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Epigenetic marking of the BDNF gene by early-life adverse experiences

Tania L. Roth[1,2] and **J. David Sweatt**[1,*]

[1] Department of Neurobiology and Evelyn F. McKnight Brain Institute, University of Alabama at Birmingham, Birmingham, AL 35294

Abstract

Studies over the past half-century have made it clear that environmental influences in development, particularly stress and traumatic experiences, can remain pervasive across the lifespan. Though it has been hypothesized for some time that the long-term consequences of early-life adversity represent epigenetic influences, it has not been until recently that studies have begun to provide empirical support of experience-driven epigenetic modifications to the genome. Here we focus on this theme, and review current knowledge pertaining to the epigenetics of behavioral development. At the center of our discussion is the brain-derived neurotrophic factor (BDNF) gene, as abnormal BDNF gene activity is a leading etiological hypothesis by which early-life adverse experiences persistently modify brain and behavioral plasticity.

Keywords

early-life experience; abuse; stress; epigenetic; DNA methylation; histone modification; BDNF gene

Introduction

Early-life stress and traumatic experiences are known to promote long-term neurobiological changes. For example, the experiences of childhood abuse and neglect are associated with elevated rates of anxiety, depression, and psychosis (e.g. Bremner, 2003; Heim and Nemeroff, 2001; Kaufman, et al., 2000; Schore, 2002). Imaging studies on adults who report such experiences have identified a number of lasting neural consequences, and suggest that aberrant function and responsiveness of the prefrontal cortex, amygdala, hippocampus, and hypothalamic-pituitary adrenal (HPA) axis likely have some role in the cognitive dysfunction associated with childhood maltreatment (e.g. De Bellis, 2005; Gunnar and Quevedo, 2007; Lupien et al., 2009; Perry, et al., 1995; Teicher, et al., 2003).

Adverse experiences (i.e. social interactions and environmental stressors) in developing rodents and non-human primates are equally associated with behavioral dysfunction, and common behavioral abnormalities include deficits in information processing, impaired

[*]Address correspondence to: J. David Sweatt, Ph.D., University of Alabama at Birmingham, Department of Neurobiology, 1825 University Blvd., SHEL 1010, Birmingham, AL 35294-2182, Phone: (205) 975-5196, Fax: (205) 975-5097, dsweatt@nrc.uab.edu.
[2]Current address: Department of Psychology, University of Delaware, Newark, DE 19716

memory, heightened fear- and anxiety-like behaviors, altered drug-seeking behavior, and social withdrawal (e.g. Gunnar and Quevedo, 2007; Kaffman and Meaney, 2007; Korosi and Baram, 2009; Pryce and Feldon, 2003; Sanchez, 2006). While rodent and non-human primate studies replicate the vulnerability of the prefrontal cortex, amygdala, hippocampus, and HPA axis to early-life adversity, they also highlight the lasting negative impact manifest at the cellular and molecular levels. A number of structural and functional consequences have been identified, and include aberrant synaptic density and structure, altered NMDA-receptor mediated signaling, attenuated neurogenesis, and deficits in synaptic long-term potentiation (Aisa, et al., 2009; Bock, et al., 2005; Brunson, et al., 2005; Fenoglio, et al., 2006; Gruss, et al., 2008; Huot, et al., 2002; Korosi, et al., 2010; Mirescue, et al., 2004).

Altogether, clinical and basic research efforts have made it clear that the developing brain is extraordinarily sensitive to environmental influences and that early-life experiences, particularly those occurring during heightened periods of brain plasticity, help determine life-long structural and functional aspects of brain and behavior. With the renewed interest in understanding the effects of early-life conditions on life-long health and behavior, this has prompted several recent investigations into whether the long-term consequences of early-life adverse conditions reflect sustained CNS gene effects that occurred as result of epigenetic modifications (McGowan, et al., 2008, 2009; Mueller and Bale, 2008; Murgatroyd, et al., 2009; Roth, et al., 2009).

