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REVIEW

EPIGENETIC MECHANISMS IN PUBERTAL BRAIN MATURATION

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Abstract—Puberty is a critical period of development during which the reemergence of gonadotropin-releasing hormone secretion from the hypothalamus triggers a cascade of hormone-dependent processes. Maturation of specific brain regions including the prefrontal cortex occurs during this window, but the complex mechanisms underlying these dynamic changes are not well understood. Particularly, the potential involvement of epigenetics in this programming has been under-examined. The epigenome is known to guide earlier stages of development, and it is similarly poised to regulate vital pubertal-driven brain maturation. Further, as epigenetic machinery is highly environmentally responsive, its involvement may also lend this period of growth to greater vulnerability to external insults, resulting in reprogramming and increased disease risk. Importantly, neuropsychiatric diseases commonly present in individuals during or immediately following puberty, and environmental perturbations including stress may precipitate disease onset by disrupting the normal trajectory of pubertal brain development via epigenetic mechanisms. In this review, we discuss epigenetic processes involved in pubertal brain maturation, the potential points of derailment, and the importance of future studies for understanding this dynamic developmental window and gaining a better understanding of neuropsychiatric disease risk.

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Key words: puberty, adolescence, epigenetics, brain maturation, sex differences.

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INTRODUCTION

The brain undergoes critical organizational changes during the pubertal window, when reemergence of gonadotropin-releasing hormone (GnRH) triggers a cascade of hormone-dependent processes. While previous reports have primarily focused on the classic role of hormones in driving neural and behavioral maturation during puberty, epigenetic mechanisms may also play an important role in guiding pubertal brain development. Further, epigenetic machinery is highly responsive to the environment and therefore may lend to this period of growth a greater vulnerability to external insults. As epidemiological studies demonstrate, individuals who experience early life adversity prior to and during puberty are at increased risk for psychiatric disease, especially affective disorders (Kendler and Eaves, 1986; Kendler et al., 1993; Stein et al., 1996; Wise et al., 2001; Heim et al., 2010; Kendler and Gardner, 2011).

The epigenome has been implicated in development from its earliest phase, as epigenetic stability is globally perturbed when gametes fuse, allowing the newly formed zygote to reacquire totipotency (reviewed in Cantone and Fisher (2013)). Disruption of the normal epigenetic environment during early development has serious consequences, and epigenetic dysfunction is a significant factor in precipitating human genetic disorders (as reviewed in Berdasco and Esteller (2013)). The epigenome is similarly poised during puberty to both regulate development and to potentially affect disease risk, though these regulatory mechanisms of pubertal development are largely understudied. However, recent evidence linking polycomb group protein-driven transcriptional silencing to the timing of

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Abbreviations: AVP, arginine vasopressin; BNST, bed nucleus of the stria terminalis; DNMT, DNA methyltransferase; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; GnRH, gonadotropin-releasing hormone; HDAC, histone deacetylase; HPA, hypothalamic–pituitary–adrenal; miRs, microRNAs; PFC, prefrontal cortex; PN, postnatal day.

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pubertal onset in female rodents offers some insight into the relationship between the epigenome and puberty (Lomniczi et al., 2013). In this review, we focus on the proposed role of epigenetic mechanisms in driving pubertal brain development, both under normal conditions and in the face of external perturbations.

MATURATION OF THE NERVOUS SYSTEM DURING PUBERTY

Following a period of relative quiescence during childhood, massive brain reorganization and maturation occurs during puberty. Typical development of adolescent brain structure and activity has been examined in humans, where puberty is associated with a peak and subsequent decline in cortical gray matter and a continual, though sexually dimorphic, increase in cortical white matter volume, in both the frontal and parietal lobes (Pfefferbaum et al., 1994; Giedd et al., 1999; Perrin et al., 2008). Task-dependent brain activity also changes during adolescence. For example, improved performance on executive function tasks measuring working memory and response inhibition is associated with increased activity in the prefrontal and parietal cortices (Rubia et al., 2000; Luna et al., 2001; Adleman et al., 2002; Kwon et al., 2002). The development of important limbic brain areas, including the prefrontal cortex (PFC), hippocampus, and amygdala, has been demonstrated in animal models as well (Lee et al., 2003; Isgor et al., 2004; Matsuoka et al., 2010; Scherf et al., 2013).

