Published in final edited form as:

Nat Neurosci. 2013 January ; 16(1): 4–5. doi:10.1038/nn.3288.

Forgiving the sins of the fathers

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Abstract

In a case of sex-linked epigenetic inheritance, paternal cocaine use results in a heritable increase in cortical *Bdnf* gene expression that confers a cocaine-resistant phenotype in male, but not female, progeny.

The conventional view of evolution requires natural selection and the refining of mutations in DNA sequences over many generations. However, it is now known that one's environment can imprint information on DNA through the modification of chromatin structure. This epigenetic regulation, a term coined by embryologist and geneticist Conrad Waddington¹, allows heritable transfer of information from one generation to the next without the alteration of DNA sequence. A commonly used analogy likens epigenetic regulation to the software controlling our genetic hardware². As an example, in the nineteenth century, the snowy mountain province of Norrbotten in northern Sweden experienced hardships when crops failed, but bouts of rare abundance when harvests were plentiful. Men likely to have descended into gluttony briefly as boys went on to have children and grandchildren at increased risk of diabetes-related mortality³, demonstrating that perturbations in ancestral environmental conditions can profoundly affect future generations.

In this issue of *Nature Neuroscience*, Vassoler *et al.*⁴ report that paternal cocaine use causes a heritable increase in cortical brain-derived neurotrophic factor (*Bdnf*) gene expression, which then confers a cocaine-resistant phenotype in male, but not female, progeny. Male rats were allowed to self-administer cocaine or saline for 60 days (the entire duration of rat spermatogenesis) and then mated with drug-naïve females to produce 'cocaine-sired' and 'saline-sired' litters. Cocaine- or saline-experienced male rats were only allowed to have contact with females long enough for fertilization to occur and did not have any contact with the resulting litters. Using a self-administration test, the authors observed that cocaine-sired male rats displayed delayed acquisition and reduced intake of cocaine, as well as decreased motivation to work for cocaine under high-effort self-administration conditions, as compared with saline-sired controls⁴. Cocaine-sired female rats, however, were indistinguishable from saline-sired female controls. In an important series of control experiments, the authors also found that paternal cocaine experience had no effect on sucrose self-administration,

Competing Financial Interests: The authors declare no competing financial interests.

indicating that cocaine-sired rats could learn an instrumental task normally and that their valuation of a sucrose reward was unchanged.

In light of previous observations that elevated BDNF in the medial prefrontal cortex (mPFC) causes a reduction of cocaine-seeking^{5,6}, Vassoler *et al.*⁴ investigated BDNF expression in the mPFC of cocaine-sired and saline-sired rats. As predicted, male rats sired by cocaine-experienced fathers expressed higher *Bdnf* mRNA and BDNF protein levels in the mPFC before cocaine exposure. Furthermore, the diminished cocaine self-administration displayed by cocaine-sired male rats was reversed by the systemic administration of ANA-12, an antagonist of the BDNF receptor TrkB, suggesting that increased BDNF expression in the mPFC was responsible for the lower cocaine intake. To determine the molecular mechanism underlying the increase in *Bdnf* gene expression, the authors performed chromatin immunoprecipitation assays designed to detect whether acetylation of histones at the *Bdnf* promoter had been transferred to the male offspring of cocaine-using sires. Acetylation of histone proteins weakens their association with DNA, allowing increased accessibility of transcriptional regulatory proteins and enhanced gene expression⁶. Vassoler *et al.*⁴ discovered that there was more acetylation of histone protein H3 at the *Bdnf* promoter, providing an epigenetic mechanism for the elevated expression of BDNF in the mPFC of male cocaine-sired rats (Fig. 1). Future experiments should certainly investigate whether the enhancement of *Bdnf* gene expression is restricted to the mPFC, as exogenous application of BDNF in subcortical regions, such as the ventral tegmental area or the nucleus accumbens, produces opposite effects from those produced by application of BDNF in the mPFC and enhances cocaine-seeking⁷.

