Stress triggers relapse in meth abuse, study finds

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Oregon Health & Science University research showing stress triggers a relapse of methamphetamine abuse in mice could be a step toward developing a drug to curb this frustrating obstacle to recovery.

Results of the study, headed by Gregory Mark, Ph.D., associate professor of behavioral neuroscience in the OHSU School of Medicine, not only validate earlier studies on the effects of stress on drug relapse in humans, they also show a compound researchers used in the study to mimic metabolic changes that occur during periods of stress creates a useful model for studying this effect in the laboratory.

"One of the big problems we have in treating addiction is relapse. The incidence of relapse is really high," said Mark, an investigator with the Methamphetamine Abuse Research Center (MARC) at OHSU and the Portland Veterans Affairs Medical Center. "What we want to do is see if we can inhibit this response to stress."

The results are being presented today during a poster session at Neuroscience 2006, the Society for Neuroscience's 36th annual meeting in Atlanta.

Mark and study co-authors Deborah Finn, Ph.D., OHSU associate professor of behavioral neuroscience and VAMC research pharmacologist, and Larry Huang, OHSU research technician of behavioral neuroscience, trained mice to optionally administer small doses of meth to themselves by pressing a lever during daily four-hour

sessions over three weeks.

"We structured the drug availability for the mice to be relative to the model that we commonly see meth addicts following," Mark said. "This is an animal model for drug-seeking behavior. We found that getting the drug was rewarding to them."

The drug was then taken away and replaced with harmless saline solution. This caused the lever-pressing rate by the mice to immediately increase.

"We think this is a frustration response," said Mark, who likened the effect to when a person puts money in a soda machine and presses the button, but gets nothing in return. "Analogous to the human world would be 'Come on, it's got to work!'" The mice even pressed a nearby inactive lever they rarely touched before in an attempt to get the drug. But demand for the drug eventually waned. "Over a few days, (the mice) generally give up," Mark explained. When the saline doses dropped to less than one per hour for three consecutive days, the mice received either more saline or a dose of 2-deoxyglucose, or 2-DG, a drug that lowers glucose levels in the blood, creating a condition similar to hypoglycemia in humans.

"People feel stress when they're hypoglycemic," Mark explained.

Five minutes later, the mice were placed in chambers where they previously received meth. The mice that received 2-DG attempted to self-administer meth at a rate five times higher than the mice given saline, making "2-DG an effective stimulus for reinstating drug-seeking behavior."

And as a metabolic stressor, 2-DG is innocuous enough to be used in research on both animals and humans, Mark added. "You don't want to

stress a human by putting him in front of a lion."

Mark believes meth causes nerve cells that survive the drug's neurotoxic effect to be rewired or go through long-term "neuroadaptation." As a result, users respond to stress differently than nonusers, who are generally better able to cope with fatigue, motivation to achieve, peer pressure and other stressful situations.

"The drug changes the brain and those changes last a long time," he said. "This rewiring is something we need to pay attention to, to stop the cycle of taking the drug, getting off the drug and getting back to taking the drug."

One method may be a pharmaceutical therapy targeting brain regions that process stress responses, Mark suggests. These regions include the nucleus accumbens, prefrontal cortex, neostriatum and amygdala. Mark's lab also is studying the effects the neurotransmitters dopamine and acetylcholine have on stress response.

"We want to find those areas of the brain that are sensitive to the (2-DG) stressor and that area should be linked to other areas of the brain that cause the animal to push that lever again, to relapse," Mark said. "We think if we can find the candidate regions, and we can find the neurotransmitters that cause relapse, we can develop a drug that blocks one or more neurotransmitters in one or more of those brain areas. Maybe we could offer some kind of neuropharmaceutical hope."

Source: Oregon Health & Science University