

Changes in a single gene's action can control addiction and depression-related behaviors

November 10 2014

Regulation of a single, specific gene in a brain region related to drug addiction and depression is sufficient to reduce drug and stress responses, according to a study conducted at the Icahn School of Medicine at Mount Sinai and published October 27 online in the journal *Nature Neuroscience*.

The Mount Sinai study focuses on epigenetics, the study of changes in the action of human [genes](#) caused, not by changes in DNA code we inherit from our parents, but instead by molecules that regulate when, where and to what degree our genetic material is activated.

Previous research has found links between epigenetic regulation and the diseases of drug addiction and depression, in both human patients and animal models. Such regulation derives, in part, from the function of [transcription factors](#), specialized proteins that bind to specific DNA sequences and either encourage or shut down the expression of a given gene.

Using mouse models of human depression, stress and addiction, the current research team introduced synthetic- transcription factors into a brain region called the nucleus accumbens at a single gene called FosB, which has been linked by past studies to both addiction and depression. They found that changes to this single gene brought on by the transcription factors made the study mice more resilient to stress and less likely to become addicted to cocaine.

Found in every cell of the body, DNA contains genes and the instructions needed for an organism to develop and survive. To carry out these functions, DNA sequences are converted into messages that "tell" cells which proteins to make, dictating the specific function of a given cell. While all cells contain the DNA that codes for every gene, most genes are not activated at all times. The expression of a given gene depends on the action of transcription factors, proteins that regulate the structure of DNA within the cell, allowing some genes to be active and others to be repressed. Transcription factors act by epigenetic mechanisms: chemically modifying either the DNA itself, or the histone proteins packaged around DNA that change shape given the right signal to make stretches of DNA available to the protein building machinery.

"Earlier work in our laboratory found that several transcription factors and downstream epigenetic modifications are altered by exposure to drugs or to stress and that these changes, in turn, [control gene expression](#)," says Eric J. Nestler, MD, PhD, Nash Family Professor, Chair of the Department of Neuroscience and Director of the Friedman Brain Institute at the Icahn School of Medicine at Mount Sinai, who led the study. "But because such epigenetic regulation occurs at hundreds or thousands of genes, until now it had been impossible to determine the difference between the mere presence of an epigenetic modification and its functional relevance to neuropsychiatric disease."

To directly address this issue, Elizabeth A Heller, PhD, lead author on the paper, developed an innovative method to control epigenetic regulation of FosB. Dr. Heller introduced synthetic transcription factors called Zinc Finger Proteins (ZFPs), designed to target only a single gene out of 20,000, by incorporating them into a virus and injecting that virus into the reward-related brain region. Study results indicate that upon binding to that one gene, the FosB-ZFPs modified histones in the vicinity of the FosB gene, in order to either activate (turn on) or repress (turn off) expression.

Expression of the FosB gene in nerve cells is both necessary and sufficient for drug and stress responsiveness in mice. In particular, activation of FosB expression is linked to increased sensitivity to drugs and to resilience to stress and is altered by exposure to such stimuli in the brains of mouse models and in drug-addicted and depressed human patients.

"While [drug addiction](#) and depression are hereditary diseases that regulate gene expression in the brain, the field has yet to uncover relevant mutations in gene sequence that underlie these disorders," says Dr. Heller. "Therefore, we focused on changes in gene structure to probe the mechanism of action of such changes in drug and stress sensitivity. Our data is a critical first step towards developing novel therapeutics to combat these neuropsychiatric diseases. In addition, the use of engineered transcription factors has broad implications outside of neuroscience because epigenetic gene regulation underlies many diseases, including most forms of cancer."

Provided by The Mount Sinai Hospital

Citation: Changes in a single gene's action can control addiction and depression-related behaviors (2014, November 10) retrieved 3 May 2024 from <https://medicalxpress.com/news/2014-11-gene-action-addiction-depression-related-behaviors.html>

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