Epigenetics refers to the chemical modifications made to chromatin (DNA and the associated histone proteins) that help regulate transcription of the genome, and at present, DNA methylation has been the most studied epigenetic mechanism in regard to understanding early-life experiences and neurobiological outcomes. DNA methylation is increasingly being recognized for its role in mediating gene-environment interplay throughout the lifespan, as studies have now documented both dynamic (Lubin, et al., 2008; Miller and Sweatt, 2007; Miller, et al., 2008; Penner, et al., in press; Westberry, et al., 2008; Yossifoff, et al., 2008) and stable (Abdomaleky, et al., 2005; Champagne, et al., 2006; Grayson, et al., 2005; McGowan, et al., 2008, [2009]; Mueller and Bale, 2008; Murgatroyd, et al., 2009; Onishchenko, et al., 2008; Roth, et al., 2009; Weaver, et al., 2004) changes in CNS DNA methylation during early development and in adulthood. The stable nature of DNA methylation renders it an ideal substrate for mediating sustained gene effects controlling brain function and behavior. Thus we and others have proposed that the brain and behavioral dysfunction associated with early-life adverse experiences reflects the lasting imprint of such experiences on gene DNA methylation (McGowan, et al., 2008; 2009; Murgatroyd, et al., 2009; Roth, et al., 2009). Here we discuss data from these studies, including our own data demonstrating epigenetic marking of the brain-derived neurotrophic factor (BDNF) gene by adverse social interactions and environmental conditions in early infant development, and the hypothesized neurobiological consequences.

Early-life adversity, BDNF gene expression, and behavioral outcome

Since BDNF's neurotrophic actions are vital for both brain development and plasticity and because BDNF exhibits activity-regulated release in the CNS (e.g. Conner, et al., 1997; Greenberg, et al., 2009; Hennigan, et al., 2007), the BDNF gene has been the focus of numerous developmental studies aimed at understanding the relationship between early-life stress, brain responses, and behavioral outcome. Regardless of the animal model of early-life adversity, studies have consistently indicated that altered behavioral outcomes are well-correlated with stable changes in both BDNF gene transcription and protein expression.

For example, infant mice raised in communal nests where they experience higher levels of maternal care have an increased propensity for social interaction in adulthood that is

correlated with increased hippocampal BDNF protein levels (Branchi, 2009; Branchi, et al. 2006). Bouts of infant isolation from the mother and or nest have been shown to alter an array of behaviors, and in regard to BDNF, most studies indicate that isolation reduces levels of both mRNA and protein in the prefrontal cortex, amygdala, and hippocampus (e.g. Branchi, et al., 2004; Chatterjee, et al., 2007; Choy, et al., 2008; Fumagalli, et al., 2007; Lippman, et al., 2007; Nair, et al., 2007; Zimmerberg, et al., 2009). Other recent studies have demonstrated that adults who were weaned at an early age (at PN14) are more anxious and have increased stress responsivity, effects that are correlated with decreased hippocampal BDNF synthesis (Kikusui, et al., 2009), and that adolescent and adult rats who received less care from the mother have increased anxiety-related behavior that is accompanied by abnormal hippocampal and amygdala BDNF protein levels (Macri, et al., 2009).

Overall, data demonstrate that early-life events influence the BDNF gene and behavioral outcome. Hence aberrant BDNF gene activity continues to receive attention as a candidate molecular mechanism through which early-life adversity is able to produce stable modifications in brain and behavioral plasticity (Alleva and Francia, 2009; Branchi, et al., 2004; Calabrese, et al., 2009; Casey, et al., 2009; Cirulli, et al., 2009; Fumagalli, et al., 2007). It is interesting to note that other neurotrophins, such as nerve growth factor (NGF), may play similar roles (Alleva and Branchi, 2006; Cirulli and Alleva, 2009; Cirulli, et al., 2009). To provide an explanation as to how experiences so early in development are able to successfully influence transcriptional regulation of the BDNF gene and behavior into adulthood, we explored whether epigenetic modifications are involved (Roth, et al., 2009).

Epigenetic modifications regulate CNS gene activity

DNA methylation is the direct covalent modification of DNA, where at least three encoded enzymes known as DNA methyltransferases (DNMTs) are known to catalyze the addition of a -CH_3 group to cytosine residues at the 5-position of the pyrimidine ring (Bird, 2002; Miranda and Jones, 2007). DNA methylation has been recognized for some time for its role in a number of developmental processes and neurodevelopmental disorders that are associated with long-lasting phenotypic changes. These include cellular differentiation, X-chromosome inactivation, Rett syndrome, and Fragile X mental retardation (Amir, et al., 1999; Das, et al., 1997; Yang and Kuroda 2007). The phenotypic outcomes in these examples are due to patterns of DNA methylation that are set very early in development and that remain stable throughout the lifespan. From this, DNA methylation has traditionally been viewed as a static process following neural development and cell differentiation.

