

G-Protein-Coupled Receptors: the 2012 Nobel Prize in Chemistry

The Royal Swedish Academy of Sciences awarded the 2012 Nobel Prize in Chemistry to the U.S. researchers Robert J. Lefkowitz, from the Duke University Medical Center (North Carolina, USA) and to Brian K. Kobilka, from the Stanford University School of Medicine (California, USA) for their studies on the G-protein-coupled receptors (GPCRs).

Lefkowitz and Kobilka's discoveries led to the elucidation of how cells communicate with each other and perceive stimuli from the environment. GPCRs are proteins embedded in the biological membranes and help to transmit external signals to the interior of cells, acting in the regulation of several physiological functions, ranging from the detection of physical sensations (*e.g.* light) to the hormonal regulation. GPCRs play a central role in cellular and biochemical processes, acting as molecular targets for many drugs, including muscarinic, adrenergic, dopaminergic, serotonergic, opiate and purinergic, among other receptors.

About 50% of all available drugs in the therapeutics bind to any of the various subtypes of GPCRs. Important examples include the anti-ulcer ranitidine (Zantac)[®], the H₂ histaminic receptor antagonist; the antipsychotic olanzapine (Zyprexa)[®], the 5-HT₂ serotonergic receptor antagonist and the anti-allergic desloratadine (Desalex)[®], the H₁ histaminic receptor antagonist.

Several important advances have been recorded since the discovery of GPCRs, with emphasis on the elucidation of the 3D structures of different subtypes and their complexes, by means of experimental methods such as X-ray crystallography.

Such structural knowledge has enabled a better understanding of the biochemical mechanisms of this class of receptors and the establishment of the molecular bases that have led to the discovery of new drugs. GPCRs have a similar conserved 3D folding of the polypeptide chain, comprising an N-terminal extracellular domain, seven transmembrane helices and an intracellular C-terminal domain.

GPCRs interact with proteins located on the inner cell membrane. These specific proteins, known as G-proteins, are heterotrimers consisting of α , β and γ subunits. In 1980, Lefkowitz and collaborators proposed an activation mechanism involving the formation of a ternary complex of the extracellular ligand (agonist), the transmembrane GPCR and the intracellular G-protein acting as a signal activator.

In the absence of an external signal, a molecule of GDP (guanosine diphosphate) binds to the α subunit of the G-protein. The complex formed interacts with the GPCR, which remains unchanged until an external signaling molecule binds to the site of interaction of the GPCR, leading to a conformational change in the 3D structure of the receptor that activates the G-protein. One molecule of GTP (guanosine triphosphate) replaces the GDP (linked to the α subunit) and the G-protein subunits dissociate creating a complex formed by the α subunit linked to the GTP and a dimeric complex composed of the β and γ subunits.

Both complexes remain anchored to the plasma membrane and are able to interact with other proteins involved in signal transduction. Specific targets of interaction of G-proteins include enzymes that synthesize second messengers and ionic channels (*e.g.* Na⁺, K⁺, Ca²⁺, Cl⁻).

Due to its GTPase activity, the GTP bound to the α subunit, when the G-protein is in the active form, is hydrolyzed generating GDP, which leads to a new conformational change. Thus, the α , β and γ trimeric complex of the G-protein is reestablished, favoring its interaction with the GPCR.

This model has been extensively studied by means of thermodynamic methods to be finally crowned by Kobilka and collaborators with the high resolution structure determination by X-ray diffraction on single crystals of the isolated receptor and of the functional ternary complex of the β -adrenergic receptor with the agonist ligand and the G-protein. (Rasmussen *et al.* and Kobilka. Crystal structure of the β 2 adrenergic receptor-Gs protein complex. *Nature* **2011**, 477, 549).

The impact of the results initially elucidated by Lefkowitz and subsequently by Kobilka is evidenced by the innovations achieved in the design of new compounds that specifically bind to the multiple molecular sites, which determine the allosteric functional activity of the GPCRs. This is a prime example of the fine structural-molecular regulation that characterizes the activity of the molecules that constitute the living beings.

Lefkowitz was born in New York City (NY, USA) in April 1943 and Kobilka in Little Falls (Minnesota, USA) in May 1955.

