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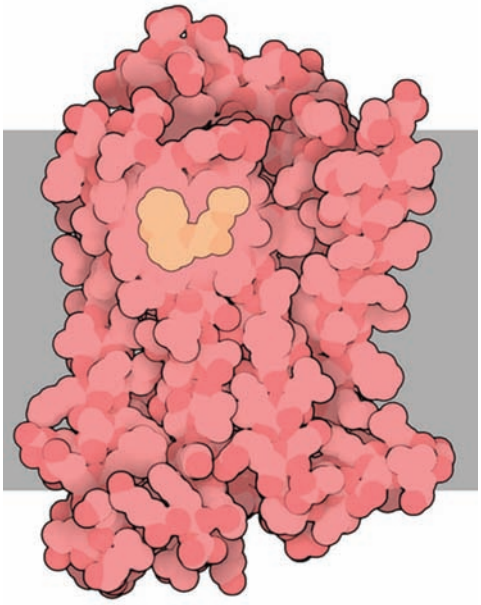
MOLECULE OF THE MONTH: ADRENERGIC RECEPTORS

About the *Molecule of the Month*

This feature on Adrenergic Receptors is the 100th installment of *Molecule of the Month*. Using selected molecules from the Protein Data Bank, each feature includes an introduction to the structure and function of the molecule, a discussion of its relevance to human health and welfare, and suggestions for viewing and accessing further details.

The *Molecule of the Month* is read by students, teachers, and scientists worldwide at www.pdb.org.

This April 2008 edition was written and illustrated by David S. Goodsell (RCSB PDB and The Scripps Research Institute).



Our bodies have many built-in defenses. Our immune system prowls through the body looking for infections by viruses and bacteria. Our blood is filled with molecules that form clots at the first sign of damage. Our nervous system is also hard-wired with instinctive defenses that stand ready to protect us in times of danger. You have probably experienced one of these defenses yourself–when you are startled or scared by an impending danger, you will feel a rush of energy flowing through your body. This has been termed the "flight or fight" response–your body is mobilizing its many resources to make you ready either to run away from danger, or stay and fight.

A Cascade of Response

The small hormone adrenaline, also known as epinephrine, is the messenger that tells cells to ready themselves in danger. It is released into the blood from the adrenal glands, which are situated on top of the kidneys. Then it spreads through the blood to cells throughout the body, where it is sensed by adrenergic receptors on the cell surface. When the adrenergic receptor is stimulated by adrenaline, it passes the message inside the cell to a G-protein. The G-protein then relays the message to a variety of other signaling enzymes, such as adenylyl cyclase, that amplify and spread the message through the cell.

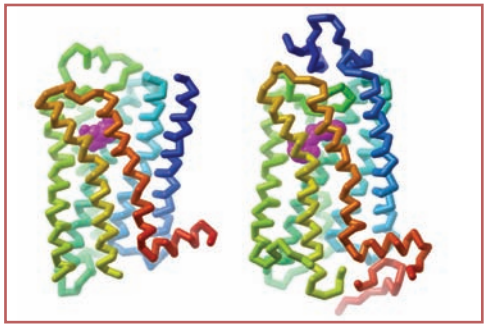
Feel the Rush

When the body is flooded with adrenaline, we focus all of our energy on the danger at hand. Defensive functions are activated, such as increasing the heart rate and providing more sugar in the blood. Normal housekeeping functions, such as digestion, are temporarily halted as we respond to the challenge. This requires different cells to respond differently to adrenaline–heart cells need to be activated, but cells in the digestive system need to wait for a better time to do their jobs. To orchestrate this range of responses, human cells build nine different types of adrenergic receptors, each with a slightly different effect. The one shown here, the beta-2 adrenergic receptor (PDB entry **2rh1**[1]), stimulates cells to increase energy production and utilization. Other types of adrenergic receptors are inhibitory, slowing the use of energy. By expressing one type or another on their surfaces, different cells tailor their responses to adrenaline, making themselves ready for an emergency.

