Novel anti-craving mechanism discovered to treat cocaine relapse

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Cocaine continues to be one of the most commonly abused illicit drugs in the United States. Pre-clinical literature suggests that targeting glucagon-like peptide-1 receptors (GLP-1Rs) in the brain may represent

a novel approach to treating cocaine use disorder. Specifically, GLP-1R agonists, which are FDA-approved for treating diabetes and obesity, have been shown to reduce voluntary drug taking and seeking in preclinical models of cocaine used disorder. However, the exact neural circuits and cell types that mediate the suppressive effects of GLP-1R agonists on cocaine-seeking behavior are mostly unknown.

New research from the University of Pennsylvania School of Nursing (Penn Nursing) has discovered that GLP-1Rs are expressed on specific cell types and neural circuits in the brain that reduce cocaine-seeking behavior. Investigators have also discovered that GLP-1Rs are expressed primarily on GABAergic neurons in the hindbrain and that the efficacy of the GLP-1R agonist exendin-4 to reduce cocaine seeking depends, in part, on activation of these GABA circuits. Moreover, activating these endogenous anti-craving circuits in the brain using viral-mediated gene delivery methods was sufficient to reduce cocaine-seeking behavior. These findings highlight GLP-1R-expressing anti-craving circuits in the brain that could serve as potential targets to reduce cocaine craving-induced relapse. The findings are published in the journal *Molecular Psychiatry*.

"Overall, the translational implications of these findings are profound in that they support GLP-1R-focused therapeutic approaches for the treatment of cocaine craving and relapse," says lead investigator Heath D. Schmidt, Ph.D., Associate Professor of Nursing at Penn Nursing.

More information: Nicole S. Hernandez et al. GLP-1 receptor signaling in the laterodorsal tegmental nucleus attenuates cocaine seeking by activating GABAergic circuits that project to the VTA, *Molecular Psychiatry* (2020). DOI: 10.1038/s41380-020-00957-3