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How drugs work

Glaring lights. Noise. Traffic congestion. Looming deadlines. None of it life-threatening, but enough to start up your body’s favourite stress response – a tension headache. Muscles in your neck and scalp tighten, perhaps constricting nearby blood vessels. The affected tissue starts to produce chemicals called prostaglandins. These act on nearby nerve endings which, in turn, send messages to the brain producing the sensation of pain.

It may not be the best long-term solution (maybe you should give up that stressful job or take up yoga) but a couple of soluble aspirin tablets will kill that headache in about half an hour, by turning off prostaglandin production. The same goes for other everyday irritations such as toothache, menstrual cramps and rheumatic aches and pains.

Swallowing a dose of aspirin releases about two thousand million million \((2 \times 10^{14})\) pain-relieving molecules into the body. They won’t all reach their target (the site of prostaglandin production), but experience of the drug over nearly 100 years has shown that this dose – around 600 milligrams – is enough to take care of most tension headaches.

The aspirin molecules first have to negotiate the digestive system to get into the bloodstream, which will carry them to the site of the pain (Fig. 1.1). The digestive system is basically a tube going from the mouth to the anus. It filters any molecules which enter it (food or drugs, that is) according to their size and chemical structure. Small, fat-soluble molecules pass easily through the walls of the small intestine into the bloodstream. Larger molecules such as proteins, fats and carbohydrates (the basic components of food) are chewed up into smaller fragments by the powerful acid juices of the stomach and the digestive enzymes produced by the stomach and pancreas. Other big molecules, like the cellulose in dietary fibre, pass unchanged through the gut.

Aspirin easily clears this first hurdle. It is a small molecule which is left alone by digestive enzymes and it is readily absorbed – mainly through the
Fig. 1.1. From pills to pain relief – the journey of an aspirin molecule. The route taken can be divided into four stages. (1) The pills dissolve in the stomach and nearly all the aspirin is absorbed by the stomach and small intestine. (2) Blood vessels from the stomach and small intestine carry the aspirin into the hepatic portal vein which leads to the liver. (3) From the liver, the hepatic vein takes the aspirin into the right atrium of the heart, which pumps blood
walls of the small intestine, although at least five per cent is absorbed through the stomach. Other drugs do not fare so well, as we shall see.

Next the aspirin molecules enter the liver, via the hepatic portal vein. The liver is a formidable obstacle for any drug; one of its main functions is to protect the body from ‘foreign’ molecules by dismantling them or modifying them in some other way (a process known as metabolism). Most drugs – and aspirin is no exception – are not found in the body under normal circumstances so the liver is bound to treat them with suspicion. The drug molecule that comes out of its first encounter with the liver (known in pharmacology jargon as the ‘first pass’) could be a very different animal from the one that went in.

The chemical name of aspirin is acetylsalicylic acid; put simply this means that its molecule consists of salicylic acid with a cluster of carbon, hydrogen and oxygen atoms known as an acetyl group tacked onto it (Fig. 1.2). The liver removes the acetyl group from at least some of the aspirin molecules, forming a compound called salicylic acid, itself a painkiller, and the historical precursor of aspirin.

Salicylic acid is an active ingredient of willow bark, and has been used as a folk remedy for pain and fever since the days of the great Greek physician Hippocrates (460–370 BC). By the 19th century it was widely used in the treatment of rheumatic fever, gout and arthritis. But salicylic acid is bitter and causes severe stomach irritation. So Felix Hoffman, a chemist at Bayer (the German company which had developed salicylic acid commercially) began to look for a related compound which would be a better drug, and came up with aspirin in 1899.

Some aspirin will sneak through the liver unchanged – the actual amount depending on the size of the dose, its formulation and the state of your liver. Along with the salicylic acid, it enters the general circulation and is transported around the body by the pumping action of the heart.

into the right ventricle, to the lungs for oxygenation, then back to the left atrium of the heart. (4) On the final leg of the journey, the aspirin passes from the left ventricle into the aorta and then to the carotid artery which serves the head and neck. The occipital artery is a branch of the carotid artery; it carries blood to the back of the head (the usual site of tension headache). It branches into smaller and smaller vessels, and through these aspirin eventually reaches the tissue where the prostaglandin pain signals are being produced.
Every part of the body now receives a dose of aspirin. But the aspirin molecules only have an effect in cells where prostaglandins are present. So they will cut off pain-producing prostaglandins and relieve that headache. But prostaglandins occur in the stomach too, where they help create a barrier of mucus which protects it from the acidic gastric juices. Aspirin turns off the production of these prostaglandins too. As a result, the stomach lining may become exposed to gastric juices, causing pain and possibly even the development of ulcers – especially if aspirin is being taken long-term.

Aspirin stops the production of prostaglandins for about four hours. The pain might come back, if the trigger that activates prostaglandins is still present. In this case, you may need another dose of aspirin; as the label on the packet says, repeat every four hours as necessary.