Although previous studies have shown that chronic cocaine exposure profoundly affects chromatin structure and, as a result, the expression of hundreds of genes^{8,9}, this study is, to the best of our knowledge, the first to show that a history of cocaine usage results in a heritable reduction of intake in later generations. The finding that cocaine-sired, but not saline-sired, male rats display an altered chromatin structure at the *Bdnf* promoter in cortical tissue raises the question of how this epigenetic imprinting is transferred from father to son. Vassoler *et al.*⁴ investigated acetylation in the original cocaine- or saline-experienced male rats used for breeding and found that there was more acetylated histone H3 in the seminiferous tubules of the testes in the cocaine-experienced rats. By investigating chromatin structure in sperm cell DNA, the authors detected an increase in acetylation of histone proteins at the *Bdnf* promoter of cells from these rats, paralleling the increased histone protein acetylation observed at the *Bdnf* promoter in the mPFC of male offspring (Fig. 1). These results present a potential mechanism for the germline inheritance of the cocaine-resistant phenotype through the transfer of epigenetic markings on spermatozoal histones and add to a growing body of evidence supporting the transgenerational transfer of environmentally induced phenotypes in response to toxin exposure¹⁰.

The findings of Vassoler *et al.*⁴ are especially noteworthy considering that studies with large cohorts of identical and fraternal twins have asserted that cocaine addiction is heavily influenced by genetic factors¹¹. In surprising contrast, the work of Vassoler *et al.*⁴ provides an epigenetic mechanism in which a father with a history of cocaine addiction may provide some protection against developing the same type of addictive disorder. It is important to

note that human genetics studies are correlational and do not prove a causal relationship, and they do not take into account the effect of drug availability and many other factors that undoubtedly contribute to the development of an addictive disorder¹¹. There is certainly more to be uncovered with regard to the genetics and heritability of addiction; however, it is possible that the effect of environmental conditions has been markedly understated. In the future, the contribution of both genetic and epigenetic factors must be considered when addressing heritability of addictive disorders.

The concept of paternal experience providing a protective phenotype contrasts with data from several groups examining the effect of paternal stress and the resulting effect on anxiety-related phenotypes in future generations. Studies using maternal separation in male mice have found that early-life stress leads to increased anxiety-related behaviors that persist in subsequent generations¹². Moreover, male mice exposed to chronic social stress transmit increased anxiety and a decreased social interaction phenotype to female offspring¹³. The epigenetic transfer of a phenotype that may be maladaptive in future generations is also consistent with the data from Norrbotten, which showed that men who overate during crucial periods of development had grandchildren with higher rates of diabetes and cardiovascular disease. Given these results, why does paternal cocaine experience give rise to progeny with lower cocaine intake? Vassoler *et al.*⁴ speculate that the elevation of mPFC *Bdnf* gene expression resulting from chronic cocaine exposure is a neuroadaptation to counteract cocaine-mediated plasticity, and that this protective adaptation was passed epigenetically to male offspring⁷.

The findings of Vassoler *et al.*⁴ raise many questions that should be addressed with further experimentation. How does paternal cocaine exposure globally effect the mammalian epigenome and, as a result, the mammalian transcriptome? How strictly does the transfer of a cocaine-resistant phenotype depend on the amount or duration of cocaine use? Would a third generation of rats also display the cocaine-resistant phenotype? Would a fourth? Despite such questions, though, these data constitute an important advance in understanding of how parental experience engages epigenetic regulation of gene expression to control the heritable transfer of genetic information.

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Figure 1.

The effect of cocaine history on the acetylation of *Bdnf* promoter histone proteins in F₀ and F₁ males. Saline-experienced males displayed normal levels of acetylation of histone proteins at the *Bdnf* promoter in sperm cell DNA (top left), and their male offspring showed normal levels of histone protein acetylation at the *Bdnf* promoter in neurons of the mPFC (bottom left). Cocaine-experienced males showed elevated acetylation of histone proteins at the *Bdnf* promoter in sperm cell DNA (top right), and their male offspring showed elevated acetylation at the *Bdnf* promoter in neurons of the mPFC, resulting in greater *Bdnf* gene expression (bottom right).