Scientists illuminate mechanism of common drug target

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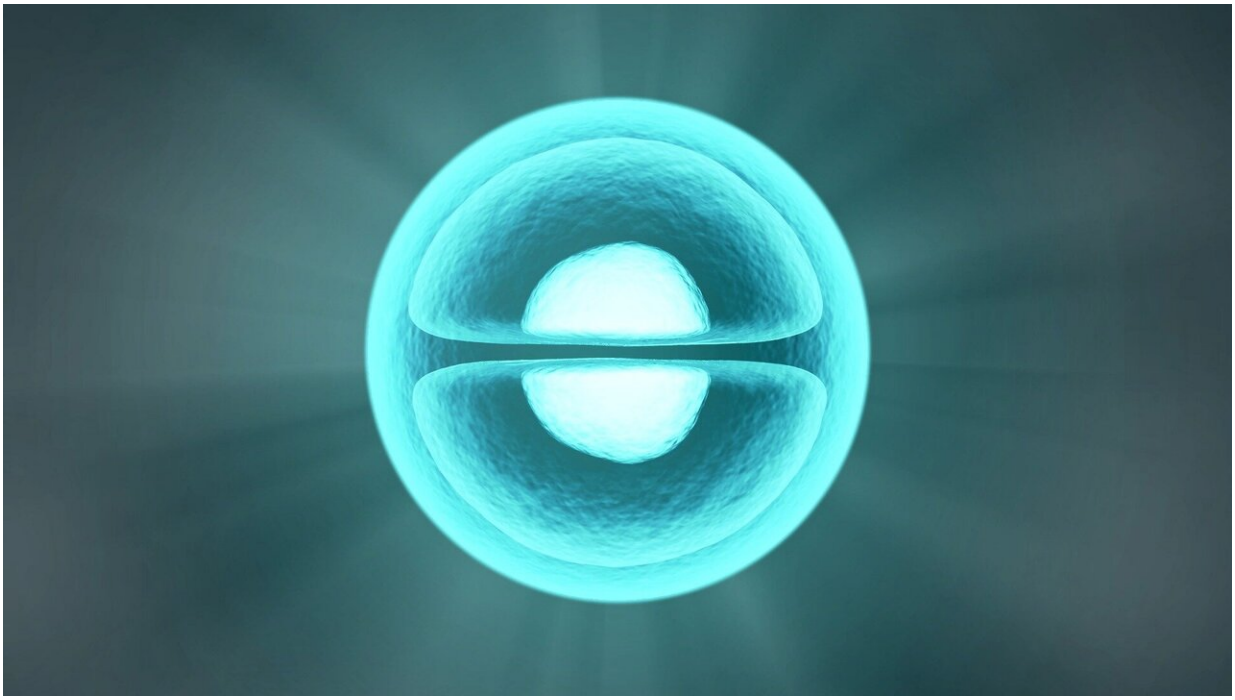

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Roughly a third of all drugs approved by the U.S. Food and Drug Administration target a large family of biomolecules, known as G protein-coupled receptors (GPCRs), whose job is to trigger cellular responses to extracellular stimuli. More than 800 different kinds of GPCRs exist in the human body and play a role in the pathobiology and treatment of countless medical conditions, including cancer, type 2

diabetes, obesity, sleep disorders, schizophrenia, and depression.

Now, an interdisciplinary team of researchers has gained new insight into the way GPCRs operate, a step toward the development of improved drugs with fewer side effects.

"Drugs that target GPCRs are used to treat a wide variety of disorders in medicine—heart disease, lung disease, sleep and neuropsychiatric disorders—and GPCRs are responsible for smell, taste, and vision as well," says senior author Jonathan A. Javitch, MD, Ph.D., the Lieber Professor of Experimental Therapeutics in Psychiatry at Columbia University Vagelos College of Physicians and Surgeons and chief of molecular therapeutics at the New York State Psychiatric Institute.

But like many therapeutics, drugs that target GPCRs often have side effects, some of which can be serious. For example, drugs that target a group of GPCRs called opioid receptors are very effective at treating pain but also have dangerous side effects such as respiratory distress and constipation. At the moment, these compounds are unable to target the pain-alleviating signaling pathway without also activating the respiratory and gut pathways.

"In our study, we use methodology that allows us to probe in unprecedented detail how drug-stimulated GPCRs activate β-arrestin, a protein involved both in terminating some signals and mediating others," says Wesley B. Asher, Ph.D., co-first author and assistant professor of clinical neurobiology in the Department of Psychiatry at Columbia, "with the ultimate goal of enabling the development of pathway-specific compounds."

The study, published April 27 in the journal *Cell*, involved the use of a cutting-edge technique called single-molecule fluorescence resonance energy transfer (smFRET) imaging. The technique, advanced by co-

senior author Scott C. Blanchard, Ph.D., from St. Jude Children's Research Hospital, captures movements within individual protein systems in unparalleled detail. Since the method visualizes structural changes of single proteins in real time, it enables insights that are obscured by other traditional approaches that average large numbers of proteins in a sample.

With smFRET, the team decided to probe the beta-adrenergic receptor—a prototypical GPCR broadly relevant to many different areas of biology. Binding of drugs or endogenous hormones to beta-adrenergic receptors or other GCPRs on the cell's exterior membrane leads to signals on the inside of the cell that are mediated by activation of G proteins. But binding of another type of protein, β-arrestins, terminates this signaling and can activate other—desired or undesired—downstream pathways.

By observing the process of β-arrestin activation by a beta-adrenergic receptor, the researchers uncovered new details about how β-arrestins interact with, and are activated by, GPCRs, processes that require release of autoinhibition of both proteins.

The findings could ultimately help to identify improved drugs that, by modulating the binding and/or activation of β-arrestin to GPCRs, affect specific pathways and not others.

The study's results also support the "barcode hypothesis," which states that different phosphorylation patterns or "barcodes" within receptors can lead to different patterns of β-arrestin activation, which in turn dictates downstream signaling outcomes.

Scientists hope that better understanding of the relationship between receptor "barcodes" and β-arrestin activation can provide important insight into how specific downstream pathways, but not others, are

targeted.

The paper, titled "GPCR-mediated beta-arrestin activation deconvoluted with single-molecule precision," was published online April 27 in the journal *Cell*.

More information: Wesley B. Asher et al, GPCR-mediated β-arrestin activation deconvoluted with single-molecule precision, *Cell* (2022). DOI: 10.1016/j.cell.2022.03.042

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