MedicalXpress

MicroRNAs play a role in cocaine addiction

July 27 2010

MicroRNAs, already linked to cancer, heart disease and mental disorders such as schizophrenia, may also be involved in addiction. A team of Rockefeller University neuroscientists has shown that a protein that plays a crucial role in the regulation of microRNAs, short stretches of RNA that silence genes, is also involved in regulating the motivation to consume cocaine. The findings, published online July 19 in the *Journal of Experimental Medicine*, have already led to the identification of several microRNAs in mice that likely play a role in drug addiction and the scientists say the work could ultimately lead to new ways of combating addictive diseases in humans.

The protein, called Argonaute 2, controls the expression of messenger RNA — the blueprint for protein production — by either suppressing or cutting messenger RNAs with complementary nucleotide sequences to specific microRNAs. The human and mouse genomes contain four different versions of the Argonaute gene, but only Argonaute 2 has a well characterized capacity to suppress messenger RNA expression. Earlier research by one of the coauthors of the current study, Donal O'Carroll at the European Molecular Biology Laboratory in Monterotondo, Italy, revealed that Argonaute 2 also contributes to the generation of microRNAs from their precursors, but it's selective and appears to affect only a fraction of microRNAs in each cell.

The new study, led by Anne Schaefer, a senior research associate in Paul Greengard's Laboratory of Molecular and Cellular Neuroscience, focused on Argonaute 2's role in a specific subset of neurons that express the dopamine 2 receptor, known as Drd2. Cocaine's addictive

properties are related to its ability to increase levels of the neurotransmitter dopamine, which in turn alters the activity of dopamine receptors in an area of the brain called the striatum.

Schaefer and her colleagues in the Greengard laboratory silenced *Argonaute 2* only in Drd2-expressing neurons in mice. In collaboration with Paul Kenny's group at The Scripps Research Institute, they found that its deficiency greatly reduces the mice's motivation to self-administer cocaine. They also identified a distinct group of microRNAs that are specifically regulated by Argonaute 2 in the striatum.

Using a new technique that allows cell-type specific microRNA analysis, the researchers compared those Argonaute 2-dependent microRNAs with microRNAs that are enriched in Drd2-neurons and upregulated in response to cocaine. The result was the identification of a set of 23 microRNAs that are likely to play a role in cocaine addiction, and which the researchers says should be investigated further. "Identification of miRNAs that contribute to addiction is just a first step in the research program that aims to identify the epigenetic mechanism of addictive behavior," says Schaefer.

"Our studies suggest that the important role of Argonaute 2 in cocaine addiction involves the presence or generation of specific microRNAs that contribute to stable changes in gene expression patterns that define neuronal cell plasticity and ultimately regulate the motivation to consume cocaine," says Greengard, who is the Vincent Astor Professor.

More information: *Journal of Experimental Medicine* online: July 19, 2010. Argonaute 2 in dopamine 2 receptor-expressing neurons regulates cocaine addiction. Anne Schaefer, Heh-In Im, Morten T. Venø, Christie D. Fowler, Alice Min, Adam Intrator, Jørgen Kjems, Paul J. Kenny, Donal O'Carroll and Paul Greengard

Provided by Rockefeller University