Differences in pubertal brain development between males and females highlight the role of gonadal hormones during this window. Though the sex-specific programing of neural maturation is widespread, the majority of studies examining sex differences during puberty focus on the neural circuitry controlling the activation of reproductive behaviors. Evidence in rats suggests that new cells are added in a sex-dependent manner to brain regions that control reproductive behavior, with more cells being added to the male sexually dimorphic nucleus of the preoptic area and medial amygdala and more cells being added to the female anteroventral periventricular nucleus of the hypothalamus (Ahmed et al., 2008). These sex differences in the number of newly added cells directly correspond to sex differences in adult volume, suggesting that the effects programed during puberty are long lasting. Gonadectomy prior to puberty eliminates such sex differences, indicating that gonadal hormones are key in driving the addition of new cells during puberty that sustain these sexual dimorphisms in adulthood. Studies in sheep have similarly described sex-specific changes in the morphology of specific limbic system brain nuclei during puberty (Nuruddin et al., 2013). Following GnRH release, both male and female sheep show reduced amygdala volume, although this loss is more substantial in females. These changes are dependent upon GnRH action at its receptor, as pharmacological blockade of the hypothalamic–pituitary–gonadal axis via a GnRH agonist results in a larger amygdala volume in both males and females. Together, these data suggest that aspects of normal brain development are dependent upon intact gonadal hormone levels, and represent an important organizational effect of the gonadal hormone surge during puberty.

While it is clear that processes initiated or guided by gonadal hormone action are integral to pubertal maturation, sexually dimorphic physiology and behavior may also originate independent of gonadal hormone levels. Investigation of the role of the sex chromosome complement (XX versus XY) independent of the hormonal milieu has been achieved with the use of the "four core" genotype mice, a line of mice where the testes determining factor gene, Sry, has been transposed onto an autosome, producing gonadal females (XX or XY−Sry, with ovaries) and males (XY or XX+Sry, with testes) (De Vries et al., 2002). Studies in these mice have demonstrated a partial dissociation between the role of sex chromosomes and the action of gonadal hormones in brain maturation and associated behaviors. Sex chromosomes contribute directly to the development of sex differences in the arginine vasopressin (AVP) system, social exploration, and reproductive behavior in adults, as indicated by both male and female XY mice being more masculine than XX mice (De Vries et al., 2002). Gonadal hormones primarily mediate other sexual dimorphisms, including cortical thickness and progesterone receptor expression, as mice with testes, irrespective of sex chromosome complement, are more masculine on these measures than mice with ovaries (Markham et al., 2003; Wagner et al., 2004). In contrast, behaviors such as intruder-directed aggression and maternal pup retrieval are determined by the interaction of both sex chromosome complement and gonadal hormone levels, as females but not males with XX differ from females with XY complement (Gatewood, 2006).

The complex processes guiding both sex-dependent and -independent pubertal maturation require precise chromatin regulation, and therefore suggest underlying epigenetic regulation. Modifications to the epigenome, by affecting gene expression without altering DNA sequence, mediate long-lasting changes in gene transcription and may serve as the link between environmental influences and gene transcription (Jessen and Auger, 2011). The most common epigenetic modifications include methylation of cytosines within CpG islands and histone modifications, chiefly the acetylation or methylation of core histone proteins (McCarthy et al., 2009; Meaney and Ferguson-Smith, 2010). Additionally, small noncoding RNAs, including microRNAs (miRs), are increasingly identified as important epigenetic modulators of neurodevelopment, largely due to their vast post-transcriptional regulation of protein-coding genes (Morgan and Bale, 2012).

Studies focused on the epigenetic control of normal pubertal brain maturation are limited; however, one notable example recently linked pubertal onset in females to methylation-driven epigenetic silencing (Lomniczi et al., 2013). The initiation of puberty in