Researchers discover how antidepressants and cocaine interact with brain cell targets

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In a first, scientists from Weill Cornell Medical College and Columbia University Medical Center have described the specifics of how brain cells process antidepressant drugs, cocaine and amphetamines. These novel findings could prove useful in the development of more targeted medication therapies for a host of psychiatric diseases, most notably in the area of addiction.

Their breakthrough research, featured as the cover story in a recent issue of *Molecular Cell*, describes the precise molecular and biochemical structure of drug targets known as neurotransmitter-sodium symporters (NSSs), and how cells use them to enable neural signaling in the brain. A second study, published in the latest issue of *Nature Neuroscience*, pinpoints where the drug molecules bind in the neurotransmitter transporter -- their target in the human nervous system.

"These findings are so clear and detailed at the level of molecular behavior that they will be most valuable to developing more effective therapies for mood disorders and neurologic and psychiatric diseases, and to direct effective treatments for drug addiction to cocaine and amphetamines," says co-lead author Dr. Harel Weinstein, Chairman and Maxwell M. Upson Professor of Physiology and Biophysics, and director of the Institute for Computational Biomedicine at Weill Cornell Medical College. "This research may also open the door to the development of new therapies for dopamine-neurotransmitter disorders such as Parkinson's disease, schizophrenia, and anxiety and depression."

To make their observations, the research team led by Dr. Jonathan Javitch, senior author of the Molecular Cell study and contributing author to the Nature Neuroscience study, and professor of Psychiatry and Pharmacology in the Center for Molecular Recognition at Columbia University Medical Center, stabilized different structural states of the neurotransmitter-sodium-symporter molecule that relate to steps in its function. This allowed the team to study how substrates and inhibitors affect the transition between these different states, and thus to understand the way in which its function is accomplished.

"Crystallography had allowed the identification of only one structural form of the molecule, but our experiments and computations were able to identify how this form changes and thereby add an understanding of the functional role of the different forms that the molecule must adopt to accomplish transport activity," says Dr. Javitch.

The main surprise was the realization that two binding sites on the transporter molecule need to be filled simultaneously and cooperate in order for transport to be driven across the cell membrane. For these studies, the scientists used the crystal structure of a bacterial transporter that is very similar to human neurotransmitter transporters. They performed computer simulations to reveal the path of the transported molecules into cells. Laboratory experimentation was used to test the computational predictions and validate the researchers' inferences.

Together, these procedures revealed a finely-tuned process in which two sodium ions bind and stabilize the transporter molecule for the correct positioning of the two messenger molecules -- one deep in the center of the protein, and the other closer to the entrance. Like a key engaging a lock mechanism, this second binding causes changes in the transporter throughout the structure, allowing one of the two sodium molecules to move inward, and then release the deeply bound messenger and its sodium partner into the cell.

In the bacterial transporter studied, antidepressant molecules bind in the outer one of two sites, and stop the transport mechanism, leaving the messenger molecule outside the cell.

The second team of researchers, involving a collaboration of the Weinstein and Javitch labs with colleagues in Denmark (the labs of Ulrik Gether and Claus Loland), found that in the human dopamine transporter cocaine binds in the deep site, unlike the antidepressant binding in the bacterial transporter. Therefore, the researchers conclude that anti-cocaine therapy will be more complicated, because interfering with cocaine binding also means interference with the binding of natural messengers.

"This finding might steer anti-cocaine therapy in a completely new direction," says Dr. Weinstein.

Molecular understanding at this level of structural and dynamic detail is rare in the world of drug development, the authors note. Only about 15 percent of all drugs have a known molecular method-of-action, even though the effects of these drugs within the body -- after very stringent and controlled laboratory testing -- are well understood pharmacologically.

Source: New York- Presbyterian Hospital