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Grabbing Addiction by the Tail

Canadian scientists have developed some clever molecular trickery that is helping to reduce the drug cravings of addicted rats. One of the problems in addiction is that neurons in some parts of the brain lose glutamate receptors from the cell surface, and those receptors are important for communication between neurons. The researchers have sidestepped this problem by crafting a peptide that mimics a portion of the tail of the glutamate receptor and, once inside a neuron, serves as a decoy to prevent the loss of glutamate receptors.

Yu Tian Wang, an HHMI international research scholar, and colleagues at the University of British Columbia in Vancouver report their findings in the November 25, 2005, issue of the journal *Science*.

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In addicted rats, cell-to-cell communication is compromised as a result of certain long-term changes at the level of individual neurons. Their research has produced a targeted drug that tricks brain cells into preventing those changes. "We think this is a good candidate for a drug against addiction that has very few side effects," said Wang, a neuroscientist. Although the initial studies are promising, Wang cautioned that the drug is in the early stages of development and is years away from testing in humans.

During addiction to drugs, cells in the nucleus accumbens—a tiny ball of tissue deep in the brain involved in pleasure and motivation—miscommunicate. Normally, one neuron triggers activity in a neighbor by using neurotransmitters such as glutamate. "This is the 'go' signal," said Wang. "The receiving cell uses glutamate receptors on its surface to listen to the signal.

But after repeated abuse of a drug, cells in the nucleus accumbens internalize glutamate receptors, compromising their ability to listen to the signals. Earlier research showed that receptor internalization in addicted rats accompanies behavioral sensitization, a model of craving.

Until now, though, no one knew how these receptors were removed from the cell surface, whether the process could be halted, and, if it could, whether the addicted rats would exhibit fewer signs of behavioral sensitization. Wang's research has made significant progress toward answering these questions.

The researchers began by building a peptide—a long molecule made from a string of amino acids—with a structure similar to the tail of the glutamate receptor that is anchored inside the cell. In addition, cellular machinery tugs on this tail, pulling the entire receptor into the cell. Without its business end sticking out into the synapse, or space between neurons, the receptor no longer works.

Wang's peptide tricks the cellular machinery into tugging on it instead of the receptor's tail. "Once it gets inside the neuron, the peptide competes with the receptor for binding to the machinery," Wang explained. With the cellular machinery otherwise occupied, the glutamate receptors stay on the cell surface, where they continue to receive signals.

After confirming these results in cell cultures, Wang and colleagues tested the peptide in rats that had been given amphetamine once every other day for 20 days. During this period, the animals displayed stereotypical behavior such as repeated sniffing, licking, and grooming, indicating a craving for the drug. Such behavior parallels the compulsive thought patterns that people addicted to drugs experience, said Anthony Phillips, Wang's colleague at the University of British Columbia and a co-author of the article.

After keeping the rats drug-free for 21 days, the researchers gave the animals a small amount of drug again. The rats immediately displayed intense stereotypical behavior—a sign of behavioral sensitization. The behavior meant that the glutamate receptors in the animals' neurons were rapidly internalized, said Wang. "It's the trigger that leads to sustained motivation to seek a drug."

In contrast, addicted animals who received an intravenous injection of the artificial peptide displayed no sensitized behavior. "The effect was immediate and very noticeable," said Wang.

There are several types of glutamate receptors involved in memory and learning, but because the artificial peptide specifically targets only the deleterious internalization process of addiction-affected neurons, and not normal receptor function, the animals who received it behaved normally and were able to learn as usual. "So far, we have not seen any obvious side effects at all," said Wang.

By inserting a tiny tube into the rats' brains, the researchers delivered the peptide directly to the nucleus accumbens and to another area of the brain involved in reward and motivation, the ventral tegmental area. The peptide reduced the rats' drug-seeking behavior only when injected into the nucleus accumbens, evidence that the structure is critical for the expression of some of the devastating behaviors of addiction.

Wang and colleagues recently received grants from the Brain Repair Program of NeuroScience Canada and the Canadian Institutes of Health Research to continue testing the peptide.