Helping the brain's messengers get from A to B

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In what has been hailed as a breakthrough, scientists from Columbia University Medical Center and Weill Cornell Medical College have outlined the molecular mechanism of membrane transport. The research shows how a protein transforms its shape to transport substances across the cell membrane in order to regulate transmission of the brain's messages across the synaptic gap from one neuron to another.

Because widely used medications for depression modulate this transport process by binding to the transporters, the new findings help explain how the medications work, and the way in which stimulants like cocaine and amphetamine produce their effects. This new understanding should also prove useful in the development of more targeted medication therapies for anxiety, depression, schizophrenia and substance abuse.

The researchers looked at transporter proteins in the family of Na+ symporters, which remove neurotransmitters from the synapse in a process called reuptake that is essential to the proper function of neural transmission. Antidepressants such as Prozac and Zoloft, which are selective serotonin reuptake inhibitors (SSRIs), and cocaine interfere with the reuptake mechanism and alter the normal exchange process between cells.

The paper describing the new findings was published in the May 13 issue of *Nature* and was lauded as a significant contribution to the understanding of the dynamics of the transport cycle in the journal's News & Views section. The reviewers note that until now biologists have

been unable to view transporters on a single-molecule detail, but the new research "lifts the curtain and shines a spotlight onto some of the choreography" of membrane transport. In this spotlight, the new research illuminates the pathway of transported molecules revealing how transporter proteins escort ions and molecules through membranes by forming passageways in a manner the researchers liken to gates opening and closing.

"The study of membrane transport proteins and the genes that encode them offers the opportunity to investigate many aspects of disease processes. The opening and closing of the transporter 'gates' is orchestrated by binding of the transported substances and by inhibitory drugs in ways that could not be determined by previous approaches that were unable to resolve movements in individual proteins," says one senior author, Dr. Jonathan Javitch, who is the Lieber Professor of Experimental Therapeutics in the Departments of Psychiatry and Pharmacology and the Center for Molecular Recognition at Columbia University Medical Center.

Exactly how the gates open and close, and why, is not yet fully understood; however, the results from this research are an important step in that direction.

"Advances in technology have enabled cell biologists to see molecular processes at a level of detail that was not possible even in the last decade. Just as the Hubble telescope and computer-assisted tomography have allowed scientists to view objects in outer space and inside the body more clearly and in greater detail, biologists now have new tools to view what is happening at the cellular level and powerful computational methods to mimic these processes in the computer. This research has brought both advances to bear on a fundamental problem in neural transmission," says study co-author Dr. Harel Weinstein, chairman and Maxwell M. Upson Professor of Physiology and Biophysics, and director

of the Institute for Computational Biomedicine (ICB) at Weill Cornell Medical College.

Dr. Weinstein credits the work of his colleague Dr. Scott Blanchard, associate professor of physiology and biophysics at Weill Cornell Medical College, in providing the expertise in a new technology that is crucial to this research. Dr. Blanchard and his team developed this new technology over numerous years and it is now at a place where functional motions of individual proteins can be directly visualized in nearly real time.

"Understanding molecular movements is important because enzyme functions hinge on motion," says Dr. Blanchard, another senior author of the new study. "To observe molecules, we attach reporter molecules called fluorophores that can be directly measured at the single-molecule scale. In so doing, motional information can be obtained about the protein to which they are linked."

In the current study, the investigators used this technique to study the LeuT transporter. They were able to monitor changes of individual molecules and reported observing two distinct states which they believe report on the open and closed states of the gating mechanism.

Dr. Weinstein notes that SSRIs were developed without a real understanding of how they work and only now researchers are beginning to understand how they bind and affect the transporters. "These medications are effective in treating many mental illnesses, including depression, obsessive-compulsive disorder and panic disorder, suggesting that these disorders have some relation to serotonin levels in the brain. Our study is the start of understanding how SSRIs work at a mechanistic level, and why they work in some people and not in others."

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