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The effects of early life stress on the epigenome: From the womb to adulthood and even before

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ABSTRACT

Exposure to early life stress (ELS), such as childhood abuse and neglect is a well established major risk factor for developing psychiatric and behavioral disorders later in life. Both prenatal and postnatal stressors have been shown to have a long-lasting impact on adult pathological states where the type and timing of the stressor are important factors to consider. There is a growing body of evidence suggesting that epigenetic mechanisms play a major role in the biological embedding of ELS. A number of studies now indicate that the epigenome is responsive to external environmental exposures, including the social environment, both during intra-uterine development and after birth. In this review, we summarize the evidence of long-lasting effects of ELS on mental health and behavior and highlight common and distinct epigenetic effects of stress exposure at different stages during development. These stages include postnatal stress, prenatal stress, i.e. in utero and stress occurring pre-conception, i.e. effects of stress exposure transmitted to the next generation. We also delineate the evidence for the possible molecular mechanisms involved in epigenetic programming by ELS and how these maybe distinct, according to the timing of the stress exposure.

Introduction

The early life is one of the most important and sensitive periods during the development of an individual (Lupien et al., 2009). At this stage, the body and especially the brain are known to be greatly responsive to environmental cues since they undergo dynamic changes (Bock et al., 2014). Early life stress (ELS) has been associated with a wide range of health problems later in life such as increase reactivity to stress, cognitive deficits, psychiatric and behavioral disorders (Heim and Binder, 2012; Loman et al., 2010; O'Connor et al., 2005). Both prenatal and postnatal stressors have been shown to have a long-lasting impact on adult psychopathology where the type and timing of the stressor as well as gender, are important moderating factors (Heim and Binder, 2012).

ELS includes various types of stressor that can occur as early as the prenatal period and up to adolescence. In humans, ELS during pregnancy include stressors such as exposure to malnutrition, exogenous glucocorticoids and maternal depression or anxiety whereas postnatal stressors include exposure to maternal postpartum depression or anxiety, child abuse and or neglect, poverty, loss of a parent and exposure to family conflict and violence, all of which have been shown to lead to increased risk for psychiatric disorders in adulthood. In the last decade, there is increasing evidence that epigenetic marks are likely to play a major role in the molecular mechanisms underlying the long-lasting effect of ELS on adult health. Indeed, there is a growing body of evidence suggesting that in addition to its role in cellular programming, the epigenome is also responsive to external environmental exposures including the social environment both during intra-uterine development and after birth in animals (Darnaudery and Maccari, 2008; Gudsnuk and Champagne, 2012) and in humans (Klengel et al., 2014; Mill et al., 2008; Sasaki et al., 2013; Szyf, 2012). This would allow priming future responses of an organism, depending on its early environment.

In this review, we will first describe some of the evidence of the long-lasting effect of ELS on mental health in humans and behavior in animal models. We will illustrate examples where long-lasting epigenetic alterations have been shown to associate with ELS at different stages during development starting with postnatal stress followed by prenatal stress, i.e. in utero and pre-conception stress defined as stress occurring in the previous generation and transmitted to the next generation. Moreover, we will attempt to delineate the possible mechanisms involved in epigenetic programming of ELS and how these may be distinct, depending on the timing of ELS.

Overview of the epigenome

The main function of the epigenome is to regulate gene transcription and compaction of the DNA into the cell nucleus. Several distinct epigenetic marks come together to achieve this, including DNA methylation and hydroxymethylation, histone modifications, ATP-dependent

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chromatin remodeling and non-coding RNAs. Briefly, post-translational modifications of histone tails, such as acetylation, methylation and phosphorylation can be classified as either transcriptionally activating or repressing marks depending on the resulting effect on the compaction of DNA and the recruitment of other protein complexes such as transcription factors and repressors. Alterations in histone acetylation and methylation status have been shown to be induced by adverse environments in animals (Tsankova et al., 2006; Weaver et al., 2004a, 2004b). However, it is believed that since these marks are more transient than other epigenetic modifications, they cannot fully explain the long-term and transgenerational effects of the environmental programming observed following ELS. Interestingly, this hypothesis has been recently challenged by a study by Brunner et al. revealing histone modifications in the sperm that can be stabilized in protamine marks and transmitted to the next generation through the germ line (Brunner et al., 2014). Nonetheless, most studies on the epigenetics of early life stressors in the past have focused on DNA methylation and microRNAs.

DNA methylation is a covalent modification of the cytosine residues that are located primarily but not exclusively at CpG dinucleotide sequences in mammals (Lister et al., 2009; Xie et al., 2012). Increased DNA methylation in the promoter region or in the first exon is usually associated with repressed gene expression (Bird, 1986) whereas DNA methylation located within the gene body, enhancer and intergenic regions (Ball et al., 2009; Lister et al., 2009; Maunakea et al., 2010; Ogoshi et al., 2011) is found to correlate both negatively and positively with gene expression (Jiang et al., 2013; Jjingo et al., 2012; Mehta et al., 2013). In addition to its role in gene expression, genomic DNA methylation also plays an important role in the maintenance of genome integrity and heterochromatin formation (Bestor, 1998; Hedges and Deininger, 2007; Miniou et al., 1994).

