Tracing water channels in cell surface receptors

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G protein-coupled receptors (GPCRs) are the largest class of cell surface receptors in our cells, involved in signal transmission across the cell membrane. One of the biggest questions is how a signal recognized at the extracellular side of a GPCR induces a sequence of conformational changes in the protein and finally evokes an intracellular response. EPFL scientists have now used computer modeling to reveal in molecular detail the structural transitions that happen inside GPCRs during the signal transduction process. They discovered that a central step in the trans-membrane signaling process is the formation of a continuous water pathway inside the G protein coupled receptors.

The work, published in *Nature Communications*, proposes that future therapeutic compounds might be selected according to their potential to interfere with the receptors' internal waters.

GPCRs amplify extracellular signals to finally evoke intracellular responses

GPCRs are membrane proteins on the cell's surface. There are approximately 800 different GPCR types, each of which can detect and bind specific molecules on the cell's surface, which are called 'ligands'. Upon binding a ligand, the GPCR transmits a signal across the cell's membrane where specialized, so-called G proteins work to amplify the signal using a cascade of biochemical reactions that evoke cellular responses.

As these processes are of central importance for the proper function of our cells, even slight malfunctions of these processes can result in severe diseases. This makes GPCRs of utmost importance as targets for modern drug development, while a large proportion of current clinical drugs target various GPCRs. Therefore, understanding how GPCRs function at a molecular level can lead to the development of novel, powerful drugs for the treatment of diseases including cancer, diabetes, neurological disorders, inflammations, immunological disorders and cardiovascular disorders.

The 3D structures of a few GPCRs have already been solved by X-ray crystallography. However, this approach generates only static structures, which are not suited to uncover the structural changes that occur within the GPCRs during the signal transduction process.

Modeling GPCRs

The team of Horst Vogel at EPFL has now used a method known as 'molecular dynamics computer simulations' to model prototypical GPCRs. The team succeeded in simulating the time course of transitions in the 3D structure of the GPCRs during the process of signal transduction across the cell membrane.

Vogel's team revealed in detail the important molecular steps of how a GPCR transmits a signal across the cell membrane. After binding a ligand on the extracellular side, the GPCR undergoes a couple of 3D changes. These then allow water molecules to enter the interior of the GPCR, reaching a 'water barrier' of amino acids.

After further structural changes, this barrier opens a gate and finally allows the formation of a continuous water channel extending from the ligand binding site to the intracellular region of the receptor. The consecutive structural changes within the receptor, combined with the

water channel are essential for the activation of G proteins on the intracellular side of the GPCR. Once activated, the G proteins can then amplify the signal.

"This discovery of these internal water channels can pave the way for novel approaches in drug development," says Horst Vogel. "By searching for compounds which bind to GPCRs and modulate their water channels, it might be possible to find more efficient therapeutic compounds."

More information: Yuan S, Filipek S, Palczewski K, Vogel H. Activation of G-protein-coupled receptors correlates with the formation of a continuous internal water pathway. *Nature Communications* 09 September 2014. DOI: 10.1038/ncomms5733

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