A mother's touch may protect against drug cravings later

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An attentive, nurturing mother may be able to help her children better resist the temptations of drug use later in life, according to a study in rats conducted by Duke University and the University of Adelaide in Australia.

A rat mother's attention in early childhood actually changes the immune response in the brains of her pups by permanently altering genetic activity, according to Staci Bilbo, an assistant professor of psychology and neuroscience at Duke, who led the research. High-touch mothering increased the brain's production of an immune system molecule called Interleukin-10, leaving these rats better able to resist the temptation of a dose of morphine much later in life.

This is the first study to show how morphine causes a molecular response in the glial cells of the brain's reward centers, which had only recently been identified as part of drug addiction's circuitry. "We set out to find out what that response looks like," Bilbo said.

To program some of the rat pups to produce more IL-10, the researchers used an established technique called the "handling paradigm," in which very young rat pups are removed from their mother's cage for 15 minutes and then returned. "As soon as they're returned, she checks them out vigorously," grooming the pups and cleaning them, Bilbo said. For a control group, another set of pups were never removed. Some of them had more attentive mothers than others, just by natural variation.

The animals then were put through a test called the "place preference chamber," a two-roomed cage in which they would be given a dose of morphine if they entered one side, or a dose of saline on the other. Over the next four weeks, the rats were returned to the two-sided chamber three times a week for five minutes, but were never given another dose of morphine. Initially, they all showed a preference for the morphine side, but over time, the handled rats showed little preference, which indicated their craving had been "extinguished," Bilbo said.

About 8 weeks after their first exposure to morphine, the animals were each given a very small dose of morphine to prime craving and then returned to the 2-sided chamber. The non-handled control rats preferred spending time in the morphine chamber; the handled rats still showed no clear preference.

Morphine activates the glial cells of the brain to produce inflammatory molecules which signal a reward center of the brain called the nucleus accumbens. But IL-10 works against that inflammation and reward. The more IL-10 the brain produces, the less likely morphine would cause an increase in craving or relapse weeks after the initial experience with the drug.

The brains of the rat pups who experienced high-touch mothering were found to have more active genes for producing IL-10 in the microglial cells of the brain, which apparently "completely knocked out this drug-seeking behavior," Bilbo said. They were producing about four times as much IL-10 as the control animals. "The nurturing moms can profoundly change outcomes," Bilbo said.

This is a change not of the genes themselves, but of the way they are controlled by something called methylation, which can keep a gene's activity suppressed. High-touch mothering removed methylation on the IL-10 gene, making these rats produce more of the anti-inflammatory

molecule.

To further prove that IL-10 levels were key to the craving, the researchers used a drug called ibudilast to artificially increase IL-10 production in a group of control rats. These rats experience craving extinction much the same as the high-touch rats.

It's important to note that the genetic modification created by the mothering didn't change the initial rewarding effect of the morphine, it altered the craving for that reward much later, Bilbo said.

Bilbo said her team next wants to look at the long-term effects of maternal stress on the brain's immune response. They'll be working with the Children's Environmental Health Initiative at Duke, which examines real-world environmental health effects in Durham, NC in collaboration with the US Environmental Protection Agency.

More information: "Early-Life Experience Decreases Drug-Induced Reinstatement of Morphine CPP in Adulthood via Microglial-Specific Epigenetic Programming of Anti-Inflammatory IL-10 Expression," Jaclyn M. Schwarz, Mark R. Hutchinson and Staci D. Bilbo. *The Journal of Neuroscience*, Dec. 6, 2011. DOI -10.1523/JNEUROSCI.3297-11.2011

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