Resistance to cocaine addiction may be passed down from father to son, study shows

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Research from the Perelman School of Medicine at the University of Pennsylvania and Massachusetts General Hospital (MGH) reveals that sons of male rats exposed to cocaine are resistant to the rewarding effects of the drug, suggesting that cocaine-induced changes in physiology are passed down from father to son. The findings are published in the latest edition of *Nature Neuroscience*.

"We know that genetic factors contribute significantly to the risk of cocaine abuse, but the potential role of epigenetic influences – how the expression of certain genes related to addiction is controlled – is still relatively unknown," said senior author R. Christopher Pierce, PhD, associate professor of Neuroscience in Psychiatry at Penn. "This study is the first to show that the chemical effects of cocaine use can be passed down to future generations to cause a resistance to addictive behavior, indicating that paternal exposure to toxins such as cocaine can have profound effects on gene expression and behavior in their offspring."

In the current study, the team used an animal model to study inherited effects of cocaine abuse. Male rats self-administered cocaine for 60 days, while controls were administered saline. The male rats were mated with females that had never been exposed to the drug. To eliminate any influence that the males' behavior would have on the pregnant females, they were separated directly after they mated.

The rats' offspring were monitored to see whether they would begin to self-administer cocaine when it was offered to them. The researchers discovered that male offspring of rats exposed to the drug, but not the female offspring, acquired cocaine self-administration more slowly and had decreased levels of cocaine intake relative to controls. Moreover, control animals were willing to work significantly harder for a single cocaine dose than the offspring of cocaine-addicted rats, suggesting that the rewarding effect of cocaine was decreased.

In collaboration with Ghazaleh Sadri-Vakili, MS, PhD, from MGH, the researchers subsequently examined the animals' brains and found that male offspring of the cocaine-addicted rats had increased levels of a protein in the prefrontal cortex called brain-derived neurotrophic factor (BDNF), which is known to blunt the behavioral effects of cocaine.

"We were quite surprised that the male offspring of sires that used cocaine didn't like cocaine as much," said Pierce. "While we identified one change in the brain that appears to underlie this cocaine resistance effect, there are undoubtedly other physiological changes as well and we are currently performing more broad experiments to identify them. We also are eager to perform similar studies with more widely used drugs of abuse such as nicotine and alcohol."

The findings suggest that cocaine use causes epigenetic changes in sperm, thereby reprogramming the information transmitted between generations. The researchers don't know exactly why only the male offspring received the cocaine-resistant trait from their fathers, but speculate that sex hormones such as testosterone, estrogen and/or progesterone may play a role.

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