Receptors Everywhere

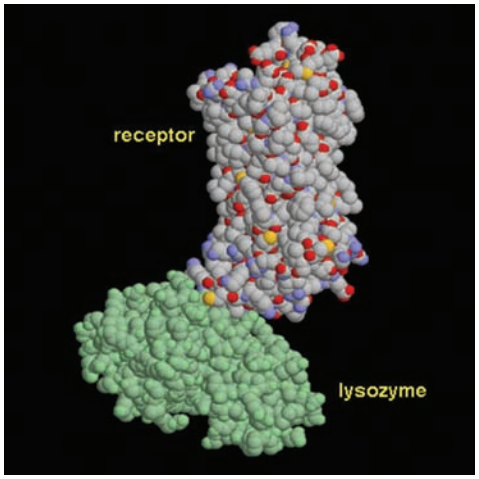
The adrenergic receptors are part of a large class of similar proteins, collectively known as G-protein-coupled receptors, often abbreviated GPCR. These receptors play many diverse and important roles in human health. By some estimates, there are almost a thousand different types in the human genome, including hundreds of receptors for taste and smell. Many widely-used drugs, such as Prozac, Claritin and Zoloft, act by binding to these receptors. In spite of their importance, they have been extraordinarily difficult to study, since they are normally buried inside a membrane. For many years, the structure of rhodopsin was the only structure available for this class of proteins, and many studies have been performed using rhodopsin as the starting point for structural study of other receptors. This is a successful approach because the receptors are all very similar. They are composed of one chain that snakes back and forth across the membrane seven times. For this reason, they are occasionally also called serpentine receptors.

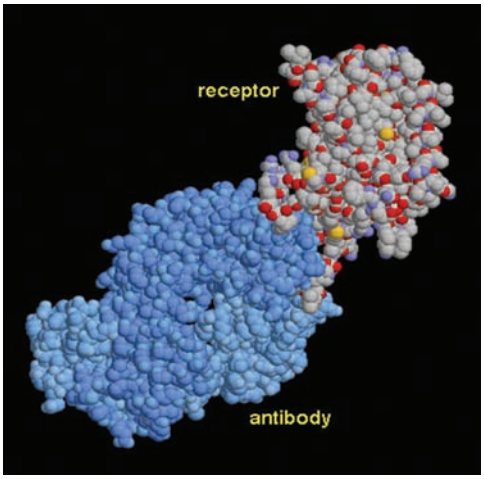
ADRENERGIC RECEPTORS



The meandering path of the protein chain is shown here for two GPCR structures: the adrenergic receptor (left, PDB entry **2rh1**[1]) and rhodopsin (right, PDB entry **1f88**[2]).

This illustration was created with the Python Molecule Viewer[3].





Exploring the Structure

To solve the structure of the adrenergic receptor, researchers had to do some unusual things. Since it is normally buried in a cell membrane, it is difficult to crystallize in purified form. Different approaches were taken for two structures. In one case, shown on the left from PDB **2rh1**[1], the protein was engineered to insert lysozyme in the middle of the chain. The fused protein chain folds normally, with the lysozyme portion hanging off the bottom of the receptor. In the other case, shown on the right from PDB entry **2r4r**[4], an antibody was discovered that binds to the receptor, and the complex of receptor with antibody was crystallized. In both cases, the extra protein–lysozyme or antibody–helped create the many protein-protein contacts needed for a stable crystal.

These pictures were created with RasMol[5].

RCSB Protein Data Bank (www.pdb.org)

The Protein Data Bank (PDB) is the single worldwide repository for the processing and distribution of 3-D structure data of large molecules of proteins and nucleic acids. The RCSB PDB is operated by Rutgers, The State University of New Jersey and the San Diego Supercomputer Center and the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of California, San Diego –two members of the Research Collaboratory for Structural Bioinformatics (RCSB).

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The RCSB PDB is a member of the worldwide PDB (**wwPDB; www.wwpdb.org**).

Additional Reading

D.M. Rosenbaum, V. Cherezov, M.A. Hanson, S.G. Rasmussen, F.S. Thian, T.S. Kobilka, H.J. Choi, X.J. Yao, W.I. Weis, R.C. Stevens, and B.K. Kobilka (2007) GPCR engineering yields high-resolution structural insights into β2-adrenergic receptor function. *Science* **318**: 1266-73.

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G. Milligan, P. Svoboda and C. M. Brown (1994) Why are there so many adrenoreceptor subtypes? *Biochem. Pharm.* **48:** 1059-1071.

An interesting paper about controversy regarding the use of "adrenaline" versus "epinephrine"
J. K. Aronson (2000) "Where name and image meet"–the argument for "adrenaline." *British Medical Journal* **320**: 506-509.

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