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New form of brain signaling affects addiction-related behavior

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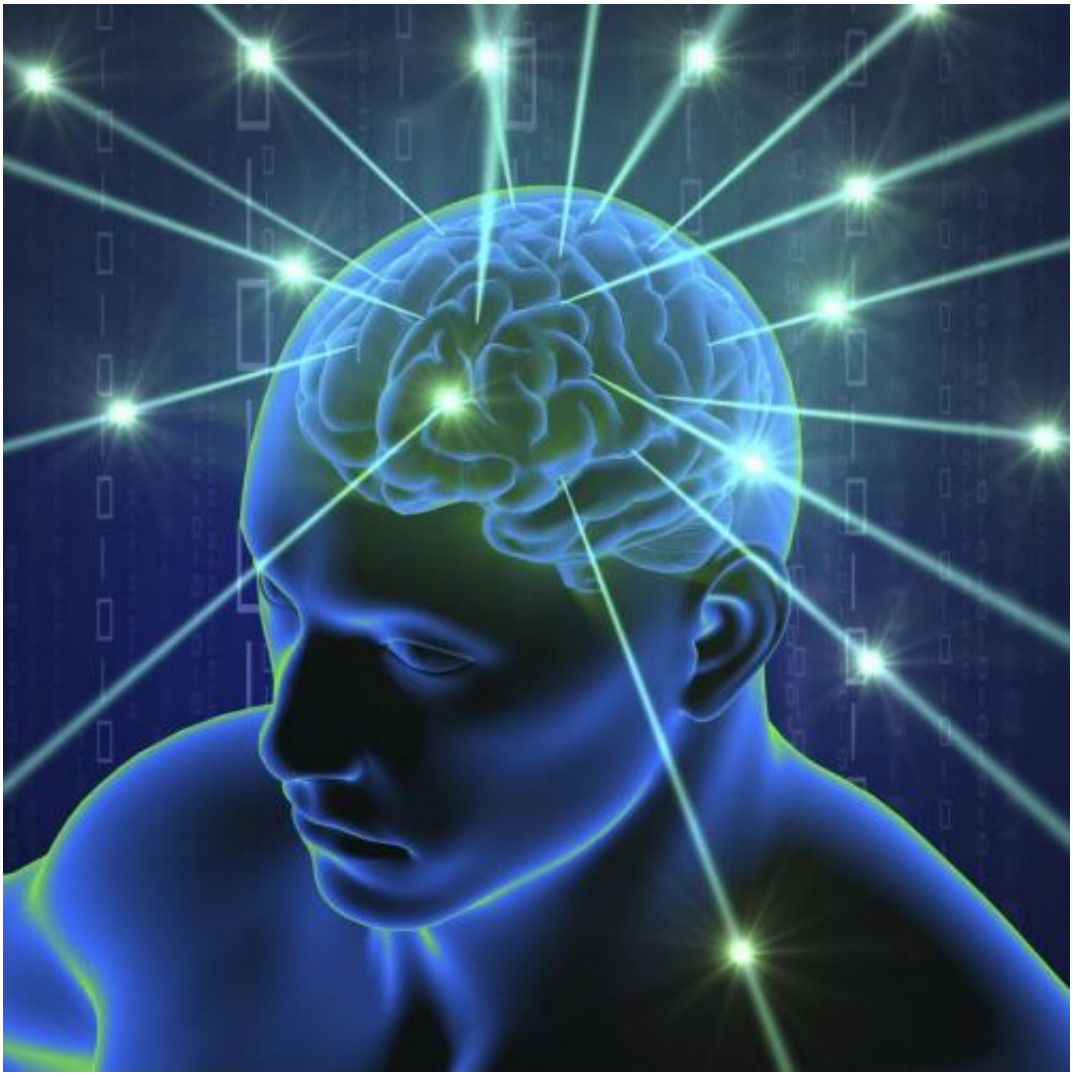

Credit: Rice University

University of Iowa researchers have discovered a new form of neurotransmission that influences the long-lasting memory created by addictive drugs, like cocaine and opioids, and the subsequent craving for these drugs of abuse. Loss of this type of neurotransmission creates changes in brains cells that resemble the changes caused by drug addiction.

The findings, published June 22 in the journal *Nature Neuroscience*, suggest that targeting this type of neurotransmission might lead to new therapies for treating drug addiction.

"Molecular therapies for drug addiction are pretty much non-existent," says Collin Kreple, UI graduate student and co-first author of the study. "I think this finding at least provides the possibility of a new molecular target."

The new form of neurotransmission involves proteins called acid-sensitive ion channels (ASICs), which have previously been shown to promote learning and memory, and which are abundant in a part of the brain that is involved in drug addiction. The researchers, led by John Wemmie, MD, PhD, professor of psychiatry in the UI Carver College of Medicine, reasoned that disrupting ASIC activity in this brain region (the nucleus accumbens) should reduce learned addiction-related behaviors. However, their experiments showed that loss of ASIC signaling actually increases learned drug-seeking in mice.

When mice learned to associate one side of a chamber with receiving cocaine, animals that lacked the ASIC protein developed an even stronger preference for the "cocaine side" than control mice, suggesting that loss of ASIC had increased addiction behavior. The same result was seen for morphine, another drug of abuse, which has a different mechanism of action than cocaine.

"Always before, the data suggested that when you get rid of ASICs, learning and memory are impaired," Wemmie says. "So we expected the same trend when we studied reward-related learning and behavior and we were surprised to find the opposite."

In a second experiment, rats learned to press a lever to self-administer cocaine. Blocking or removing ASIC in the rat brains caused the animals to self-administer more cocaine than control animals. Conversely, increasing the amount of ASIC by over-expressing the protein seemed to decrease the animals' craving for cocaine.

"There are many forms of addiction," Wemmie says. "We'd like to see if these mechanisms also apply to other addictions besides cocaine and morphine. And, we want to move forward to see if this pathway can be used to target addiction."

Protons are neurotransmitters

As the name suggests, acid-sensitive ion channels are activated by acid, in the form of protons. This research and a second UI study recently published in PNAS show that protons and ASICs form a previously unrecognized neurotransmitter pair that helps neurons communicate in a novel way; and appear to influence several forms of learning and memory, including fear, as well as addiction.

Manipulating the activity of ASICs or the level of protons (acidity) may provide a new way to treat addiction.

"We are still a long way from using these findings to create a therapy," notes Yuan Lu, PhD, co-first author and UI postdoctoral scholar. "The key significance of this study is that we have found new, different targets [that might allow us to inhibit the addiction behavior]."

Drugs change the brain

Previous research has shown that drug abuse and addiction physically alter the connections between neurons (synapses) that are important for the creation and storage of memories. Although normal learning requires synapses to be dynamic and plastic, exposure to addictive drugs abnormally increases synaptic plasticity in a way that is thought to underlie drug-related learning and addiction behaviors. The UI study found that absence of ASIC-proton mediated neurotransmission also increased synaptic plasticity in a way that resembled the changes created by addiction and drug withdrawal.

"It seemed like everything we looked at (physiology and structural changes) really paralleled what you would see in an animal undergoing drug withdrawal, even though these animals missing ASIC had never been exposed to drugs," Kreple says.

Overall the study findings suggest that ASIC-related neurotransmission in the nucleus accumbens may play a role in reducing synaptic plasticity and appropriately stabilizing synapses.

More information: *Nature Neuroscience*, www.nature.com/neuro/journal/v … nt/full/nn.3750.html

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