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Review

Epigenetic dynamics in psychiatric disorders: Environmental programming of neurodevelopmental processes

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ABSTRACT

Epigenetic processes have profound influence on gene translation and play a key role in embryonic development and tissue type specification. Recent advances in our understanding of epigenetics have pointed out that epigenetic alterations also play an important role in neurodevelopment and may increase the risk to psychiatric disorders.

In addition to genetic regulation of these processes, compelling evidence suggests that environmental conditions produce persistent changes in development through epigenetic mechanisms. Adverse environmental influences in early life such as maternal care, alcohol exposure and prenatal nutrition interact with epigenetic factors and may induce neurodevelopmental disturbances that are related to psychiatric disorders. This review outlines recent findings linking environmentally induced modifications of the epigenome to brain development and psychopathology. Better understanding of these modifications is relevant from the perspective that they may be reversible and, therefore, offer potential for novel treatment strategies. We present the current state of knowledge and show that integrative approaches are necessary to further understand the causal pathways between environmental influences, epigenetic modification, and neuronal function.

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1. Introduction

Development of the central nervous system (CNS) starts early in embryogenesis. Distinct patterns of gene expression lead neural stem cells to differentiate into various types of neurons. Later, molecular signaling cascades guide the formation of neuronal

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circuits that govern endocrine, cognitive, and behavioral functions. Disruption of such regulatory pathways may have pernicious consequences for brain development, thereby increasing susceptibility to psychiatric and other CNS-related disorders in adulthood. Besides genetic factors, environmental influences during critical stages of prenatal and early postnatal periods affect neurodevelopmental processes and mental health, even long after the time of exposure. Given the low rate of evolutionary change in the genome, such influences are largely mediated by processes that do not involve genetic mutations (Colvis et al., 2005). In recent years, epigenetic modifications have been identified as an important mechanism that mediates effects of environmental exposures.

Initially, the field of epigenetics investigated mitotic and meiotic changes in gene transcription that could not be attributed to genetic mechanisms (Bird, 2007). Later, epigenetics also referred to dynamic changes to the epigenome which are not transmitted through the germline. Epigenetic mechanisms produce a wide variety of molecular changes, including DNA methylation of cytosine residues in CpG dinucleotides and post-translational histone modifications (Meaney and Ferguson-Smith, 2010). Both DNA methylation and histone modifications regulate the accessibility of specific DNA regions to transcription factors without altering the genetic code itself. Growing evidence indicates that prenatal and early postnatal environmental conditions can affect epigenetic programming, leading to stable changes in gene transcription. Hence, epigenetic modifications have the potential to mediate long-term effects of environmental exposure on neural gene expression and thus to influence the risk of developing mental disorders (Tsankova et al., 2007).

Here we summarize recent evidence from both animal and human research supporting the view that environmental influences during prenatal and postnatal development are linked to disease phenotypes through epigenetic programming. After a brief outline of epigenetic marks, we review examples of environmental factors which have been found to influence neurodevelopment through epigenetic modifications of the genome and to modulate disease susceptibility in adulthood. Finally, we discuss pathological pathways underlying gene–environment interactions in complex psychiatric disorders.

2. Epigenetic modifications

Epigenetic mechanisms alter gene activity without changing the genetic code of the DNA. There are numerous of such mechanisms, but many are not fully understood to date (for review see Portela and Esteller, 2010). The most extensively studied epigenetic mechanisms are modifications of the chromatin structure and of the DNA itself. The basic chromatin structure is the nucleosome, a DNA section of 147 base pairs wound around a core histone octamer consisting of two copies each of H2A, H2B, H3, and H4. The strength of physical DNA–histone interactions roughly correlates with the accessibility of the genome to transcription factors and thus gene activity. While loosely packed chromatin (euchromatin) favors binding of transcription factors, decondensed forms of chromatin (heterochromatin) tend to inhibit gene transcription (Bannister and Kouzarides, 2011) even though some heterochromatic loci are actively transcribed (Yasuhara and Wakimoto, 2006). In addition, displacement of the nucleosome by ATP-dependent chromatin remodeling complexes influences transcription factor binding and activity of RNA polymerase II (Cairns, 2009). Some of these are cell-type specific as indicated by the BRG1/brm-associated factor (BAF) remodeling complexes, which regulate dendritic cell development and contain neuron-specific subunits (Wu et al., 2007).

