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THE ROYAL SWEDISH ACADEMY OF SCIENCES

The Royal Swedish Academy of Sciences has decided to award the Nobel Prize in Chemistry for 2012 to **Robert J. Lefkowitz** and **Brian K. Kobilka** "for studies of G-protein–coupled receptors".

The Nobel Prize 2012 **in Chemistry**

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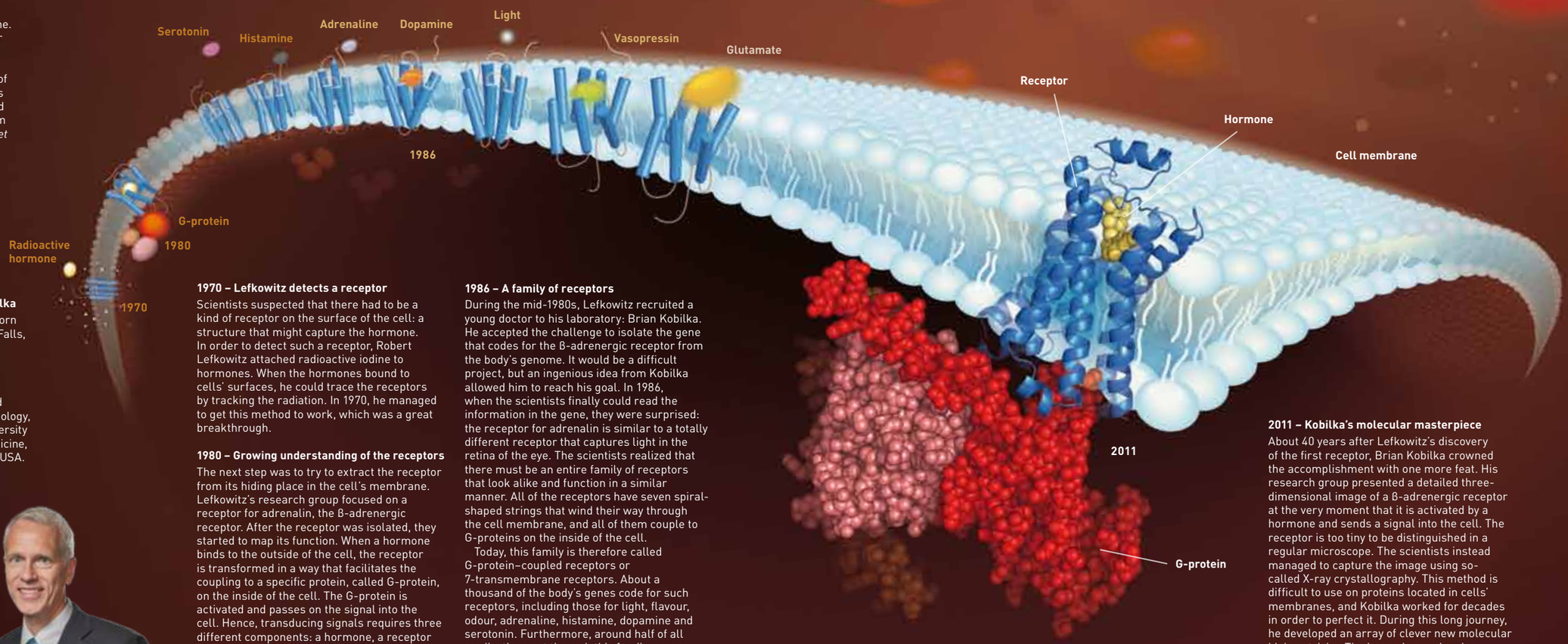
Cells and sensibility

Your body is a fine-tuned system in which billions of cells interact. Each cell has tiny receptors that enable it to sense its environment, so it can adapt to new situations. Robert J. Lefkowitz and Brian K. Kobilka are awarded the 2012 Nobel Prize in Chemistry for groundbreaking discoveries that reveal the inner workings of an important family of such receptors: G-protein–coupled receptors.

Think of the last time you got really scared: your heart probably started to beat faster, your breathing became rapid, and your body started to shake. When stress hormones like adrenaline (also known as epinephrine) are released into the blood, cells around the body immediately sense the change.

Over a century ago, scientists were already aware of the power of adrenaline. However, how hormones triggered their effects in different cells in the body remained a mystery. When scientists administered adrenaline to the *outside* of the cell, this led to biochemical changes *inside* the cell. Each cell is encapsulated by a membrane, which separates it from its surroundings. *How could the signal get through this membrane?*



Structure of an activated G-protein–coupled receptor, Brian K. Kobilka.

