

REVIEW

MECHANISMS OF TRANSGENERATIONAL INHERITANCE OF ADDICTIVE-LIKE BEHAVIORS

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Abstract—Genetic factors are implicated in the heritability of drug abuse. However, even with advances in current technology no specific genes have been identified that are critical for the transmission of drug-induced phenotypes to subsequent generations. It is now evident that epigenetic factors contribute to disease heritability and represent a link between genes and the environment. Recently, epigenetic mechanisms have been shown to underlie drug-induced structural, synaptic, and behavioral plasticity by coordinating the expression of gene networks within the brain. Therefore, the epigenome provides a direct mechanism for drugs of abuse to influence the genetic events involved in the development of addiction as well as its heritability to subsequent generations. In this review we discuss the mechanisms underlying intergenerational epigenetic transmission, highlight studies that demonstrate this phenomenon with particular attention to the field of addiction, and identify gaps for future studies.

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Key words: transgenerational inheritance, epigenetics, cocaine, BDNF, prefrontal cortex.

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Abbreviations: BDNF, brain-derived neurotrophic factor; Dnmt-1, DNA methyltransferase 1; miRNAs, microRNAs; mPFC, medial prefrontal cortex; piRNA, Piwi interacting RNAs.

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INTRODUCTION

Drug addiction is a chronic, relapsing disorder characterized by compulsive drug taking and seeking despite undesirable consequences (Mendelson and Mello, 1996). Genetic susceptibility together with early life experiences such as environmental factors contributes to the development of addiction. In addition, the transition to compulsive drug seeking has been shown to arise due to altered neuroplasticity and an inability to inhibit drug-associated cues (Luscher and Malenka, 2011). Twin and sibling studies implicate genetic factors in the heritability of drug abuse susceptibility (Cloninger et al., 1981) and it is now clear that substance use disorders are heritable (Cloninger et al., 1981; Bierut et al., 1998; Merikangas et al., 1998; Brook et al., 2002). However, the components that are responsible for the heritability of characteristics that make an individual more susceptible to drug addiction in humans remain largely unknown given that patterns of inheritance cannot be explained by simple genetic mechanisms (Schuckit et al., 1972; Cloninger et al., 1981). The environment also plays a large role in the development of addiction as evidenced by great societal variability in drug use patterns between countries and across time (UNODC, 2012). Therefore, both genetics and the environment contribute to an individual's vulnerability to become addicted following an initial exposure to drugs of abuse.

Recently, it has been demonstrated that epigenetic factors contribute to disease heritability (Danchin et al., 2011; Bohacek and Mansuy, 2012) and may provide the missing link between environmental stimuli and genetic heritability. The definition of epigenetics has evolved to include both heritable and stable changes in gene expression within mature, post-mitotic cells without alterations in the DNA sequence (Bird, 2007; Siegmund et al., 2007; Tsankova et al., 2007). Epigenetic mechanisms translate environmental stimuli into stable alterations in chromatin structure that function to activate or repress gene transcription (Jaenisch and

Bird, 2003). Recent findings have demonstrated that epigenetic mechanisms contribute to drug-induced structural, synaptic, and behavioral plasticity by orchestrating expression of gene networks in discrete brain nuclei (Renthal and Nestler, 2008; Russo et al., 2010). Thus, epigenetics provides a direct molecular mechanism for drugs of abuse to influence the genetic events involved in the development as well as heritability of addiction.

The goal of this review is to discuss the potential mechanisms whereby environmental exposure to drugs of abuse can cause alterations in the epigenome and thereby be transmitted to future generations. First we will review known mechanisms of transgenerational epigenetic inheritance. Next, we highlight a few recent studies that directly examine potential mechanisms of transgenerational epigenetic inheritance following various environmental stimuli, and lastly we focus on known mechanisms of transmission in preclinical drug addiction studies.