Epigenetic marks modulate gene expression either by directly altering the chromatin structure or by creating bindings sites for chromatin and transcription regulatory subunits. This review focuses on the two basic epigenetic mechanisms: post-translational histone modifications and DNA methylation. Other mechanisms, such as transcriptional regulation through non-coding RNAs (ncRNAs) (Zhou et al., 2010) and prion proteins (Halfmann and Lindquist, 2010), have also been identified, but will not be discussed in this review as their functional significance is less well established at this point in time.

2.1. Histone modifications

Histones are composed of a globular core and N- and C-terminal tails protruding from the nucleosomal particle. Post-translational modifications of histones are achieved through enzymes that catalyze chemical modifications of specific amino acids, commonly located within histone tails, including phosphorylation, acetylation, methylation and ubiquitylation (Bannister and Kouzarides, 2011; Berger, 2007). Phosphorylation takes place on serine, threonine, or tyrosine residues of histone tails, and has been associated with both transcriptional activation and repression (Ito, 2007; Wei et al., 1998). During mitosis massive phosphorylation occurs on threonine and serine residues of histone H3 (Pérez-Cadahía et al., 2009). In interphase cells, phosphorylation is more localized and it can serve to inhibit binding of chromatin regulatory proteins or adjacent modifications of the H3 tail (Rossetto et al., 2012; Varier et al., 2010). Ubiquitylation of H2B is associated with transcriptionally active chromatin, whereas H2A ubiquitination mediated by Polycomb complexes is linked to repressive chromatin (Du, 2012). The most comprehensively studied modifications are histone methylation and acetylation. While acetylation marks are recognized for their permissive effect on gene transcription, histone methylation can both result in transcriptional activation and repression, which depends on the position of the lysine acceptor. Histone acetylation marks, which are generated by histone acetyltransferases (HATs) and removed by histone deacetylases (HDACs), mainly occur at the ε-amino group of lysine (K) residues of histones H2A, H2B, H3, and H4, but also within the nucleosome core (Bannister and Kouzarides, 2011). The addition of acetyl reduces the positive charge of histones, which may relax the chromatin structure (Shahbazian and Grunstein, 2007). When HDACs remove acetyl groups, the positive charge of histones increases, which may promote condensation of chromatin (Shahbazian and Grunstein, 2007). More importantly, acetylated histone residues can be recognized by bromo-domains, which are present in many HATs and chromatin remodeling complexes. One example of a bromodomain-containing effector is the SWI2/SNF2 subunit of the SWI/SNF complex, which activates gene transcription by remodeling chromatin in an ATP-dependent manner (Dhalluin et al., 1999; Syntichaki et al., 2000). Recently, small molecule inhibitors of bromodomain proteins binding to acetylated lysines have been identified, which have therapeutic potential for treatment of certain cancers (Prinjha et al., 2012).

Histone methylation is achieved by covalent attachment of methyl groups to lysine (K) or arginine (R) residues, whereby K residues undergo mono-, di-, or trimethylation, while R residues are either mono- or dimethylated (Bannister and Kouzarides, 2011). Arginine methylation is achieved through protein arginine methyltransferases (PRMTs), whereas lysine methylation is catalyzed by histone lysine methyltransferases (KMTs). In general, these KMTs are specific for the K-residue and not all yield the three methylation states (Bannister and Kouzarides, 2011; Martin and Zhang, 2005). With one known exception, DOT1L (DOT1-like) KMT for H3K79, the KMT enzymatic activity is carried by SET-domains.