How proteins find one another

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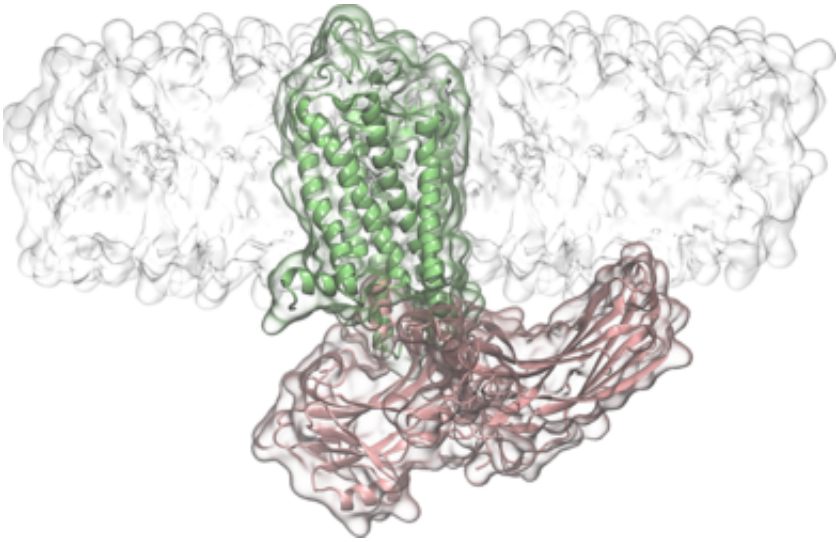

Arrestin loops interact directly with the membrane adjacent to the GPCR. Credit: Jana Selent, Pompeu Fabra University.

Researchers from Charité – Universitätsmedizin Berlin have been studying two proteins that play a vital role in many bodily processes. The aim of the research was to establish how G-protein-coupled receptors (GPCRs) and arrestin form complexes. The human GPCR family consists of nearly one thousand different types of membrane proteins, with the majority involved in sensory and neuronal processes. Results from this research, which has been published in the current issue of the journal *Nature Communications*, identify a previously unknown binding element critical to the arrestin - GPCR interaction.

As crucial drug targets, G-protein-coupled receptors are responsible for the effectiveness of nearly half of all medicines prescribed today. GPCRs are integral membrane proteins that control and modulate the processing of sensory and physiological stimuli, such as those relevant to our sight and taste, or those involved in controlling our heart rate. Arrestins play a key role in controlling the activity and signal transduction of GPCRs inside the cells of the body. "GPCRs are the target of a wide variety of drug-based treatments, which is why it is so important for us to understand their structure and function, and to fully understand how these membrane proteins interact at the molecular level. In order to develop better drugs with fewer side effects, this knowledge is necessary," explains Dr. Martha Sommer, who chairs the Arrestin Working Group at Charité's Institute of Medical Physics and Biophysics.

Some of the side effects that occur with certain medicines (such as morphine-based drugs) are the result of arrestin-dependent signaling pathways. The researchers' close observation of the interactions between arrestins and GPCRs yielded crucial conclusions. "We asked ourselves how these two proteins manage to find each other, and what happens when they come together to form a complex. The recent crystal structure of a GPCR-arrestin complex prompted us to ask whether a section of arrestin called the C-edge might interact with the membrane adjacent to the GPCR," explains Dr. Sommer. "Using a combination of computer simulations, which we conducted in cooperation with Dr. Jana Selent at the UPF Barcelona, and site-directed fluorescence spectroscopy, we were able to show that loops within the C-edge of arrestin binds to the membrane." The existence of this type of interaction was previously unknown, and its discovery opens up a whole new field of research regarding how the membrane influences the function of arrestin. A better understanding of GPCR-arrestin interactions is essential if we are to develop drugs with fewer side effects. Dr. Sommer's team have already begun to explore the role of the membrane on the structure and interactions inside the GPCR-arrestin complex.

More information: Ciara C M. Lally et al, C-edge loops of arrestin function as a membrane anchor, *Nature Communications* (2017). DOI: 10.1038/ncomms14258