Drugs to treat cocaine abuse?

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The authors of a new study in *Biological Psychiatry* explore pharmacological strategies for reducing cocaine self-administration in animals that may have implications for treating cocaine dependence in humans.

Glutamate is the primary excitatory neurotransmitter in the brain, which has been implicated in drug addiction. Metabotropic glutamate receptors (mGluRs) represent a family of G-protein coupled receptors that modulate glutamate transmission. Glutamate is an important neurotransmitter involved in learning and memory. Today, these receptors are considered to be promising targets for drug discovery, with therapeutic potential to treat various neurological and psychiatric disorders, including drug addiction.

Scientists from The Scripps Research Institute examined whether dysregulation of mGluRs function is a factor in escalating cocaine self-administration in rats. Rats with a history of daily short (1 hour) or long (6 hours) access to cocaine were tested for differences in cocaine consumption after receiving treatment with LY379268, an mGluR2/3 agonist, and MTEP, an mGluR5 antagonist.

They found that the capacity of LY379268 and MTEP to diminish cocaine use changed into opposite directions during development to addiction. LY379268 became more effective, whereas MTEP lost its effect in cocaine dependent rats (long-access). These behavioral changes were paired with distinct changes in the function of mGlu2/3 and mGlu5 receptors.

Dr. Yue Hao, corresponding author of this study, explains their findings: "We provide novel evidence that during the transition from 'casual' cocaine use to addiction, dysregulation develops in both mGlu2/3 and mGlu5 function as reflected by enhanced mGlu2/3 activity and decreased mGlu5 expression." These data suggest that changes in the function of mGlu2 and mGlu5 receptors may play a role in the transition to cocaine addiction.

According to the authors, these new findings identify mGlu2/3 receptors as a particularly promising treatment target for severely cocaine-addicted individuals.

In contrast, the treatment target potential of mGlu5 receptors may be limited to early stages of cocaine abuse.

"This type of study highlights an aspect of the complexity that may be associated with the pharmacotherapy of treating cocaine dependence. All types of cocaine use may not be alike," comments Dr. John Krystal, Editor of *Biological Psychiatry*. "Cocaine exposure to different extents may produce different adaptations in the brain systems. The different profile of the effects of mGluR2/3 agonists and mGluR5 antagonists is interesting and it should stimulate further research."

More information: "Behavioral and Functional Evidence of Metabotropic Glutamate Receptor 2/3 and Metabotropic Glutamate Receptor 5 Dysregulation in Cocaine-Escalated Rats: Factor in the Transition to Dependence" , Yue Hao, Rémi Martin-Fardon, and Friedbert Weiss.

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