

# Study shows how G proteins get 'turned on' by receptors

by Bill Snyder

To smell or see or taste, to respond to danger with a racing heart, to focus the mind or experience joy — all require marvelous intracellular switches known as G proteins.

Although the structure of G proteins was solved nearly 20 years ago, exactly how they are "turned on" by their G protein-coupled receptors (GPCRs) has remained a mystery — until now.

Reporting in the *Proceedings of the National Academy of Sciences* earlier this year, researchers at Vanderbilt University and the University of California, Los Angeles (UCLA) describe how a G protein "swings open" after binding to its GPCR.

This is a fundamental discovery, said Vanderbilt Pharmacology Chair Heidi Hamm, Ph.D., who led the research with Wayne Hubbell, Ph.D., Jules Stein Professor of Ophthalmology and Distinguished Professor of Chemistry and Biochemistry at UCLA, and Jens Meiler, Ph.D., associate professor of Chemistry at Vanderbilt.

It reveals a mechanism that may be essential for every G protein-activated pathway, Hamm said, and suggests that G proteins could be targets for new, more effective drugs.

G proteins consist of three subunits, alpha, beta and gamma, and are named for the energy-transferring molecules they carry — guanosine diphosphate (GDP) and guanosine triphosphate (GTP).

In its inactive state, the G protein carries GDP. But when activated by its receptor, the "Galpha" subunit jettisons its low-energy GDP cargo in favor of a higher-energy molecule of GTP and

splits off from the beta/gamma subunits.

In 1993, while at the University of Illinois at Chicago, Hamm solved the structure of the Galpha subunit with the late Paul Sigler, M.D., Ph.D., and his colleagues at Yale.

At about the same time, Hubbell and his colleagues at UCLA were developing a powerful new technique, called site-directed spin labeling or SDSL, to study how protein structure changes over time.



Hamm

Not long after Hamm arrived at Vanderbilt in 2000 to chair the Department of Pharmacology, she and Hubbell and their colleagues began working together to solve a biological mystery.

They knew that when a G protein called transducin binds to and is activated by its light-sensitive receptor — rhodopsin — in rod cells in the retina, it triggers a cascade of events that enables vision in dim light or at night. But how exactly does activation happen?

In 2006, using SDSL along with double electron-electron resonance (DEER) spectroscopy, the researchers pinpointed the site of the activation to a critical region of the Galpha subunit.

In the latest study, they combined DEER, biochemical analysis and state-of-the-art molecular modeling to measure the distance between two "domains," or chains of amino acids of the Galpha

subunit — before and after activation.

They discovered that the domains swing widely apart upon activation, allowing release of the GDP molecule — a crucial step in the transmission of the visual signal.

"Back in 1993 when we solved the first crystal structure of (the alpha subunit), we predicted that the two domains must open to allow GTP-GDP exchange," said Hamm, the Earl W. Sutherland Jr. Professor of Pharmacology.

"It is gratifying to actually be able to demonstrate this domain movement biochemically."

Anita M. Preininger, Ph.D., research assistant professor of Pharmacology at Vanderbilt, Vanderbilt graduate student Nathan Alexander, and Ned Van Eps, Ph.D., of the UCLA Jules Stein Eye Institute, were joint first authors of the *PNAS* paper. Vanderbilt's Ali I. Kaya, Ph.D., and Scott Meier, also contributed.

The research was supported by the National Institutes of Health. □



Meiler

## VUMC Reporter

Volume XXI, Number 31

Aug. 12, 2011

*VUMC Reporter* (USPS 005-635 or ISSN 1053-3079), is published weekly by Vanderbilt University Medical Center, 1161 21st Avenue South, Nashville, TN. 37232-2390. Call (615) 322-4747 with story ideas and suggestions.

**POSTMASTER:** Send Address changes to *The Reporter*, Vanderbilt University Medical Center Office of News and Communications, D-3237-A, Medical Center North, Nashville, TN 37232-2390.

Vanderbilt University is an equal opportunity, affirmative action university.