Reduced Cocaine Reinforcement in the Male Offspring of Cocaine-Experienced Sires

Mounting evidence suggests that parental ingestion of abused drugs influences the physiology and behavior of future generations in the absence of prenatal exposure (Vassoler *et al*, 2014). However, few studies have examined potential mechanisms of transmission of addiction-related phenotypes. Therefore, we developed a rat model to delineate a heritable phenotype resulting from the self-administration of cocaine. Our research indicates that the male offspring of cocaine-experienced male rats find cocaine-less reinforcing, leading them to consume considerably less cocaine than controls (Vassoler *et al*, 2013). Increased levels of cortical brain-derived neurotrophic factor (BDNF) may be the underlying cause of the cocaine resistance observed in the sons. These findings show that cocaine-induced changes in physiology can be inherited by sons from their fathers. The reason for the sex specificity is unclear, but may be due to intergenerational effects on gene transcription interacting with subsequent hormonal influences.

We usually think about inherited changes in physiology occurring via natural selection on an evolutionary timescale. However, a growing body of evidence indicates that environmental information can be transmitted from one generation to the next. For example, epidemiological data show that a fetus exposed to famine early in pregnancy will tend to be born small but will be more prone to obesity, diabetes, and mental health issues as an adult (Lumey *et al*, 2011). Some of these health problems also plague the grandchildren of mothers malnourished in early pregnancy (Lumey *et al*, 2011). The latter is a potential example of epigenetic inheritance, defined as changes in phenotype caused by mechanisms other than alterations in DNA sequence.

In our paradigm, male rats self-administered cocaine for 60 days (controls were administered saline) and were then paired with naive females. The offspring of these matings were tested for acquisition of cocaine self-administration. Our results indicated that the male, but not female, offspring of cocaine-experienced sires 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 single cocaine infusions than the cocaine-sired rats, suggesting a decrease in the reinforcing effectiveness of cocaine. The cocaine-sired rats did not have generalized learning deficits, as there was no difference in acquisition of food self-administration. We next looked at BDNF expression in the prefrontal cortex of naive littermates. The cocaine-sired male offspring had increased histone acetylation association with a *Bdnf* promoter and augmented *Bdnf* mRNA, which enhanced BDNF protein levels in the prefrontal cortex. Importantly, blocking the action of BDNF reversed the cocaine-resistance phenotype.

These findings raise the question of how paternal cocaine exposure influenced the behavior of the male offspring. Intriguingly, our results indicate that there were changes in histone acetylation of *Bdnf* promoters in the sperm of cocaine-experienced sires, which might lead to increases in BDNF protein expression in the brains of the offspring. This finding indicates that cocaine causes epigenetic changes in sperm, which may alter the physiology and behavior of offspring in the absence of changes in DNA sequence. Taken together, these results indicate that paternal exposure to toxins such as cocaine can have profound effects on gene expression and behavior of the offspring.

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De Novo Mutations in Schizophrenia Disrupt Genes Co-Expressed in Fetal Prefrontal Cortex

We recently reported that damaging *de novo* mutations in persons with schizophrenia from otherwise healthy families disrupt genes that orchestrate neurogenesis in fetal prefrontal cortex (Gulsuner *et al*, 2013). By sequencing genomic DNA from entire families, we identified point mutations and copy number variants that appeared *de novo* in 105 persons with schizophrenia and in 84 of their healthy siblings. Patients were more likely than unaffected siblings to harbor damaging *de novo* mutations (47/105 *vs* 30/84, OR = 1.91, X2 = 4.45; $p = 0.035$). The proportion of schizophrenia attributable to damaging *de novo* mutations in this sample was 21%.

Even more striking than the difference in mutation frequencies was the distinctive functional relationship among the genes harboring mutations. The genes disrupted by damaging *de novo* mutations in patients formed a network defined by protein interaction (Mostafavi *et al*, 2008) and by