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Uncovering the magical world of signalling

The Nobel Prize for Chemistry 2012

Imagine you are lying in bed. Your heart is beating. Gradually you wake, open your eyes and realise it is light outside. You get up and start the day.

All these things we tend to take for granted in life: heart beats; sleep; being able to see; being able to move at will. Yet all these functions of the human body require signals to be released, detected by a receptor in the right place and an appropriate response to be mounted. For example, hormones can be released into the blood stream but, if there is no receptor to detect the hormone level changing, there will be no response.

Scientists have discovered many different signalling molecules, among them names may be familiar such as adrenaline, dopamine and

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serotonin. Adrenaline is part of the complex system that moderates your heart beat and blood pressure. When you are scared or nervous, you feel your heart pounding. That is the body sensing and responding to an increase in adrenaline. Dopamine is a neurotransmitter, a signal that is detected by receptors on brain cells. Problems with regulating dopamine can lead to Parkinson's Disease and are also thought to be the underlying cause of many mental illnesses.

Drug design

What is interesting about these examples (and many others) is that we have used our knowledge of the signal and what it does to create drugs that mimic or inhibit their action, thereby offering treatment for many different conditions. We have done this without actually knowing the nature of the receptor that the signal or the drug will bind to. To put that in context, it is thought that over half of the medicines we use bind to these receptors that we assume are present but which nobody has yet found.

For example, in every Intensive Care Unit in every hospital in Britain, many patients' survival depends on being given infusions of adrenaline. This is because when the body is extremely sick or injured it is likely to have a very low blood pressure. This is dangerous as it stops oxygen getting to all the essential parts of the body like the brain, heart and kidneys. Giving artificial adrenaline can help the body maintain a good blood pressure and ensure that all the vital organs get as much oxygen as they need. Yet the receptor that adrenaline binds to was unknown for many years.

Patients in intensive care are often given adrenaline.

Mental illnesses such as manic depression and schizophrenia are caused by problems in signalling in the brain. As mentioned above, dopamine is a neurotransmitter signal that passes between brain cells. When dopamine activity is excessive, the brain cells are over-stimulated and the person is unable to think coherently or behave rationally. These debilitating conditions can be treated with drugs. Dopamine as a signal must have a receptor on the surface of brain cells that it binds to. Anti-psychotic drugs bind to the same receptor, and block dopamine binding. The amazing thing is that the drugs were found to be effective before we knew what the dopamine receptor looked like.

Radiolabelling uses molecules containing radioactive isotopes. These can be detected and followed as their radiation makes them stand out from other molecules.

Nobel Prize

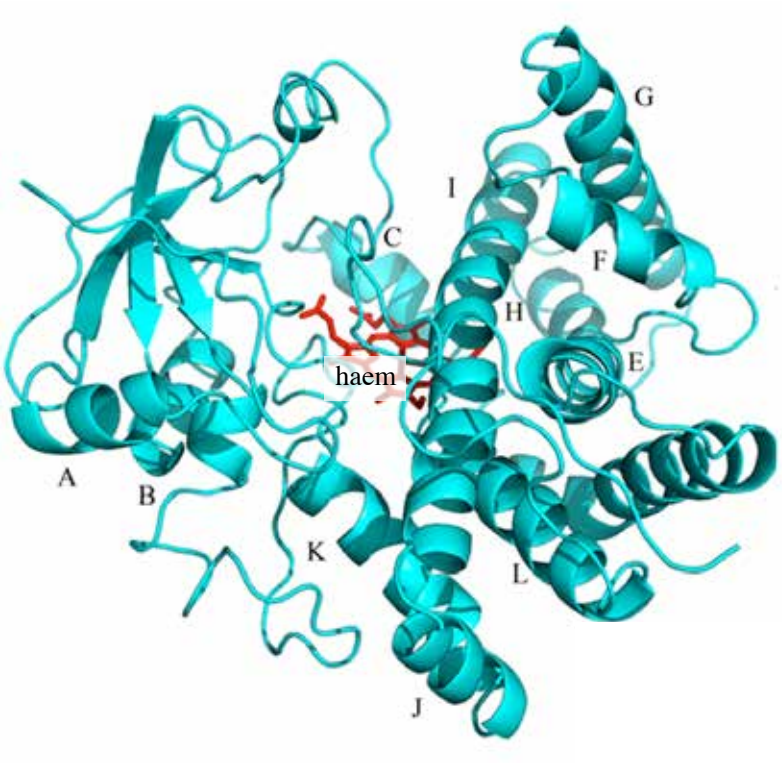
Robert Lefkowitz and Brian Kobilka, winners of the Nobel Prize for Chemistry 2012

So what has all of this got to do with the Nobel Prize for Chemistry? The 2012 prize has recently been awarded to two American scientists, Robert Lefkowitz and Brian Kobilka.

