Study finds sons of cocaine-using fathers have profound memory impairments

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A pile of cocaine hydrochloride. Credit: DEA Drug Enforcement Agency, public domain

Fathers who use cocaine at the time of conceiving a child may be putting their sons at risk of learning disabilities and memory loss. The findings of the animal study were published online in *Molecular Psychiatry* by a

team of researchers from the Perelman School of Medicine at the University of Pennsylvania. The researchers say the findings reveal that drug abuse by fathers—separate from the well-established effects of cocaine use in mothers— may negatively impact cognitive development in their male offspring.

The study, which was led by Mathieu Wimmer, PhD, a post-doctoral researcher in the laboratory of R. Christopher Pierce, PhD, a professor of Neuroscience in Psychiatry in the Perelman School of Medicine at the University of Pennsylvania, found evidence that the sons of fathers that ingested cocaine prior to conception struggle to make new memories. Their findings demonstrated that the sons—but not the daughters—of male rats that consumed cocaine for an extended period of time could not remember the location of items in their surroundings and had impaired synaptic plasticity in hippocampus, a brain region critical for learning and spatial navigation in humans and rodents.

"These results suggest that the sons of male cocaine addicts may be at risk for learning deficits," said senior author, R. Christopher Pierce, PhD, a professor of Neuroscience in Psychiatry in the Perelman School of Medicine at the University of Pennsylvania.

Pierce and his colleagues propose that epigenetic mechanisms are at the root of the problem. Epigenetics refers to heritable traits that are not caused by changes in the DNA sequence, as is the case with genetic inheritance. DNA is tightly wound around proteins called histones, like thread around a spool, and chemical changes to histones influence the expression of genes, which is an epigenetic process.

Their research showed that cocaine use in dads caused epigenetic changes in the brain of their sons, thereby changing the expression of genes important for memory formation. D-serine, a molecule essential for memory, was depleted in male rats whose father took cocaine and

replenishing the levels of D-serine in the sons' hippocampus improved learning in these animals.

In collaboration with Benjamin Garcia, PhD, presidential professor of Biochemistry and Biophysics in the Epigenetics Institute at the Perelman School of Medicine, the authors showed that cocaine abuse in dads broadly altered the chemical marks on histones in the brain of their sons, even though the offspring were never exposed to cocaine. Chemical modifications on the histones were changed to favor active transcription of genes in the hippocampus of male rats with a paternal history of cocaine taking, allowing more production of the enzyme D-amino acid oxidase, which degrades D-serine. The authors propose that increased expression of the enzyme, driven by changes in the epigenetic landscape, cause the memory problems in the sons of addicted rats.

"There is substantial interest in the development of D-serine and related compounds, which are well tolerated by humans, as drug therapies," Pierce said. "The ability of D-serine to reverse the adverse effects of paternal cocaine taking on learning adds potential clinical relevance to our research."

Provided by Perelman School of Medicine at the University of Pennsylvania