

# Study identifies potential new pathway for drug development

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A newly found understanding of receptor signaling may have revealed a better way to design drugs. A study from Nationwide Children's Hospital suggests that a newly identified group of proteins, alpha arrestins, may play a role in cell signaling that is crucial to new drug development. The study appears in *PLOS ONE*.

More than one-third of drugs on the market work by targeting G protein-coupled receptors that control how cells communicate and function. With many hundreds of members, G protein-coupled receptors are the largest family of signaling receptors throughout the body.

Once a cell's G protein-coupled receptor binds with a natural ligand or a drug, intracellular G proteins and beta arrestins independently mediate various signals. Immediately following, beta arrestins block further signaling of [G proteins](#) and recruit proteins to remove the receptor to halt cell signaling. Those receptors can subsequently recycle to the cell surface or be destroyed.

"Receptor down regulation caused by beta arrestins can interfere with drug efficacy because the G protein-coupled receptor that the drug has been targeting is absent from the [cell surface](#)," said Carlos E. Alvarez, PhD, principal investigator in the Center for Molecular and [Human Genetics](#) at The Research Institute at Nationwide Children's Hospital and lead study author. "This is why patients who are prescribed long-term medication can become drug-tolerant and require higher and higher doses."

In some cases, a drug's ability to trigger beta arrestin effects and block G protein signaling is preferential. Take beta blockers, for example. As the name suggests, beta blockers interfere with the binding to the receptor for epinephrine and other [stress hormones](#), weakening the hormones' effects and therefore being useful in treating irregular heartbeats, prevention of second heart attacks, hypertension and other conditions. Screening has revealed that the beta blocker [Carvedilol](#) may be the most ideal for treatment of [heart conditions](#) as it reduces the cardiotoxic effects of G protein signaling, while increasing the cardioprotective effects of beta arrestin signaling.

Yet, it seems that beta arrestins may only be part of the cell signaling story. In 2008, Dr. Alvarez discovered a subfamily of arrestins that his team named alpha arrestins. In the current study, Fortune Shea in Dr. Alvarez's lab used biochemical and imaging approaches to further identify the role alpha arrestins play in [cell signaling](#).

He found that alpha arrestins respond to receptor binding and recruit enzymes that chemically modify the receptor to initiate aspects of down regulation. These effects occur in the first five minutes after the receptor is bound, the same time frame that beta arrestins are known to have roles in triggering down regulation. The team is also the first to find that alpha arrestins function coordinately with beta arrestins.

"Our findings suggest that alpha arrestins, like beta arrestins, are ubiquitous regulators of G-protein coupled receptor signaling," says Dr. Alvarez. "It seems that like beta arrestins, alpha arrestins could have great pharmacological relevance."

A major effort in pharmacology is to develop drugs with functional selectivity that either target G protein or beta arrestin signaling effects. Dr. Alvarez foresees alpha arrestins becoming a big player in the refining of such efforts.

"Just as has been discovered with [beta blockers](#) and beta arrestin, I expect we'll find drugs that also have significant alpha arrestin effects," he says. "I believe that targeting alpha arrestins will allow us to develop compounds that are more effective and have reduced side effects," says Dr. Alvarez.

**More information:** Shea F, Rowell J, Li Y, Chang TH, Alvarez C. Mammalian alpha arrestins link activated seven transmembrane receptors to Nedd4 family E3 ubiquitin ligases and interact with beta arrestins. *PLOS ONE*. [www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0050557](http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0050557)

Provided by Nationwide Children's Hospital

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