Graduated in Medicine from the Columbia University, Lefkowitz completed his residency at the Massachusetts General Hospital in Boston (Massachusetts, USA).

Currently, he is a Professor of Medicine, Pathology and Biochemistry at the Duke University and a Researcher at the Howard Hughes Medical Institute (Maryland, USA).

Graduated in Biology and Biochemistry from the University of Minnesota and in Medicine from the Yale University (Connecticut, USA), Kolbika completed his residency at the Barnes Hospital in St. Louis (Missouri, USA) and spent some time as a Researcher in the Lefkowitz laboratory at the Duke University. He is currently a Professor in the Department of Medicine and Molecular and Cellular Physiology at the School of Medicine, Stanford University.

Lefkowitz and Kobilka will share an 8-million Swedish kronor (SEK) prize, the equivalent of US\$ 1.2 million. They will also receive a gold medal and a diploma.

It is worth learning a bit more about the history of the Nobel Prize and, in particular, about the Nobel Prize in Chemistry.

The Nobel Prize was established following a wish of the chemist Alfred Nobel, expressed in his will. Nobel was born in October 1833 in Stockholm, Sweden and died in San Remo, Italy in December 1896. In 1867, his work in the field of Chemistry led to the invention of dynamite, a nitroglycerin-based explosive mixed with inert absorbent and porous material, which would have a major impact on road and railway constructions, on the opening of tunnels and channels, on mining activities and on wars, among others.

Since 1901, the Nobel Prize has been awarded in the fields of Chemistry, Physics, Physiology or Medicine, Literature and Peace. In 1968, the Central Bank of Sweden (Sveriges Riksbank) established the Prize in Economic Sciences, which was first awarded in 1969. The awards are announced annually in October and delivered on December 10th, the anniversary of its creator's death.

From 1901 to 2012, the Nobel Prize in Chemistry was awarded 104 times to 162 scientists, with the exception of years 1916, 1917, 1919, 1924, 1933, 1940, 1941 and 1942. It has been awarded to a single winner 63 times, 23 times to two winners and 18 times to three researchers. According to the statutes of the Nobel Foundation, the Nobel Prize can not be granted to more than three people.

Jacobus Henricus van't Hoff was the first winner in 1901. Frederick Sanger was the only one to be laureated twice, in 1958 and in 1980. The average age of all Nobel laureates in Chemistry from 1901 to 2011 is 57 years. The youngest one was Frédéric Joliot, who received the award at the age of 35 in 1935, along with his wife Irène

Joliot-Curie. The oldest one was John B. Fenn, who was honored in 2002 at the age of 85.

Among the 162 winners, four are women: Marie Curie in 1911, Irène Joliot-Curie (Marie Curie's daughter) in 1935, Dorothy Crowfoot Hodgkin in 1964 and, more recently, Ada Yonath, in 2009. Marie Curie was also awarded the Nobel Prize for Physics in 1903, being the only woman in history to win the Nobel Prize twice.

It is also worth noting that Linus Pauling was awarded twice as the sole winner, unheard until now. Pauling received the Nobel Prize in Chemistry in 1954 and the Nobel Peace Prize in 1962.

Scientific research in general can be divided between basic and applied research. Essentially, basic research is the investigation of new phenomena and their foundations, so that knowledge in a particular field can advance. Applied research starts from the knowledge gained from basic research to generate results in economic terms or to solve problems related to other needs.

The work that led the American researchers to the Nobel Prize in Chemistry this year is a great example of the integration and exchange of knowledge and, ultimately, of the interdisciplinary research of high scientific value and high complexity in the areas of Science. So, this is how this story developed: in the mid-1980, Lefkowitz and colleagues cloned the first gene for the β -adrenergic receptor. And later, this knowledge, added to the knowledge generated in other areas, was used to develop several other researches, which resulted in investigations and applications of great importance, bringing benefits to society.

Finally, every year, fascinating scientific discoveries come into reality as a result of the inspiration that springs from the Nobel Prize, which enchants and awakens the curiosity of people. Many and valuable are the lessons gained. To build knowledge and expertise with excellence is critical to ensure a more prosperous and just nation's tomorrow. To educate our young people with quality and responsibility, prioritizing ethical, academic and scientific values, is our hope that the professionals of the future will be able to paint that source of inspiration green and yellow. May the future come soon!

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