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Common drugs initiate a molecular pas de quatre at the surface of the cell membrane

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G protein-coupled receptors (GPCRs) are popular drug targets, accounting for about one-third of approved drugs and many hundreds of drugs currently in development. They act as molecular switches that transduce extracellular signals by activating heterotrimeric G proteins (G proteins) located at the inside of the cell.

Changes in shape of these proteins determine essential processes, including whether an eye detects light, a virus invades a cell or a drug slows a racing heart. GPCRs sit in the membranes of cells throughout the body. They pick up signals from outside the body — such as odors, flavors or light — and signals from within the body, such as neurotransmitters or hormones. Once those signals are transmitted to the inside of the cell, they activate intracellular G proteins, triggering a variety of biochemical pathways. Despite their importance in biology and medicine, the way G protein-coupled receptors couple the detection of a signals from the outside world to the activation of the G-protein at the inside of the cell has remained largely unknown – an important obstacle to understanding their function.

In an article in *Nature*, scientists from Stanford University, University of Wisconsin and VIB-Vrije Universiteit Brussel now reveal the complete three-dimensional atomic structure of an activated GPCR — the beta-2 adrenergic receptor (beta-2AR) — in a complex with its G protein. This is an important step towards the understanding of how the receptors actually work.

Beta-2 AR is activated by the hormones adrenaline and noradrenaline. Activation of the receptor lies at the basis of the body's fight-or-flight response by speeding up the heart, increasing blood pressure and opening airways. As a result, it is a key target for anti-asthma and blood pressure medications.

Adrenaline binds from the outside of the cell to the adrenergic receptor that is embedded in the cellular membrane, causing the heterotrimeric G protein (Gs) to fall apart in two pieces (G-alpha-S and G-beta-gamma). One piece (G-alpha-S) transmits the adrenaline signal to an effector enzyme; the other piece (G-beta-gamma) transmits the signal to an effector ion channel.

Although the receptor beta-2AR been discovered 20 years ago, the exact mechanism of its function remained unknown, impeding improvements of the drugs that act on this receptor. To explain the function of this receptor, it was important to catch the signaling complex in the act, a dance in two parts featuring four key players: the hormone (adrenaline or noradrenaline), the receptor and the G protein that is built from G-alpha-S and G beta-gamma.

Now, 20 year later, this is exactly what the researchers Stanford University, University of Wisconsin and VIB-Vrije Universiteit Brussel have accomplished. They produced two key freeze-frame pictures of this dance. In January 2011, they produced the first images of an active receptor, coupled to a drug-like molecule that acts like the hormone. In a follow-up article in Nature, they now present the poignant moment in the ballet – the four-partner embrace that includes the hormone, the receptor, G-alpha-S and G-beta-gamma. These findings provide the very first three dimensional insights in transmembrane signaling trough GPCRs, a molecular process that is considered to be one of the most fascinating problems in biology. The discovery is important because the interactions between the GPCR and G-alpha-beta-gamma are

pharmacologically relevant and unlock the secrets of functional selectivity, the ability of different drugs to coax distinct downstream effects from a single kind of receptor.

Obtaining a 3D image of the Hormone:GPCR:G-alpha-beta-gamma complex proved to be very complicated. The large and membrane embedded complex is unstable, difficult to prepare and the components are difficult to express and purify. Jan Steyaert and Els Pardon in Brussels produced a Xaperone™, that binds simultaneously on G-alpha-S and G-beta-gamma and holds these proteins together in the complex. The structure of this stabilized complex was determined using X-ray crystallography techniques. The Advanced Photon Source beamline 23 ID-B at the Aragon Synchrotron, one of the most powerfull X-ray sources worldwide was used as a molecular camera.

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