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Study identifies potential treatment target for cocaine addiction

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A study led by investigators from Massachusetts General Hospital and the Perelman School of Medicine at the University of Pennsylvania has identified a potential target for therapies to treat cocaine addiction. In their study receiving advance online publication in *Molecular Psychiatry*, the investigators find evidence that changing one amino acid in a subunit of an important receptor protein alters whether cocaine-experienced animals will resume drug seeking after a period of cocaine abstinence. Increasing expression of the enzyme responsible for that change within the GluA2 subunits of AMPA receptors – which receive nerve impulses carried by the neurotransmitter glutamate – reduced cocaine seeking in animals allowed to self-administer the drug.

"The critical role of the AMPA receptor in cocaine addiction is clear," says Ghazaleh Sadri-Vakili, PhD, director of the NeuroEpigenetics Laboratory in the MassGeneral Institute for Neurodegenerative Disease, senior author of the report. "We have known that activation of the AMPA receptor in the nucleus accumbens – an area of the brain important for drug addiction – promotes the resumption of cocaine seeking in animal models, and this study identifies an increased contribution of calcium-permeable AMPA receptors to this process."

AMPA receptors consist of four subunits that can be of four different types – GluA1 through GluA4 – and their involvement in cocaine addiction was previously described by study co-author, R. Christopher Pierce, PhD, of the Perelman School of Medicine at the University of Pennsylvania. The GluA2 subunit determines whether the receptor is

permeable to calcium, which would enhance the strength of signals transmitted through the receptor.

In the normal adult brain, 99 percent of GluA2 subunits have been edited at the RNA processing stage into a form that renders the receptor impermeable to calcium, and disruptions in GluA2 editing that create a calcium-permeable receptor have been associated with disorders including depression, epilepsy and amyotrophic lateral sclerosis. Since chronic cocaine exposure produces major changes in glutamate transmission in the brain – including the nucleus accumbens, a structure deep within the brain known to be involved in reward and addiction – the research team investigated the relationship of GluA2 editing within the accumbens to cocaine seeking in an animal model.

Study lead author Heath Schmidt, PhD, of the Perelman School of Medicine, first allowed a group of rats to self-administer cocaine for 21 days, then withheld cocaine from the animals for a week. Examination of the animals' brains after 7 days of drug abstinence found that levels within the nucleus accumbens of both edited GluA2 and of the enzyme responsible for editing were reduced, compared with the brains of animals not exposed to cocaine. These findings suggest that activation of AMPA receptors containing unedited GluA2 could potentially stimulate cocaine craving. In a different group of animals, Schmidt found that inducing overexpression in the nucleus accumbens of the editing enzyme, called ADAR2, both increased the presence of edited GluA2 in the AMPA receptor and reduced the resumption of cocaine seeking in habituated animals given access to the drug after 7 days of abstinence.

Sadri-Vakili explains, "Our findings support the novel hypothesis that calcium-permeable AMPA receptors containing unedited GluA2 subunits contribute to cocaine seeking and that repairing the deficient editing of GluA2, possibly by regulation of ADAR2 expression, could be a treatment strategy for cocaine addiction." She is an assistant professor

of Neurology at Harvard Medical School; Schmidt is an assistant professor of Psychiatry, and Pierce is a professor of Neuroscience in Psychiatry at the Perelman School of Medicine at the University of Pennsylvania.

Provided by Massachusetts General Hospital

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