The main purpose of DNA methylation and other epigenetic marks is to confer cell-specific gene expression identity that is formed during embryonic development (Lister et al., 2009; Razin and Szyf, 1984; Vire et al., 2006). To accurately maintain the DNA methylation profiles and prevent a drift in the DNA methylation pattern during the life course, several biochemical elements come into play. DNA methyltransferase 1 (DNMT1) maintains the methylation pattern during cell division by copying the parent strand (Bestor, 1998) and DNMT3a and 3b are responsible for active DNA methylation by de novo methylation (Okano et al., 1998). In addition to passive demethylation with cell division, several processes have now been proposed to be responsible for active DNA demethylation, mostly in response to environmental triggers. These include direct action of a demethylase that removes the methyl group from the DNA (Ramchandani et al., 1999) as well as more complex DNA repair-based mechanisms (Barreto et al., 2007; Ma et al., 2009; Morgan et al., 2004; Rai et al., 2008; Schmitz et al., 2009). The more recently discovered 5-hydroxymethylcytosine in stem cells and neurons is proposed to serve as an intermediate modification of 5-methylcytosine, which is catalyzed by ten-eleven translocation (TET) proteins (Kriaucionis and Heintz, 2009; Tahiliani et al., 2009), and leads to replacement by an unmethylated cytosine through nucleotide and/or base excision repair factors (Guo et al., 2011a, 2011b). Hydroxymethylation may not only serve as an intermediate step in active demethylation, but was also proposed to alter gene expression on its own by recruiting transcription regulators (Ficz et al., 2011; Jin et al., 2010; Mellen et al., 2012; Spruijt et al., 2013) or through binding of TET1 (Zhang et al., 2010a, 2010b, 2010c) and/or TET3. Hydroxymethylation was also shown to dynamically mediate behavioral adaptations (Li et al., 2014).

Q6 Another component of the epigenome is the non-coding RNA (ncRNA). ncRNAs were shown to regulate genes translation and transcription as well as chromatin stability (Zhou et al., 2010). Such ncRNAs include short microRNAs, PIWI-interacting RNAs and long non-coding RNAs. ncRNAs can regulate gene expression through post-transcriptional binding to the 3′UTR of mRNA (Filipowicz et al., 2008), by directly binding to promoters and interfering with polymerases (Wassarman and Storz, 2000), or by localizing transcriptionally repressive complexes onto the heterochromatin (Zaratiegui et al., 2007).

It is important to keep in mind that even if these epigenetic components are often studied separately, they interact to exert a combined modulation of gene transcription/translation. These marks can prime not only current but also future gene expression and translation modifications. The true nature of such relationships can only be revealed if longitudinal as well as intergenerational epigenetic studies are conducted in parallel.

Postnatal stress

The importance of postnatal stressful environments on child development is well illustrated in a study performed by Kolominsky et al. who investigated infants whose mothers were exposed to radiation during pregnancy in the atomic accident of Chernobyl in 1985. Surprisingly, researchers found that not the level of exposure to radiation, as anticipated, but rather the mothers' and fathers' level of stress due to evacuation and relocation best explained the infants' psychological symptoms (Kolominsky et al., 1999). While childhood adverse life events include a number of factors ranging from early parental loss to low socioeconomic status, the most profound long-term impact is seen in individuals exposed to childhood abuse and/or neglect. In fact, reports from the World Health Organization (2002) indicate that Q7 about 20% of women and 5–10% of men are exposed to sexual and or physical child abuse and that an approximately 20% of children are neglected worldwide. Child abuse and neglect have been associated with increase risk for developing a range of psychiatric disorders later in life such as mood and anxiety disorders (Heim and Nemeroff, 2001), PTSD (Bremner et al., 1993; Widom, 1999) and antisocial behavior (Rutter, 1998; Widom, 1989). The early programming of systems involved in emotion and stress regulations seem to mediate this increase risk later in life.

Therefore, the most investigated hypothesis on how ELS can alter the child's development in utero and postnatally is that this is mediated by long-term effects of on the function an activity of genes involved in the stress hormone or hypothalamic–pituitary–adrenal (HPA) axis (see Fig. 1). Upon activation of the HPA axis, corticotropin releasing hormone (CRH) and vasopressin are released from the hypothalamus and stimu- Q8 late adrenocorticotropic hormone (ACTH) release from the pituitary into the blood. This results in glucocorticoid (cortisol in humans and corticosterone in rodents) secretion from the adrenal cortex. The main features of the HPA axis are a basal circadian activity rhythm, a negative feedback mechanism moderated by corticosteroids that limit the response of the axis after its activation, and molecular and cellular differences in the response to acute vs. chronic stress. These actions are mediated through binding to the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR) that act as transcription factors and are expressed in most tissues (Larsson et al., 2012; Sanchez et al., 1993). Binding of cortisol to the GR and MR induces their translocation into the nucleus where they can exert their function as transcription factors regulating adaptive responses to stress, including metabolism, immune activation and cell proliferation and differentiation. At multiple levels of the HPA axis, the activation of the GR will initiate a negative feedback loop that is responsible for terminating the stress response and therefore the secretion of cortisol. A decrease in GR expression/activation is generally associated with an increase in the response to stress due to an impaired negative feedback.

Dysregulation of the HPA axis is one of the most robust findings in biological psychiatry. Since the HPA axis is one of the main systems activated after exposure to a stressor, genes regulating this system are prime candidates for epigenetic research on the biological embedding of ELS. The following section will discuss evidence for associations of epigenetic alterations with long-lasting effects of postnatal stress with a focus on key regulator genes of the HPA axis.

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