Cocaine use alters gene expression in brain reward circuits

A study in Biological Psychiatry investigates transcriptome-wide alterations in response to cocaine self-administration in mice

Philadelphia, May 31, 2018 – A study in Biological Psychiatry has identified unique genetic changes in the brain’s reward circuitry that are associated with cocaine use, including first-time use, withdrawal, and re-exposure to the drug after prolonged withdrawal. The findings reveal important information on how cocaine addiction reprograms gene expression and provide insight into the molecular basis of cocaine addiction in unprecedented detail.

In the study, mice were allowed to self-administer cocaine as a model of human addiction, and the gene expression changes were associated with their addiction-like behavior.

“This study elegantly highlights the complexity of the brain's molecular response to self-administered cocaine, pointing to mechanisms that might be targeted by treatments,” said John Krystal, Editor of Biological Psychiatry.

Previous studies have been limited, focusing either on specific genes, a particular brain region, or one aspect of cocaine addiction. But molecular studies aimed at improving addiction treatment have been complicated by alterations in genes that differ throughout the brain—increasing in some regions and decreasing in others.

“This study is the first of its kind to characterize the global transcriptome in brain during the life-cycle of cocaine self-administration,” said senior author Eric Nestler, MD, PhD, of Icahn School of Medicine at Mount Sinai, New York. The researchers examined six regions composing the brain’s reward circuitry, providing an enormous resource of information for studying the biological basis of cocaine addiction.

To characterize the entire life-cycle, Dr. Nestler and colleagues looked for differences in gene expression when mice were first exposed to cocaine; in cocaine-addicted mice after a short (24 hours) or long (30 days) period of withdrawal from the drug; and when addicted mice were re-exposed to cocaine after the 30-day withdrawal. “The experimental design thus allowed us to study how gene expression across brain reward regions changes over time as a result of volitional cocaine intake,” said Dr. Nestler.

The analysis revealed changes in many transcripts involved in key biological processes, providing clues into the brain functions that might lead to cocaine addiction. Many changes were in the same direction (increased or decreased) throughout the reward circuitry, suggesting they may be good targets for new treatments. Interestingly, the size of the changes depended on the condition—where the mice were in the life-cycle of cocaine self-administration—highlighting unique gene changes associated with the different
stages of drug taking. The study also identified several molecules responsible for regulating the expression of the genes associated with addiction-like behavior.

---

Notes for editors

Copies of this paper are available to credentialed journalists upon request; please contact Rhiannon Bugno at Biol.Psych@UTSouthwestern.edu or +1 214 648 0880. Journalists wishing to interview the authors may contact Elizabeth Dowling at Elizabeth.dowling@mounsinai.org or +1 646 605 5944.

The authors’ affiliations and disclosures of financial and conflicts of interests are available in the article.

John H. Krystal, MD, is Chairman of the Department of Psychiatry at the Yale University School of Medicine, Chief of Psychiatry at Yale-New Haven Hospital, and a research psychiatrist at the VA Connecticut Healthcare System. His disclosures of financial and conflicts of interests are available here.

About Biological Psychiatry
Biological Psychiatry is the official journal of the Society of Biological Psychiatry, whose purpose is to promote excellence in scientific research and education in fields that investigate the nature, causes, mechanisms and treatments of disorders of thought, emotion, or behavior. In accord with this mission, this peer-reviewed, rapid-publication, international journal publishes both basic and clinical contributions from all disciplines and research areas relevant to the pathophysiology and treatment of major psychiatric disorders.

The journal publishes novel results of original research which represent an important new lead or significant impact on the field, particularly those addressing genetic and environmental risk factors, neural circuitry and neurochemistry, and important new therapeutic approaches. Reviews and commentaries that focus on topics of current research and interest are also encouraged.

Biological Psychiatry is one of the most selective and highly cited journals in the field of psychiatric neuroscience. It is ranked 6th out of 142 Psychiatry titles and 10th out of 258 Neurosciences titles in the Journal Citations Reports® published by Thomson Reuters. The 2016 Impact Factor score for Biological Psychiatry is 11.412.

About Elsevier
Elsevier is a global information analytics business that helps institutions and professionals advance healthcare, open science and improve performance for the benefit of humanity. Elsevier provides digital solutions and tools in the areas of strategic research management, R&D performance, clinical decision support and professional education, including ScienceDirect, Scopus, SciVal, ClinicalKey and Sherpath. Elsevier publishes over 2,500 digitized journals, including The Lancet and Cell, 38,000 e-book titles and many iconic reference works, including Gray's Anatomy. Elsevier is part of RELX Group, a global provider.
of information and analytics for professionals and business customers across industries.

www.elsevier.com

**Media contact**

Rhiannon Bugno
Editorial Office, *Biological Psychiatry*
+1 214 648 0880
Biol.Psych@UTSouthwestern.edu