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Scientists uncover molecular changes underlying amphetamine and antidepressant action

Although our neurons make a mess when they talk to each other, they come equipped with their own maid service of sorts. Nerve endings are studded with proteins called transporters that act as molecular vacuum cleaners, clearing the synapse of released chemical messengers.

Transporters are critical to normal communication in the brain, and they are targets for both therapeutic drugs and drugs of abuse. The transporter for the neurotransmitter serotonin, for example, is blocked by antidepressants like Prozac and is a site of action for cocaine and amphetamines.

Vanderbilt University Medical Center scientists studying the serotonin transporter have discovered novel regulatory mechanisms that move the transporter on and off the cell surface. They report their findings, which point to new actions for antidepressants and psychostimulants, in the July 30th issue of Science.

"We thought for a long time that transporters sat there and basically drained away neurotransmitter," said Randy D. Blakely, Ph.D., Allan D. Bass Professor of Pharmacology and director of the Center for Molecular Neuroscience. "We've learned that these machines are much more complicated than we once thought."

Earlier studies had demonstrated that the transporter could be chemically modified in response to activated signaling pathways inside the neuron. The modification -- an addition of phosphate groups called phosphorylation -- of the transporter is linked to its disappearance from the cell surface.

"But the problem is, you could have a situation where other signals pull the transporter off the cell surface right when it needs to be there to clear away serotonin," Blakely said. "In this case, the signals coming into the neuron would have more priority than the neurotransmitter itself."

He and Sammanda Ramamoorthy, Ph.D., research assistant professor of Pharmacology, wondered whether there was a way for the transporter to 'ignore' these inside signals when it needed to stay on the surface to do its job. They found that if serotonin is around and needs to be cleared, the transporter has less phosphate groups added onto it.

"We tried serotonin and other substrates for the transporter like amphetamines. We found that anything that goes through the transporter blocks this phosphorylation," Blakely said.

By blocking the phosphorylation, serotonin and other substrates prevent the transporter from moving off the surface.

"We call it our use-it-or-lose-it model for transport," Blakely said. "If the transporter is not active, it becomes susceptible to other pathways and regulators that pull it off the cell surface. It was a big surprise that the activity of the transporter itself would play such an important role in regulation."

Drugs that block transporter activity -- antidepressants and cocaine -- prevent serotonin from sustaining the transporter at the cell surface. This is a very different action than simply blocking transporter activity to influence the level of neurotransmitter in the synapse.

"We don't understand why antidepressants take a certain period of time to have activity, or why use-dependent changes occur with respect to addiction," Blakely said. "What we're hinting at is that a long term consequence of these drugs occupying the transporter will be an influence on the number of transporters at the cell surface."

Characterizing the signals that participate in the dynamic process of moving transporters on and off the surface opens up possibilities for developing new antidepressant drugs. Such drugs would have the same functional effects as a drug like Prozac, but they would work in an entirely new way -- from the inside of the neuron.

"New antidepressants might manipulate these regulatory pathways that we didn't recognize as being so important before we did these studies," Blakely said.

The research also offers new insight to the actions of psychostimulants like amphetamines and cocaine. Although these psychostimulants have similar behavioral effects, their molecular level actions are quite different. Like serotonin, amphetamines pass through the transporter and keep it on the cell surface. Cocaine, on the other hand, allows the transporter to become susceptible to the signals that pull it off the surface.

"We think this difference will play out chronically in the spectrum of activities that these different drugs have, and in how they are abused and tolerated," Blakely said.

Blakely and Ramamoorthy's findings demonstrate the important role of the neurotransmitter itself in determining whether or not it is actively cleared from the synapse. The transporter's sensitivity to its external environment is likely to be important in shaping and re-shaping individual connections between neurons.

"The fact that the transporter is so highly regulated from both inside and outside the neuron underscores the importance of setting the exact tone for neurotransmitter clearance. We believe that there are disease processes where that tone is disrupted," Blakely said.

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