Penn Medicine Points to New Ways to Prevent Relapse in Cocaine-Addicted Patients

Commonly Used Neurological Medication Proves Successful at Blocking Brain's Reward System Triggers

PHILADELPHIA — Relapse is the most painful and expensive feature of drug addiction—even after addicted individuals have been drug-free for months or years, the likelihood of sliding back into the habit remains high. The National Institute on Drug Abuse estimates that 40 to 60 percent of addicted individuals will relapse, and in some studies the rates are as high as 80 percent at six months after treatment. Though some relapse triggers can be consciously avoided, such as people, places and things related to drug use, other subconscious triggers related to the brain's reward system may be impossible to avoid— they can gain entry to the unconscious brain, setting the stage for relapse.

Researchers at Penn Medicine's Center for Studies of Addiction have now found that the drug baclofen, commonly used to prevent spasms in patients with spinal cord injuries and neurological disorders, can help block the impact of the brain's response to "unconscious" drug triggers well before conscious craving occurs. They suggest that this mechanism has the potential to prevent cocaine relapse. The new findings are reported in the *Journal of Neuroscience.*

"The study was inspired by patients who had experienced moments of 'volcanic craving', being suddenly overcome by the extreme desire for cocaine, but without a trigger that they could put their finger on," says senior author Anna Rose Childress, PhD, research professor of Psychiatry, director of the Brain-Behavioral Vulnerabilities Division in the Perelman School of Medicine at the University of Pennsylvania. Dr. Childress and colleagues previously found that subliminal drug "reminder cues" (the sights, sounds, smells, and memories of the drug) could activate the brain's reward circuit. "Now, we wanted to understand whether a medication could inhibit these early brain responses," said Childress.

Kimberly Young, PhD, an NIH/NIDA Post-doctoral Fellow at Penn, and first author of the study explained that, "Drug reward and motivation is largely mediated by dopamine transmission in the brain's reward circuit—even drug "reminder cues" can cause dopamine release. Since baclofen and similar medications reduce these effects in laboratory animals, we wanted to examine whether it could prevent drug-cue induced activation in the human brain."

The study tested baclofen, which was approved by the U.S. Food and Drug Administration in 1977 for spasm, on 23 cocaine-dependent men, ages 18 to 55. Each reported using cocaine on at least eight of 30 days before screening. Inclusion in the study required that they stay for up to 10 days in a supervised inpatient drug treatment facility, be drug-free for the duration, not be on any medication affecting dopamine or neurotransmitter response, and have no history of psychosis, seizures, or brain syndromes unrelated to cocaine use.

Upon admission, patients were randomized to receive baclofen (12) or placebo (11). Over the first six days, patients in the baclofen group received the medication in increasing dosage to 60 mg. While on the full 60 mg dose of baclofen, patients were placed in an fMRI and shown a series of images, to measure their neural responses to "ultra-brief" pictures of cocaine or other comparison pictures. Each of the ultra-brief 33 msec "target" pictures was immediately followed by longer picture of non-drug objects or scenes. Under these conditions, the participants are aware of the longer pictures, but the ultra-brief target pictures remain completely outside conscious awareness—they are "backward-masked".

“We wanted to present the key stimulus: images of drug use and preparation, sexual images, and other aversive images in a way such that the brain could not consciously process them, but so that we could measure their earliest, subconscious effect on the brain,” said Childress.

What the team found was that the patients who were treated with baclofen showed a significantly lower response in the reward and motivational circuits to subliminal cocaine cues versus neutral cues, as compared to the placebo-treated control group. In addition, no difference was seen in the active versus the control group in their response to sexual and aversive cues, indicating that the effects of baclofen on cue-induced brain activation were specific to drug cues.

“These findings suggest that the brain response to drug cues presented outside of awareness can be pharmacologically inhibited, providing a mechanism for baclofen’s potential therapeutic benefit in addiction,” says Young. “Further studies will show whether the prevention of these early brain responses is associated with reduced rates of craving and relapse in cocaine-dependent patients,” added Childress.

This work was supported by NIH grants T32, R01 DA010241, and P50 DA12756, and the Commonwealth of Pennsylvania CURE Addiction Center of Excellence. The authors declare no completing financial interests.

###

http://www.uphs.upenn.edu/news/News_Releases/2014/04/childress/