# Discovery of 'overdrive' protein could broaden drug design options

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New research by scientists at the University of North Carolina at Chapel Hill shows for the first time that an important family of proteins known to function at the cell surface also functions at a site within the cell.

The findings have potential implications for drug development as they involve G protein-coupled receptors (GPCRs). These molecules are the target of forty to fifty percent of modern medicinal drugs, such as antihistamines and drugs for high blood pressure.

The study identified the first protein to activate the G-protein signaling pathway from within a cell. In humans, reactions to everything from taste and smell to stimulants like adrenaline or caffeine requires G-protein signaling.

Until now, the only known way to turn on a G-protein was via a receptor sitting on a cell's surface membrane. This receptor acts like a telegraph operator, accepting outside signals and relaying them inside the cell. It converts an external signal, like caffeine, into action – in this case, a nerve signal to the brain.

More than half of all drugs, from asthma and heart medicine to antidepressants, target G-protein receptors. Discovering a protein that activates G-proteins from inside a cell could open up an entirely new pathway for drug development, said Henrik Dohlman, Ph.D., senior study author and a professor of biochemistry and biophysics in UNC's School of Medicine.

“No drug is 100 percent effective, 100 percent free of side effects and 100 percent safe. The more options we have biochemically, the more selective we can be in designing new drugs. If we can find another way of modulating G-proteins, we could expand the drug targets that are available to pharmacology,” Dohlman said.

The study appeared online Feb.7, 2008, in the journal *Current Biology* and will be published in the Feb. 14, 2008, print edition. Funding was provided by the National Institutes of Health and a UNC Cell and Molecular Biology Program predoctoral fellowship.

Despite 20 years of study, G-protein signaling continues to produce surprises. The advent of the human genome project revealed that some three percent of our DNA is dedicated to these messenger molecules. However, the genomic data also drew biologists away from the research technique the UNC team used to discover the new protein, Dohlman said. “People stopped looking for things that could activate G-proteins using functional criteria,” he said. Instead, they searched for new receptors and activators based on common genetic patterns.

Mike Lee, a graduate student in the UNC School of Medicine’s department of pharmacology, identified the new protein, called Arr4, in yeast cells. Lee employed a mutant form of G-protein to search for any messengers inside the yeast cell with an affinity for G-proteins.

“We went looking for things that could activate G-proteins but don’t resemble known receptors,” Lee said.

He identified seven proteins that weren’t receptors, but did bind to G-proteins, and did further tests on one of the seven proteins, Arr4, to determine its function.

In yeast, Arr4 is involved in cell fusion, a process in which two yeasts

fuse together to form one cell, combining their genetic data. A G-protein coupled receptor (GPCR) controls cell fusion, while Arr4 appears to play a supporting role.

Lee said he thinks that Arr4 may allow the cell to go through several additional rounds of signal activation without needing to go back to the receptor.

“Our current thinking is it’s not so much that this is the ignition for signaling, it’s more like an overdrive. Once the pathway is activated by the hormone outside, Arr4 sustains the activity inside,” Lee said. “What we don’t know is if Arr4 is itself simulated by some signal, and of course we’re very interested in finding out if that’s the case.”

Source: University of North Carolina at Chapel Hill