. This block stops nerve conductance and prevents further signals reaching the brain (**C**).

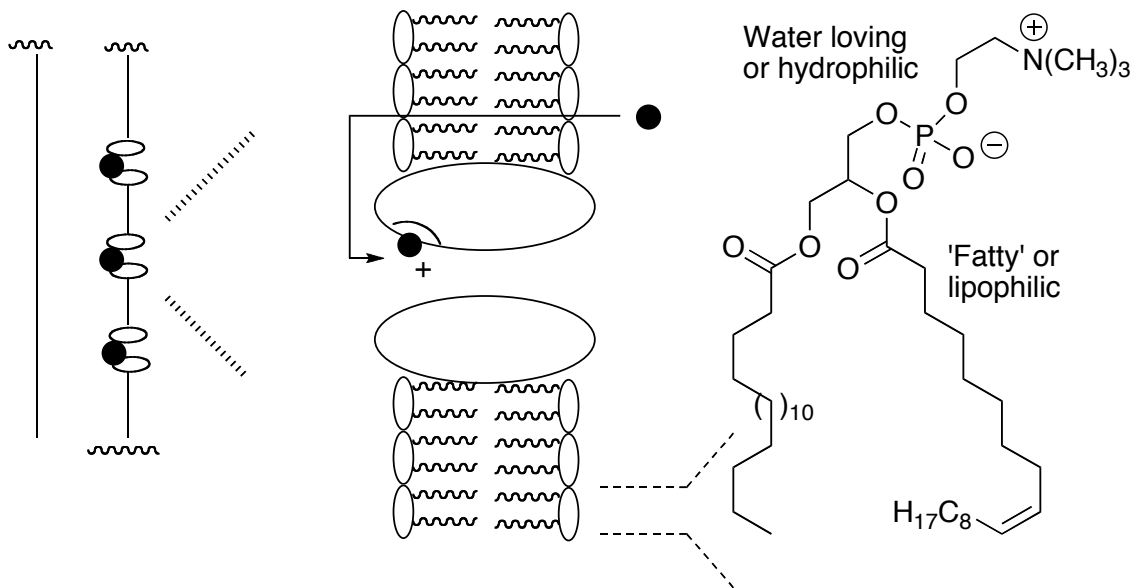


Figure 3: Composition of the cell wall (● is lidocaine)

If we look at an expansion of (C) then we can see how the membrane that defines the surface of the cell is composed (Figure 3).

It can be seen that it is a bilayer of molecules that are very polar (hydrophilic) at one end and fatty (lipophilic) at the other end. The fatty ends are attracted to one another and repelled from the aqueous environment of the body while the polar ends are attracted to the water that is both inside and outside the nerve cell. The 'sodium channel' spans this bilayer which is about 50 Å (50 x 10<sup>-10</sup>m) wide. An interesting point is that the anaesthetic binds much more tightly to the channel when charged and yet cannot cross the fatty centre of the membrane when so charged. It is this interesting balancing act that we mentioned earlier and we will see how the structure and properties of lidocaine allows us to square this particular circle. In fact this is an aspect of a common problem in the discovery of new drugs and has been summarised by Hansch. He discussed drug action in terms of two stages:

- (i) Pharmacokinetics: how the drug gets to the site of action and,
- (ii) Pharmacodynamics: how the drug interacts (binds) with its target.

We will now attempt to understand the details of how this drug works by applying some basic chemistry covered at both A-Level and in first year work. Some of the synthetic work will require you to look up work that you will study in more detail after Christmas.