New details of the transmission of stimuli in living organisms unveiled

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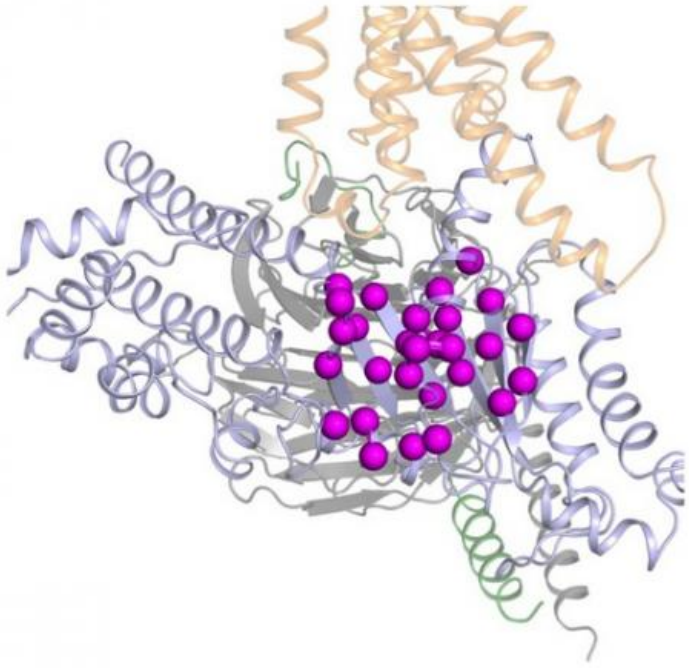

Simplified depiction of the structure of the G-protein studied (in grey) and the receptor coupled to it. The spheres represent the amino acids that are crucial for the activation of the G-protein. Credit: Dawei Sun

Researchers unveil new details about how cells in a living being process stimuli. The study, partly funded by the Swiss National Science Foundation SNSF, focuses on so-called G-proteins, which help transmit external stimuli that reach a cell into its interior. Using a technique developed at the Paul Scherrer Institute PSI, the study authors discovered which parts of the G-proteins are vital for their functioning. In particular, they demonstrated that only a few amino acids, protein building blocks, have a major influence on their function. Other amino acids, however, can be altered without compromising their function. The new findings significantly improve our understanding of processes such as sensory perception and hormone activity, and aid the development of new drugs. Researchers from PSI, ETH Zurich, the pharmaceutical company Roche and the British MRC Laboratory of Molecular Biology report their results in the journals *Nature* and *Nature Structural and Molecular Biology*.

When we see an object, the following essentially happens: the light emanating from the object hits our eye, whereupon nerve cells transmit a signal to the brain, which the brain interprets as an image of the object. The signal transmission is triggered by the protein rhodopsin, a so-called G-protein-couple receptor. This protein in the retinal cells is activated as soon as light reaches the eye. Rhodopsin acts as a switch which, once flicked, transmits the signal to G-proteins inside the cell. These amplify the signal and relay it in the cell. Many pairs of G-protein-coupled receptors and G-proteins work in a similar way. The adrenalin receptor in muscle cells, for instance, is activated when the body releases the hormone adrenalin in a stress situation. In this case, the corresponding G-protein relays the signal, which culminates in the tensing of the muscles. A team headed by researchers from the Paul Scherrer Institute (PSI) and ETH Zurich together with the the British MRC Laboratory of Molecular Biology and the pharmaceutical company Roche provide new details of how the activation of these proteins takes place. The findings can be transferred to other processes, such as smell, taste and many more where

similar proteins are involved in the signal transmission. Moreover, they could help to develop novel, improved drugs.

Nobel Prize-winning research

Thanks to decades of research scientists have learnt a great deal about the interplay between G-proteins and the corresponding receptors (G-protein-coupled receptors or GPCRs for short). In 1994 and 2012, for instance, Nobel Prizes were awarded for the discovery of these receptors and the clarification of their coupling mechanism with the G-proteins. The details of how the G-protein is activated, however, were not clear until now. The new study plugs this gap, revealing how the shape of G-proteins is altered during their activation and which protein components are behind these changes.

A few components set the tone

Like all proteins, G-proteins are made up of building blocks which experts refer to as amino acids. In proteins, these amino acids are linked to each other in a particular sequence according to a precise blueprint encoded in our DNA. The G-protein studied here is composed of 354 amino acids. In order to find out how this G-protein is activated, the authors of the study exchanged every single one of these 354 amino acids with another amino acid. They then measured how the exchange affected the degree of activation of the G-protein.

"The analysis of the measurements reveals that only one small group of around twenty amino acids plays a major role in activating the G-protein," explains Dawei Sun, who conducted the experiments as part of his PhD dissertation at PSI. Sure enough, only exchanging these particular amino acids had a significant influence on the activation of the G-protein, while swapping the remaining amino acids produced no

significant effect. The researchers detected the influence of the essential amino acids in changes in the shape of a section of the G-protein, which resembled a rolled-out streamer (helix structure) in a deactivated state. "When the key amino acids were switched, this structure lacked its usual twists," explains Dmitry Veprintsev, the leading researcher on the study at PSI's Laboratory of Biomolecular Research. "This enabled us to demonstrate that the helix structure disappears at least temporarily during the activation of the G-protein," adds Veprintsev.

Useful for almost one in three drugs

The significance of this result is not limited to one single protein: the newly discovered mechanism is universal. In other words, it is not only involved in the particular G-protein examined in this study, but rather in all G-proteins. This conclusion is supported by extensive computer calculations conducted by a team led by Madan Babu from the MRC Laboratory of Molecular Biology and recently published in the journal *Nature*. Veprintsev stresses that the present study has identified the essential amino acids that play a role in the activation mechanism of a G-protein. Gebhard Schertler, the head of the Biology and Chemistry Research Department at PSI, explains that this knowledge significantly aids the development of drugs that function through the activation of a GPCR receptor and the corresponding G-protein. The potential benefit is not to be underestimated: today, around 30 per cent of all available drugs already unleash their effect in this way. Moreover, the consequences could go beyond the G-proteins. "Our method can be applied in future to other important proteins to understand their activation mechanism," assures Veprintsev.

More information: "Probing Gαi1 protein activation at single–amino acid resolution." *Nature Structural & Molecular Biology*, 10 August 2015 DOI: 10.1038/nsmb.3070

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