Structure of cell signaling molecule suggests general on-off switch

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A three-dimensional image of one of the proteins that serves as an on-off switch as it binds to receptors on the surface of a cell suggests there may be a sort of main power switch that could be tripped. These surface receptors are responsible for helping cells discern light, set the heart racing, or detect pain.

The finding, published online April 21, 2013, in the journal *Nature* by a research collaboration involving this year's Nobel laureates in chemistry, could help in the development of more effective drugs to switch on or off the cell receptors that regulate nearly every bodily function. Already, up to half of all drugs engage these receptors, including antihistamines and beta blockers, but many of the intricacies of how these important proteins work remain unknown.

"It's important to understand how this extraordinary family of receptors work," said co-author Robert J. Lefkowitz, M.D., James B. Duke Professor of Medicine and Howard Hughes Medical Institute Investigator. "This is the kind of finding that answers a basic curiosity, but can also be of benefit if we can develop new drugs or improve the ones we have."

The research marks a collaborative reunion between Lefkowitz and Brian K. Kobilka, M.D., chair of molecular and cellular physiology at Stanford University School of Medicine. The two researchers – friends who first collaborated when Kobilka was a trainee in Lefkowitz's laboratory at Duke - shared the 2012 Nobel Prize in Chemistry for their

discoveries involving the G-protein coupled receptors (GPCRs), which are activated by signaling proteins to detect hormones, neurotransmitters, pain, light.

In the current work, the researchers used X-ray crystallography to develop an atom-scale image of one of the principal signaling molecules that regulate GPCRs. This protein is called beta-arrestin1, which, among other things, works to dim a cell's response to hormones such as adrenalin.

The researchers were able to isolate and capture the beta-arrestin1 protein in an active state as it binds to a segment of the GPCR – a first. That snapshot, in high resolution, revealed that the structural conformation or shape of the protein in its active state is strikingly different than when it is inactive.

Such changes suggest there may be a general molecular mechanism that activates the beta-arrestin1 – a sort of main switch that controls the multi-functional signaling proteins.

"It's like there are brakes on in beta-arrestin1, and then when the beta-arrestin1 binds to a GPCR, the brakes are released, thereby activating beta-arrestin1," said Arun K. Shukla, PhD, assistant professor of medicine at Duke and co-lead author of the study.

The researchers are now pursuing additional structural imaging of the signaling complex consisting of beta-arrestin1 and the entire receptor protein.

More information: Structure of active b-arrestin-1 bound to a G-protein-coupled receptor phosphopeptide, DOI: 10.1038/nature12120

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