Once they have done their job the aspirin molecules (which are chemically changed into salicylic acid when they block prostaglandins, as we shall see) do not linger, but are swept away by the general circulation. They may pass through the liver again and be metabolised into smaller fragments, or they may pass straight out of the body via the kidneys. All the aspirin, in whatever form, has gone from the body within 24 hours.

This everyday story of pain relief illustrates the main problems in getting drugs to hit their targets. First it helps to know as precisely as possible what the target is. The way aspirin works was not known until nearly 70 years
Many drugs work by homing in on molecular targets

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There are hundreds of thousands of different molecules in the human body. Some are simple, like sodium chloride (common salt) and water; others like DNA, proteins and carbohydrates contain many thousands of atoms arranged to give a complex, three-dimensional structure. It is the interplay between these various molecules – biochemistry – which makes life possible. Digesting a meal, reading a newspaper, playing a game of badminton – these, and all other activities which involve muscular action, thought processes, or perception of the world around us are driven by biochemistry.

Biochemistry happens at the level of the cell – the basic building block of
the body – although its results are often apparent at the level of the whole body. Two main groups of molecules, known as enzymes and receptors, lie at the heart of the biochemical activity of the cell. Most drugs work by interfering with the way in which either an enzyme or a receptor functions, with the knock-on effect of causing some change in the way the body functions.

Enzymes are biological catalysts. They speed up the chemical reactions that occur in the body so that they occur at a rate that is compatible with life. Without digestive enzymes, for example, it would take 50 years to break down the proteins, fats and carbohydrates in a typical meal into fragments that can be absorbed into the blood.

Crucial to an enzyme’s action is its shape. Enzymes are proteins; they consist of a long chain of hundreds of basic building blocks called amino acids linked together. The chain is coiled up, under the influence of chemical bonds between the amino acids, into a roughly spherical shape. From a distance, all of the 50,000 to 100,000 enzymes in the human body would appear to have the same shape. Close up however, you would notice some subtle differences between them. Each enzyme has a cleft somewhere on its surface known as the active site. The chemical which the enzyme will transform into a product – known as the substrate – fits snugly into the active site like two pieces in a jigsaw (Fig. 1.3).

The enzyme’s active site and the substrate have groups of atoms which attract one another, forming a weak chemical bond. Once the two have come together, the enzyme can get to work – perhaps snipping a chemical bond in the substrate, or creating a new one between two different substrates to make a larger molecule. Once the chemical action is over, the product molecule emerges from the enzyme, which is itself unchanged and ready to get to work on the next substrate molecule.

Each enzyme has its own specific substrate. For example pepsin, the enzyme that breaks down proteins, cannot stand in for amylase which breaks down starch. And if you put amylase and proteins together, nothing will happen.

If a drug molecule has a shape which is similar to that of a particular substrate, then it may drift into the active site – blocking the approach of the substrate. Such drugs are known as enzyme inhibitors (Fig. 1.3). Aspirin inhibits the enzyme cyclooxygenase (COX), which normally converts arachidonic acid (the substrate) into prostaglandins. The COX molecule is anchored to the membrane of a cell component called the endoplasmic reticulum. The arachidonic acid molecules are a component of this membrane,
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Fig. 1.3. Enzyme inhibitors. (a) The substrate approaches the active site of the enzyme, and binds to it – whereupon it is transformed into products. (b) An enzyme inhibitor binds to the active site in place of the substrate. Without binding to the active site, the substrate cannot be transformed into products. Note this figure is not to scale; substrates and inhibitors are normally much smaller than shown in comparison to the enzyme molecule.

and the active site is a long, narrow passage within the cyclooxygenase molecule. If an aspirin molecule gets into the passage, it blocks the entrance of arachidonic acid. So no prostaglandin is produced, and the net effect is to turn off the sensation of pain, as well as inhibiting the production of stomach mucus and thromboxane (Fig. 1.4). Drugs related to aspirin, such as ibuprofen and paracetamol, are thought to act in a similar way.

Many other drugs act as enzyme inhibitors, including angiotensin converting enzyme (ACE) inhibitors used in heart disease, certain antidepressants, penicillin (which acts on bacterial enzymes) and the new HIV protease inhibitors for the treatment of AIDS.

Like enzymes, receptors are proteins whose surfaces are pitted with nooks and crannies which smaller molecules can home in on. These ‘keys’ for the receptors’ ‘locks’ are called ligands (Fig. 1.5). Receptors are found on the cell surface (whereas enzymes are usually inside the cell). They act as a link between the inside and outside of the cell.