Robert J. Lefkowitz
U.S. citizen. Born 1943 in New York, NY, USA. Investigator, Howard Hughes Medical Institute, James B. Duke Professor of Medicine, and Professor of Biochemistry, Duke University Medical Center, Durham, NC, USA.

Brian K. Kobilka
U.S. citizen. Born 1955 in Little Falls, MN, USA. Professor of Medicine, and Professor of Molecular and Cellular Physiology, Stanford University School of Medicine, Stanford, CA, USA.

1970 – Lefkowitz detects a receptor

Scientists suspected that there had to be a kind of receptor on the surface of the cell: a structure that might capture the hormone. In order to detect such a receptor, Robert Lefkowitz attached radioactive iodine to hormones. When the hormones bound to cells' surfaces, he could trace the receptors by tracking the radiation. In 1970, he managed to get this method to work, which was a great breakthrough.

1980 – Growing understanding of the receptors

The next step was to try to extract the receptor from its hiding place in the cell's membrane. Lefkowitz's research group focused on a receptor for adrenalin, the ß-adrenergic receptor. After the receptor was isolated, they started to map its function. When a hormone binds to the outside of the cell, the receptor is transformed in a way that facilitates the coupling to a specific protein, called G-protein, on the inside of the cell. The G-protein is activated and passes on the signal into the cell. Hence, transducing signals requires three different components: a hormone, a receptor and a G-protein.

1986 – A family of receptors

During the mid-1980s, Lefkowitz recruited a young doctor to his laboratory: Brian Kobilka. He accepted the challenge to isolate the gene that codes for the ß-adrenergic receptor from the body's genome. It would be a difficult project, but an ingenious idea from Kobilka allowed him to reach his goal. In 1986, when the scientists finally could read the information in the gene, they were surprised: the receptor for adrenalin is similar to a totally different receptor that captures light in the retina of the eye. The scientists realized that there must be an entire family of receptors that look alike and function in a similar manner. All of the receptors have seven spiral-shaped strings that wind their way through the cell membrane, and all of them couple to G-proteins on the inside of the cell.

Today, this family is therefore called G-protein–coupled receptors or 7-transmembrane receptors. About a thousand of the body's genes code for such receptors, including those for light, flavour, odour, adrenaline, histamine, dopamine and serotonin. Furthermore, around half of all medications act through this family, among them, beta blockers, antihistamines and various kinds of psychiatric medications.

2011 – Kobilka's molecular masterpiece

About 40 years after Lefkowitz's discovery of the first receptor, Brian Kobilka crowned the accomplishment with one more feat. His research group presented a detailed three-dimensional image of a ß-adrenergic receptor at the very moment that it is activated by a hormone and sends a signal into the cell. The receptor is too tiny to be distinguished in a regular microscope. The scientists instead managed to capture the image using so-called X-ray crystallography. This method is difficult to use on proteins located in cells' membranes, and Kobilka worked for decades in order to perfect it. During this long journey, he developed an array of clever new molecular biology tricks. The image is a molecular masterpiece that will most likely be important for the design of new drugs.

FURTHER READING! Information on the Nobel Prize in Chemistry 2012: http://kva.se and http://nobelprize.org. **ARTICLES:** ● **Buchen, L.** (2011) Cell signalling caught in the act, *Nature* 475:273–274. ● **Buchen, L.** (2011) It's all about the structure, *Nature* 476:387–390. ● **Snyderman, R.** (2011) Introduction of Robert J. Lefkowitz, *The Journal of Clinical Investigation* 121(10):4192–4200. ● **Williams, R.** (2010) Robert Lefkowitz: Godfather of G Protein-Coupled Receptors, *Circulation Research* 106:812–814. **LECTURES (VIDEO):** ● **Lefkowitz, R. J.** (2010) Part 1 Seven Transmembrane Receptors, http://www.youtube.com/watch?v=gPyo7k9E_-w ● **Lefkowitz, R. J.** (2010) Part 2 Beta-arrestins, http://www.youtube.com/watch?v=IP4zsbemW8I

Editors: Sven Lidin and Sara Snogerup Linse, the Nobel Committee for Chemistry, The Royal Swedish Academy of Sciences; Ann Fernholm/Katalys Media, science writer; Annika Moberg, editor, Sandra Flygare Baas, Nobel Assistant, The Royal Swedish Academy of Sciences.
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Box 50005, SE-104 05 Stockholm
Phone: +46 8 673 95 00
e-mail: info@kva.se, http://kva.se

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