The prize was awarded for 'studies of G protein-coupled receptors' or GPCRs. These two scientists have led the way to finding those elusive receptors, and trying to characterise them as much as possible, to advance our understanding of how our bodies work and how we can medicate them when things go wrong.

In the 1980s, Lefkowitz started work on receptors which he describes as 'gateways' to the cells for all the hormones and signal transmitters. He radiolabelled hormones so he could visualise how they get through the cell membrane. It became apparent that the hormone would bind to a specific receptor (GPCR) in the membrane. The GPCR then activates a specific protein inside the cell, and a response to the signal is made. Over 1000 different receptors have now been identified. They are known to mediate the senses (sight, taste and smell), pain tolerance, glucose metabolism and a huge variety of other physiological responses.

The first receptor to be characterised by Lefkowitz and his colleagues was an adrenergic receptor – the receptor responsible for detecting adrenaline and noradrenaline. They rapidly found several other receptors, and it became clear that they all shared great similarity. The receptors make up a protein family, with specific amino acid sequences common to all. Over time, the GPCR family have been described in more detail. They are large proteins which sit in the membrane (thereby having contact with the outside and inside of the cell simultaneously). The proteins all have a long stretch of amino acids that winds back and forward through the membrane seven times.



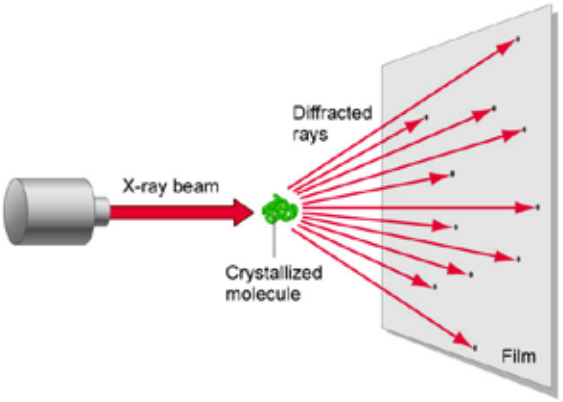
This is the kind of model that can be generated from X-ray crystallography. The blue is the protein, the curly tubes are common structures (called motifs) and give the protein its 3D shape. This is a protein that complexes with haem groups; this is shown in red. The crystal of this protein was grown by the author, and the X-ray crystallography was by Bin Zhao at Vanderbilt University, USA. It was published this year in Int J Mol Sci.

Protein structures

These properties of GPCRs make them very difficult to work with. Crystallisation is the best way to characterise the structure of any protein, but this requires the protein to be isolated in high quantity and purity. GPCRs rely on the membrane of the cell to keep all the 7-fold structure intact, and removing them from the membrane can easily result in the protein falling apart. GPCRs, like many membrane proteins, were found to be unstable in solution. This again makes any manipulation or characterisation very difficult.

One of the junior scientists who worked with Lefkowitz during the 1980s was Brian Kobilka. He was involved in the work on adrenergic receptors, and when he set up his own lab in 1989 he continued working on GPCRs. Kobilka was particularly interested in producing GPCRs in sufficient quantity and purity that he could use them for X-ray crystallography to determine their structure. As mentioned above, these processes were fraught with difficulty.

Kobilka used DNA sequencing (devised by fellow Nobel prize winner Fred Sanger) to identify and clone the genes coding for GPCRs. This allowed the protein to be produced in insect cells, using the cell membranes to keep the protein intact until it could be coaxed out without becoming unstable. It took over 20 years of lab work for him to have big enough crystals of pure GPCR protein that crystallography could be used to solve the 3D structure of the receptor. This work has improved understanding of how signals and receptors work and means drugs can now be designed to target specific receptors.



How X-ray crystallography works: the beam of X-rays is diffracted by the regular array of protein molecules in the crystal; the crystal structure can be deduced from the pattern of the diffracted beams.

Kobilka and Lefkowitz fully deserve their Nobel Prize for Chemistry. They recognised the need for identifying and understanding these receptors and the vital role they play in maintaining homeostasis. When asked what kept him going on such a difficult challenge, Kobilka's response is typical of many passionate scientists. 'I just wanted to know how they work.'

Suzy Moody is a microbiologist who investigates signalling in bacteria.

Look here!

The official Nobel Prize website description of Lefkowitz and Kobilka's work: *http://tinyurl.com/8q7psvo*

Find out about the work of two important British crystallographers: Rosalind Franklin and Dorothy Hodgkin.

Search the Catalyst archive for earlier articles about Nobel prize winners in the Sciences: *www.catalyststudent.org.uk*