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Study of Cocaine Addiction Reveals Targets for Treatment

Scientists at UC Santa Barbara are researching cocaine addiction, part of a widespread problem, which, along with other addictions, costs billions of dollars in damage to individuals, families, and society. Laboratory studies have revealed that the diminished brain function and learning impairment that result from cocaine addiction can be treated -- and that learning can be restored.

Karen Szumlinski, a professor in the Department of Psychological & Brain Sciences, and her colleagues Osnat Ben-Shahar and Tod Kippin, have worked in the field of addiction for many years. Senior author of a paper on this topic published recently in *The Journal of Neuroscience*, Szumlinski is particularly interested in the part of the brain called the prefrontal cortex, where the process of "executive function" -- or decision-making -- is located. This area is involved in directing one's behavior in an appropriate manner, and in controlling behavior.

With her research team, Szumlinski discovered that a drug that stimulates a certain type of glutamate receptor -- when aimed at the prefrontal cortex -- could restore learning impairment in rats with simulated cocaine addiction.

"Needless to say, this (the prefrontal cortex) is one of the last parts of the brain to develop, and, of relevance to our students, continues to develop through about age 25 to 28," said Szumlinski.

Szumlini explained that in the prefrontal cortex there seems to be "hypo-frontality," or reduced functioning, in drug addicts, as well as in patients with a range of neuropsychiatric diseases, including schizophrenia, depression, and attention deficit disorder.

Szumlini calls the prefrontal cortex a late-developing brain area that is critical for making proper decisions, and inhibiting behavior. "You damage this brain region and you lose the ability to self-regulate, you make impulsive decisions like engaging in risky sexual behavior or drug-taking, you basically go off the deep end in terms of function," she said. "So we were very much interested in how drugs of abuse impact the prefrontal cortex, given that human drug addicts show deficits in this brain area when you put them into a scanner. They show hypo-activity." She said this hypo-activity, or hypo-frontality, might relate to a neurotransmitter that scientists know is involved in exciting the brain.

A key question, according to Szumlini, is this: "Was that hypo-frontality there in the first place, and that's why they became an addict; or did the drugs change their prefrontal cortex, to cause it to become hypo-functioning and thus they're not able to control their drug use? You can't parse that out in humans. So that's why we turn then to animal models of the disorder, and we do have this rat model that we use in the paper."

Szumlini pointed out a key difficulty in the development of treatments for addiction: There is little money targeted to the study of this disease. Hence, in addition to studying the brain mechanisms that are involved, she is joining forces with researchers who study other neurological diseases that are well-funded, to help find cures. She hopes that government approval of new drugs for these other diseases would eventually make the drugs available for clinical trials to study their effects on cocaine addiction.

Szumlini cited statistics, calculated by scientists M.K. Bird and A.J. Lawrence of Australia, indicating that addiction can cost up to 3.5 percent of gross domestic product in Western countries, equaling \$485 billion in the U.S. in 2007. In that year, addiction research received less than 2 percent of public and private funding of all cancer research.

Co-authors of the paper are Osnat Ben-Shahar, Tod E. Kippin, Arianne D. Sacramento, Bailey W. Miller, Sierra M. Webb, Melissa G. Wroten, Hannah E. Silva,

Amanda L. Caruana, Evan J. Gordon, Kyle L. Ploense, and Jennifer Ditzhazy, all from the Department of Psychological and Brain Sciences, and the Neuroscience Research Institute.

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† Top image: Summary of cocaine-seeking behavior (lever-presses) during 30 minute sessions conducted on Days 3 and 4 of withdrawal (Test1 and 2, respectively) from daily high amounts of IV cocaine. When tested across days, vehicle-induced (VEH) controls exhibit a reduction in cocaine-seeking, indicating extinction. In contrast, rats infused intracranially into the ventromedial prefrontal cortex (vmPFC) with antagonists for mGluR5 (MTEP PreRx) or mGluR1 (JNJ PreRx) prior to Test 1 failed to show this learning. Similarly, rats injected intracranially with the mGluR1 blocker following Test 1 (to influence memory consolidation processes) also failed to exhibit learning. These data indicate that mimicking a cocaine-induced deficit in mGluR1/5 function within this frontal cortical region results in persistent cocaine-seeking behavior, reflecting a deficit in learning and memory processes.

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