MedicalXpress

Three new studies converge on promising new target for addiction treatment

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The latest issue of *Biological Psychiatry* presents the results of three studies implicating metabotropic glutamate receptor 2 (mGluR2) as a new molecular target for the treatment of addiction.

Group II metabotropic glutamate receptors, which include the subtypes mGluR2 and mGluR3, have been known targets for addiction treatment. Unfortunately, mGluR2/3 agonists studied to date have shown important limitations, including development of tolerance and decreasing food intake along with drug intake. Thus, scientists have been working to identify novel targets with selective compounds that would have a more promising therapeutic profile.

The first study, by Dr. Michael Scofield and colleagues, investigated whether non-neuronal glial cells regulate the activity of brain circuits that mediate relapse to cocaine. They used a molecular switch called Gq-DREADD to activate glial release of the chemical messenger glutamate in a key reward center of the brain, the nucleus accumbens. The authors found that activating glutamate release prevented relapse to cocaine use in rodents who previously self-administered this drug. They also found that the effect of glial activation was mediated by stimulating mGluR2 and mGluR3.

Scofield, from the Medical University of South Carolina, explained further, "Our findings show that glutamate homeostasis regulated by astroglia can profoundly alter neuronal circuitry, in particular the brain synapses mediating relapse to cocaine."

The second and third studies reported encouraging anti-addiction effects of AZD8529, an AstraZeneca drug, which works by selectively enhancing the stimulation of mGluR2.

Dr. Zuzana Justinova, from the National Institute on Drug Abuse, and colleagues reported that AZD8529 reduced nicotine self-administration and prevented relapse to nicotine seeking following withdrawal in squirrel monkeys. They also showed that this drug decreases the ability of nicotine to stimulate dopamine release in brain regions implicated in reward in rodents.

"Our results from non-human primate models suggest that AZD8529 could provide a novel safe and effective treatment for nicotine addiction ," said Justinova.

A different research team, led by Daniele Caprioli also at the National Institute on Drug Abuse, discovered that AZD8529 reduced cravings to self-administer methamphetamine in rodents following voluntary abstinence. This novel animal model importantly differs from the more traditional model of experimenter-forced abstinence, as it more closely simulates the human condition of relapse after periods of voluntary abstinence associated with addiction treatment.

Caprioli said, "Our results suggest that AZD8529 can serve as a novel treatment for decreasing methamphetamine relapse and craving in humans with methamphetamine addiction."

Altogether, these three studies conducted using different addictive substances suggest that the use of compounds that selectively target mGluR2 have the potential to successfully treat addiction.

Dr. John Krystal, Editor of Biological Psychiatry, summarized, "It is unusual to have three papers supporting a new treatment mechanism

emerge at the same time. Enhancing mGluR2 function may hold promise for the treatment of addiction."

More information: "The Novel Metabotropic Glutamate Receptor 2 Positive Allosteric Modulator, AZD8529, Decreases Nicotine Self-Administration and Relapse in Squirrel Monkeys" DOI: 10.1016/j.biopsych.2015.01.014

"Effect of the Novel Positive Allosteric Modulator of Metabotropic Glutamate Receptor 2 AZD8529 on Incubation of Methamphetamine Craving After Prolonged Voluntary Abstinence in a Rat Model" DOI: 10.1016/j.biopsych.2015.02.018

"Gq-DREADD Selectively Initiates Glial Glutamate Release and Inhibits Cue-induced Cocaine Seeking" DOI: 10.1016/j.biopsych.2015.02.016

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