Unlike an enzyme, a receptor does not transform the ligand which binds to it. Instead the act of binding sends a signal to the cell – causing it to
Fig. 1.4. Cyclooxygenase and the action of aspirin. The cell membrane bounding the interior of the cell is composed of a double layer of fatty molecules called phospholipids. Arachidonic acid, the substrate of cyclooxygenase (COX), is derived from a phospholipid molecule. It fits into the active site of COX (1) and enzymic action transforms it into a prostaglandin. But aspirin and related drugs also fit, to a greater or lesser extent, into the active site, blocking the enzymic action. Prostaglandins, depending upon where in the body they are produced, lead to pain (2), blood clotting via the action of thromboxane (3) or production of stomach mucus (4). Aspirin’s action on COX can affect all three functions.

start up some biochemical activity which will culminate in a physiological response. So the ligand has an ‘action at a distance’ effect; it does not need to enter the cell to affect it. Hormones, and brain chemicals called neurotransmitters are two important classes of ligand. For instance, when the hormone insulin binds to its receptor it signals to the cells that there is plenty of glucose in the bloodstream. The cell responds by taking steps to store some of this in the liver, and other parts of the body, so that glucose levels in the bloodstream stay more or less constant.

So it is possible to manipulate the actions of cells by using drugs that bind to receptors. Some drugs – known as agonists – have a ‘positive’ effect, making the cell do what it does when its natural ligand binds. Morphine, a
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![Diagram of receptor agonists and antagonists](image)

Fig. 1.5. Receptor agonists and antagonists. (a) A ligand approaches a cell surface receptor and binds to it. This sets off a cascade of biochemical reactions inside the cell which result in a physiological effect. (b) An agonist molecule acts similarly to the natural ligand, also producing action inside the cell. (c) An antagonist molecule merely binds to the cell surface receptor, blocking access to the ligand. It does not produce any action inside the cell.

A drug used to relieve severe pain in cancer and heart attack patients, is an example of a receptor agonist. It binds to so-called opioid receptors in brain cells which normally respond to endorphins, the body’s natural painkillers.

Other drugs bind to receptors but do not cause the cell to respond to them. They have a ‘negative’ effect and are known as receptor antagonists or blockers; when they are in position on the receptor, the ligand that normally binds to it is denied access, hence the blocking effect.

Important drugs in this category include the beta blockers, which are used to treat high blood pressure and heart disease. They act on so-called beta-adrenergic receptors which normally respond to the hormone adrenaline. This is the ‘fight or flight’ hormone which puts the body on ‘red alert’ by increasing blood pressure, heart rate, and breathing. Beta blockers counteract these effects; they decrease the heart rate and so lower blood pressure and reduce the workload on the heart.

There are many other ways in which drugs can act. Some interfere with the normal traffic of substances in and out of cells. The ion channel blockers

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are an important group in this category. Ion channels are tiny pores in the cell membrane that allow the passage of minerals such as calcium and sodium. When calcium ions pass through an ion channel, the end result is muscle contraction. Calcium antagonists, such as verapamil, can block the ion channel on heart muscle cells and so reduce the strength of the muscle contractions of the heart. Like the beta blockers, this has the effect of reducing the heart’s workload, and so helps in cases of heart failure or angina.

There are also drugs which do not interfere directly with the body’s chemistry, but remedy deficiencies in the supply levels of vitamins, minerals and enzymes. For instance, iron is needed to make the oxygen-carrying pigment haemoglobin. Iron deficiency can lead to anaemia, which is characterised by symptoms such as weakness, breathlessness and faintness. According to a report carried out by the British Nutrition Foundation up to ten per cent of women could be deficient in iron – either because of heavy periods, faulty diet, or both. If they are not able to boost their iron levels by eating more iron-rich foods such as meat or fortified cereals, they might be prescribed iron tablets, which contain ferrous sulphate, an easily absorbed form of the mineral.

Not all biochemical deficiencies are so easily remedied, and some can be life-threatening. Around one per cent of the population suffers from an inherited single-gene disorder. Genes are the blueprints from which enzymes and other proteins, such as haemoglobin, are synthesised. Defective genes may have a profound effect upon cellular biochemistry by giving wrong instructions for the synthesis of these proteins. In genetic disease, a key protein may be missing from the cell entirely, or it may be made in a form which does not work properly.

Some 5700 single-gene disorders have been discovered. Some are extremely rare and some are fatal before birth. Many are still poorly understood, usually because the gene affected is unknown. However, some single-gene disorders – such as haemophilia and cystic fibrosis – have been intensively studied. Therapy for these diseases consists of supplying the protein which the patient lacks. In the commonest form of haemophilia, for example, the missing or defective protein is known as factor VIII. Without factor VIII the blood cannot clot properly and the patient suffers from prolonged bleeding after dental treatment, for instance, or perhaps spontaneous internal bleeding into the joints with swelling and intense pain.

The development of drugs for haemophilia owes a great deal to advances in gene technology. The first treatment was with factor VIII extracted from human blood. This is effective, but puts the patient at risk of infection