Sticky proteins provide new insight into drug action

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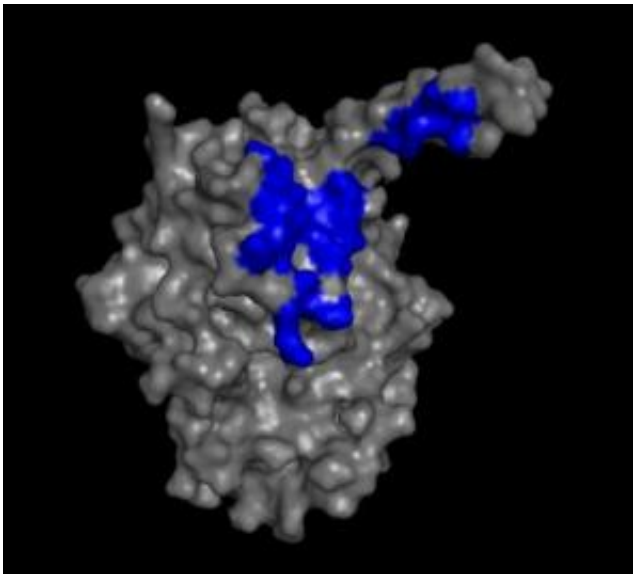

This is a representation of a G protein alpha subunit after the beta-gamma pair dissociated. The blue patches represent the places where alpha and beta-gamma were previously attached. Credit: Medical College of Georgia

How drugs such as adrenalin do primarily one thing – in this case, increase the heart rate – now makes more sense to scientists. "Any time you get a sudden jolt, adrenaline (a.k.a. epinephrine) is why your heart rate goes up," says Dr. Nevin A. Lambert, a biophysicist at the Medical College of Georgia. "If your heart is about to stop and the doctor administers epinephrine, that is what he or she is trying to do."

New research, to be published in the Nov. 21 print issue of *Proceedings of the National Academy of Sciences* and already available online in Early Edition, may help explain how cells respond correctly to epinephrine.

Most drugs never get inside cells; they interact with external receptors that activate G proteins roaming inside cells. "If you are going to change the way the cell works, you have to transduce a signal from outside a cell inside," says Dr. Lambert. "It's like a relay. G proteins interact with receptors; they run into them, they collide with them. The receptor itself does not do anything other than turn on these G proteins."

There are only four classes of G proteins, but cells contain thousands of copies of them which interact with hundreds of surface receptors. Each G protein is actually three protein subunits stuck together: alpha, beta and gamma.

Textbooks have long said that once G proteins are activated, the alpha protein splits from the beta and gamma subunits, which are irrevocably stuck together as a beta-gamma pair. Each half of the now dissociated G protein can cause the cell to do something different. "Sometimes they help each other out; sometimes they work at cross purposes," says Dr. Lambert.

With epinephrine, that should mean the alpha subunit enables production of cyclic AMP, which increases the heart rate, while the beta-gamma pair should activate ion channels, making cells less electrically excitable and decreasing the heart rate.

However, it has been known for some time that while epinephrine does increase cyclic AMP in heart cells, it does not activate ion channels. While this situation makes sense because the cell isn't asked to respond in two completely opposite ways, it has not been at all clear how the cell allows one response and suppresses the other.

That likely is because the G proteins activated by epinephrine receptors don't readily dissociate, contrary to the textbook picture. MCG researchers have also shown that at least one other class of G proteins does dissociate, suggesting the textbook picture is at least partly correct.

Why the difference? Previous work on G proteins, including the discovery of the G proteins and their role in signal transduction, was mostly done in test tubes using purified proteins. MCG researchers used a technique they developed to actually look at G protein function inside living human cells.

Their findings suggest that epinephrine interacts with a G protein that doesn't let go of the beta-gamma subunit.

"There was a constant question about how drugs sometimes avoid doing unwanted things," says Dr. Lambert. "This helps us understand how drugs can be specific. The flipside of the coin is some drugs acting on some receptors will have multiple actions because the G proteins do dissociate."

No doubt, the newfound information about G proteins is just one step toward better understanding how hundreds of receptors can act through just four classes of G proteins and produce so many physiologic results. "It's like how can 100 cars drive down four roads and end up in 100 different places," Dr. Lambert says.

But it's a timely piece as science moves toward designer drugs, including some that could actually target G proteins directly, bypassing intermediary receptors, with the hope of getting a more robust response.

In Dr. Lambert's lab, MCG graduate student Gregory J. Digby, first author on the PNAS paper, is now looking at G protein subunits that do and don't fall apart with the long-range goal of designing ones that do

what they want. "Right now, it's all engineering for the sake of understanding how they work," says Dr. Lambert.

Researchers suspect it's literally the stickiness between the subunits that determine whether they split, and that the bottom line will be two classes of G proteins dissociating and two not.

Source: Medical College of Georgia