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The sins of the fathers: Transgenerational effects of paternal cocaine

Abstract:

Paternal environmental perturbations including exposure to drugs of abuse can produce profound effects on the physiology and behavior of offspring via epigenetic modifications. Here, we show that adult drug-naïve male offspring of cocaine-exposed sires have memory formation deficits and associated reductions in NMDA receptor-mediated hippocampal synaptic plasticity. Reduced levels of the endogenous NMDA receptor co-agonist D-serine were accompanied by increased expression of the D-serine degrading enzyme d-amino acid oxidase (Dao1) in the hippocampus of cocaine-sired male progeny. Increased Dao1 transcription was associated with enrichment of permissive epigenetic marks on histone proteins in the hippocampus of male cocaine-sired progeny, some of which were enhanced near the Dao1 locus. Finally, hippocampal administration of D-serine reversed both the memory formation and synaptic plasticity deficits. Collectively, these results demonstrate that paternal cocaine exposure produces epigenetic remodeling in the hippocampus leading to NMDA receptor-dependent memory formation and synaptic plasticity impairments only in male progeny, which has significant implications for the male descendants of chronic cocaine users.