CHEMISTRY

Studies of a ubiquitous receptor family

The Nobel Prize in Chemistry was awarded to Robert J. Lefkowitz and Brian K. Kobilka for their work in characterizing G-protein-coupled receptors (GPCRs) — the proteins that enable cells to sense and respond to their environment (see figure).

BIOLOGICAL INSIGHTS

by Bryan L. Roth

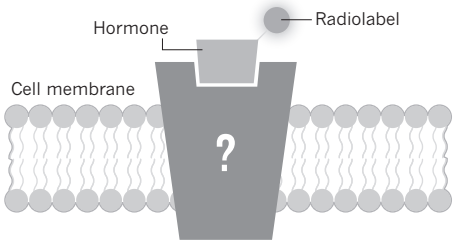
The idea that drugs exert their effects through specific interactions with receptors has captivated scientists' imagination[1] since 1905. But it was not until 1986 that Lefkowitz, Kobilka and colleagues' cloning of β-adrenergic receptors, which mediate the effects of adrenaline and noradrenaline, provided the first definitive proof that receptors are physical entities encoded by the human genome. This finding ushered in one of the most exciting eras of pharmacology and biochemistry, because it allowed other GPCRs to be identified on the basis of their similar transmembrane-domain architecture. Perhaps as many as 900 human GPCRs have been discovered in this way[2].

The identification of these GPCRs has revealed that more than 50% are 'orphan' receptors[3,4] — those for which ligands have not been identified. Working out the function of even one orphan GPCR, as Kobilka, Lefkowitz and co-workers did for the 5-HT_{1A} receptor[5] (the most abundant of the receptors that bind the signalling molecule serotonin), is a great achievement and can open up entire fields of research. 'De-orphanizing' such GPCRs represents a major challenge for scientists.

Lefkowitz and colleagues also discovered that GPCRs have two signalling modes: one that acts through G proteins and another facilitated by cell-scaffolding proteins such as β-arrestins[6]. It seems that β-arrestin-facilitated signalling is responsible for many of the physiological effects of GPCR activation, although the full panoply of events mediated by β-arrestins is unknown. Elucidation of the molecular basis of these effects should reveal the full repertoire of β-arrestin-mediated signalling and provide ample opportunities for drug-discovery programmes for years to come.

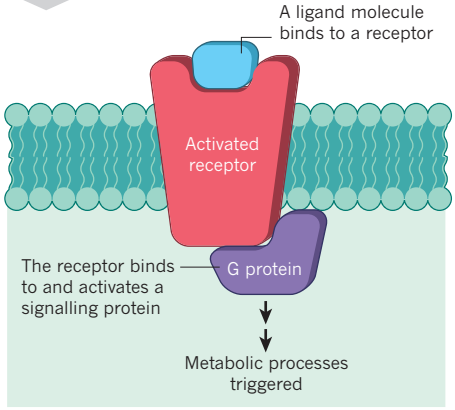
1968

Lefkowitz began using radiolabelled hormones to identify several of the receptors that enable cells to sense their environment.



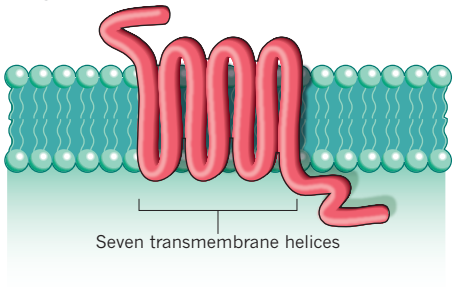
1980

Lefkowitz and colleagues proposed the widely accepted 'ternary complex model' for receptor activation.



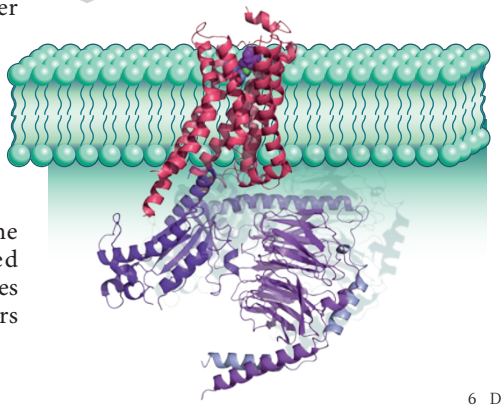
1986

Lefkowitz, Kobilka and co-workers cloned the gene that encodes the β_2-adrenergic receptor, revealing its transmembrane structure. They concluded that it was part of a family of functionally similar receptors.



2011

Kobilka and colleagues solved the crystal structure of the β_2-adrenergic receptor in complex with an activating ligand and a G protein.



ENABLING DRUG DISCOVERY

by Fiona H. Marshall

For many years, pharmaceutical companies screened for drugs that act at GPCRs by using live animal tissues suspended in baths to test chemicals related to natural hormones. The introduction of assays based on radiolabelled ligands, such as those developed by Lefkowitz, was a breakthrough, because it allowed larger numbers of compounds to be tested, together with accurate measurement of their affinities for their receptors. This allowed medicinal chemists to identify the relationships between the molecular structure of a ligand and its biological activity.

Lefkowitz, Kobilka and colleagues' cloning of GPCR genes had two notable effects on drug discovery. It enabled the high-throughput screening of libraries of millions of compounds against human receptors, and led to the identification of many GPCRs. A range of genomic technologies has since been applied to discover the function of these orphan receptors, and drugs that target them — for example, suvorexant, a treatment for insomnia[7] — are now approaching the market.

Despite some successes, high-throughput screening is a hit-and-miss process. The availability of X-ray structures of GPCRs instigated a new era of rational design[8] for drug discovery that targets these receptors — compounds that fit perfectly into 'pockets' of the receptors can now be selected using computational techniques. Kobilka and colleagues' recently reported structure of the active form of a GPCR in complex with its signalling protein suggests that drugs that activate the receptor, rather than just block it, can also be designed. GPCR-targeting drugs discovered using such structure-based techniques are already in development. ■

Bryan L. Roth *is in the Department of Pharmacology, University of North Carolina Medical School, Chapel Hill, North Carolina 27514, USA.*
e-mail: bryan_roth@med.unc.edu
Fiona H. Marshall *is at Heptares Therapeutics Ltd, Welwyn Garden City AL7 3AX, UK.*
e-mail: fiona.marshall@heptares.com

1. Langley, J. N. *J. Physiol. (Lond.)* **33,** 374–413 (1905).
2. Zhang, Y., DeVries, M. E. & Skolnick, J. *PLoS Comput. Biol.* **2,** e13 (2006).
3. Kroeze, W. K., Sheffler, D. J. & Roth, B. L. *J. Cell Sci.* **116,** 4867–4869 (2003).
4. Allen, J. A. & Roth, B. L. *Annu. Rev. Pharmacol. Toxicol.* **51,** 117–144 (2011).
5. Fargin, A. *et al. Nature* **335,** 358–360 (1988).
6. Luttrell, L. M. *et al. Science* **283,** 655–661 (1999).
7. Cox, C. D. *et al. J. Med. Chem.* **53,** 5320–5332 (2010).
8. Congreve, M. *et al. J. Med. Chem.* **55,** 1898–1903 (2012).

F.H.M. declares competing financial interests.
See go.nature.com/mo5rfy for details.