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Stress steroid mediated withdrawal anxiety in dependent rats reversible by flumazenil

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SUNY Downstate Medical Center announced today that Sheryl Smith, PhD, professor of physiology and pharmacology, has published new findings demonstrating a reproducible pathology that may help shed light on anxiety and mood volatility in methamphetamine dependence. In her animal study, Dr. Smith demonstrates that neuroactive stress steroids can trigger identifiable changes to the brains of methamphetamine dependent rats in withdrawal. Interestingly, Dr. Smith notes, these changes appear to be reversible by an existing pharmacological agent – flumazenil.

The paper, titled, "A Stress Steroid Triggers Anxiety via Increased Expression of a4bd GABAA Receptors in Methamphetamine Dependence," was recently published online in *Neuroscience*.

"Methamphetamine is an addictive stimulant drug. Dependence on this drug is difficult to treat because of the severity of the symptoms of methamphetamine withdrawal," said Dr. Smith. "In addition to drug craving and lethargy, withdrawal from methamphetamine is associated with stress-triggered anxiety that may compromise therapeutic intervention. In our recent publication, we show that the system that provides inhibitory control in the brain is dysregulated during methamphetamine dependence in laboratory rodents."

The novel inhibitory receptor that is increased by exposure to methamphetamine is also the target for a stress steroid that produces anxiety during withdrawal from methamphetamine. This receptor is also

a novel target for flumazenil, a drug commonly used to treat tranquilizer overdose. Flumazenil reduced expression of the inhibitory receptor and also prevented the anxiety triggered by the stress steroid during methamphetamine withdrawal. These findings suggest a novel mechanism for stress-triggered anxiety in methamphetamine dependence where flumazenil may have important therapeutic value.

One component of the stress response is the release of the steroid allopregnanolone or THP. This steroid modulates GABAA receptors, with ?4?? GABARs the most sensitive target. These receptors are extrasynaptic and generate a tonic current that is neuroprotective. They also exhibit a high degree of plasticity in response to increases in neuronal excitability, which would accompany METH exposure. In some cases, flumazenil was administered during the 24 hour withdrawal period. Although this drug is a benzodiazepine antagonist, it also binds to ?4?? GABARs and has been shown to regulate ?4 expression.

The study results show that chronic METH treatment and its withdrawal significantly increased expression of ?4 and ? GABAR subunits by 2 to 3-fold. This effect was prevented, however, by flumazenil administration during the withdrawal period. Dr. Smith continued, "Our results suggest that increased ?4?? GABARs mediate the anxiety response to stress steroids after METH withdrawal, an effect prevented by flumazenil. Because stress-triggered anxiety can result in drug relapse, flumazenil may have important therapeutic benefit in METH dependence."

Provided by SUNY Downstate Medical Center