EPIGENETIC MECHANISMS

Epigenetics and genetics work together to provide an integrated mechanism of gene expression. Briefly, chromatin consists of DNA wrapped around octamers of histone proteins. The genomic DNA sequence provides the stable nature of an organism, and the access of transcription factors and basal transcriptional machinery to DNA sequences including promoter regions is

regulated by chromatin structure (Berger, 2007; Li et al., 2007). Chromatin exists in two basic states that are characterized by different levels of condensation. Heterochromatin (condensed chromatin) is associated with inactive gene transcription due to tight packaging of DNA around histone cores, and euchromatin (open chromatin) is associated with active gene transcription due to a more relaxed chromatin structure and accessible DNA sequences (Berger, 2007). The primary epigenetic mechanisms, and the ones discussed in this review, are DNA methylation, histone post-translational modifications, and small noncoding RNAs (see Fig. 1). Together, these modifications alter chromatin structure and gene expression and allow cells to respond and adapt in response to their environments. In addition, epigenetic markers allow for the transmission of gene expression from one cell to its daughter cells. These modifications comprise the epigenome, which is defined as the collection of plastic regulatory mechanisms that are responsive to the environment (Waddington, 1942; Holliday and Pugh, 1975; Skinner, 2011a).

GERMLINE TRANSFER

In general, characteristics are inherited by the transfer of DNA through the germline. However, it is now clear that traits can be inherited through the epigenome as well (Anway et al., 2005, 2006; Guerrero-Bosagna et al., 2010; Danchin et al., 2011; Skinner, 2011a). Until recently, epigenetic modifications were thought to be

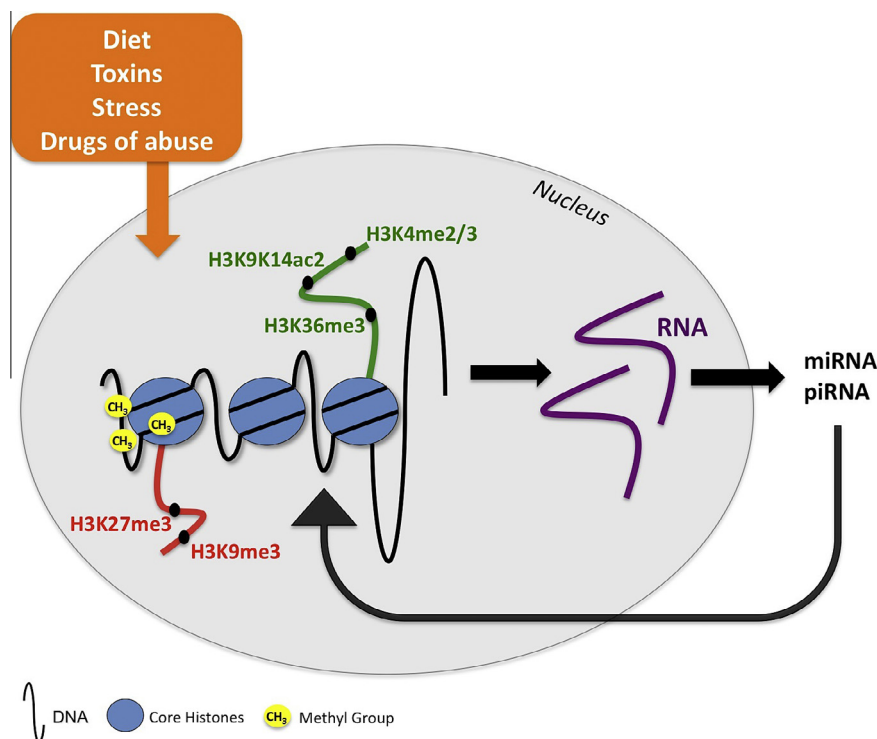


Fig. 1. Schematic representation of the epigenetic mechanisms involved in transgenerational epigenetic inheritance. Environmental stimuli such as diet, toxins, stress, and drugs of abuse lead to epigenetic changes in the germline of the exposed individual that can be transmitted to the subsequent generations. Epigenetic alterations that have thus far been described include changes in DNA methylation (yellow circles with methyl groups); repressive histone marks (H3K9me3, H3K27me3; red); permissive histone marks (H3K4me2/3, H3K9K14ac2, H3K36me3; green), and noncoding RNAs (miRNA, piRNA). Abbreviations: miRNA, microRNAs; piRNA, Piwi-interacting RNAs.

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