If however, DNA methylation is a mechanism contributing to the effects of early-life adversity, DNA methylation and its enzymatic machinery would need to remain labile and capable of responding to environmental factors. Indeed studies continue to challenge the static view of DNA methylation by providing evidence that DNA methylation remains an active process in post-mitotic cells (i.e. neurons). For example, robust levels of DNMTs are present in CNS neurons in the adult brain (Brooks, et al., 1996; Brown, et al., 2008; Goto, et al., 1994). Additionally, evidence continues to mount that changes in gene activity throughout the lifespan as a result of exposure to a variety of environmental factors, including toxins, diet, and stress, involve epigenetic mechanisms (e.g Jirtle and Skinner, 2007; Liu, et al., 2009; Onishchenko, et al., 2008). Furthermore, work continues to indicate that DNA methylation and demethylation can be rapidly and transiently induced in order to dynamically regulate gene transcription even in the adult brain (Levenson, et al., 2006; Lubin, et al., 2008; Miller and Sweatt, 2007; Miller, et al., 2008; Nelson, et al., 2008; Penner, et al., in press; Tian, et al., 2009 Westberry, et al., 2008).

DNA methylation in concert with histone post-translational modifications and their associated enzymatic machinery are increasingly being recognized for their important role in regulating gene transcription in the CNS. Our current understanding is that transcriptionally active genes are characterized by unmethylated cytosines and both histone acetylation and phosphorylation. Acetylation of the lysine residues of histone tails is catalyzed by enzymes known as histone acetyltransferases (HATs). This modification effectively decreases the affinity between the protein tail and DNA, relaxes chromatin, and thus promotes gene transcription (Marmorstein and Trievel, 2009).

Conversely, transcriptionally inactive chromatin is characterized by methylated cytosines and both histone deacetylation and histone methylation (Bird, 2002; Miranda and Jones, 2007). Histone deacetylases (HDACs) catalyze the reversal of histone acetylation (Haberland, et al., 2009), while DNMTs catalyze cytosine methylation. Methylated cytosines in turn bind repressor proteins, including the methyl-binding domain protein MeCP2, as well as HDAC1 (Bird, 2002; Miranda and Jones, 2007). This effectively condenses chromatin and thus suppresses transcription. However, recent studies have suggested that DNA methylation might also be associated with transcriptional activation (Chahrour et al., 2008; Cohen, et al., 2008; Yasui, et al., 2007).

Early-life adversity and epigenetic modifications to the BDNF gene

To determine whether DNA methylation could be a mechanism by which adverse infant experiences render some of their neurobiological consequences, we exposed infant rats to a stressed, “abusive” caregiver for 30 min daily during the first seven days of life (Roth, et al., 2009). We potentiated the maladaptive behaviors from mothers, such as pup dragging and rough handling, by placing them in an unfamiliar environment with limited bedding material. A limited bedding regimen has been used in other laboratories to produce stressful early-life environmental conditions that evoke changes in later behavior, increase levels of the stress hormone corticosterone, and elicit amygdala responsivity (Gilles, et al., 1996, Ivy, et al., 2008; Moriceau, et al., 2009; Roth and Sullivan, 2005). For control conditions, we exposed littermates to either a non-stressed, positive caregiver or kept littermates in the homecage.

At least 3 months following these adverse conditions, rat had significantly lower levels of BDNF mRNA in their prefrontal cortex, an observation well in-line with previous findings where early-life experiences are known to having a lasting impact on this gene. Using a variety of techniques to assess DNA methylation within the prefrontal cortex, adults with adverse experiences during infancy were also found to have hypermethylated BDNF DNA, an effect that for the most part arose in infancy and persisted through adolescence and into adulthood. As depicted in Figure 1, sequencing of an important regulatory region of the BDNF gene (exon IV), revealed that across 12 CG dinucleotide sites within that regulatory region, normal adults (i.e. history of normal infancy) had either no or very little cytosine methylation. This is in sharp contrast to the adults who had experienced the adverse conditions during infancy, where sequencing revealed that those same CG sites were all highly methylated. Overall, our data illustrate that adverse experiences in early development can induce a lasting change in the methylation status of BDNF DNA. Variations in the level of normal maternal behaviors during the first week of life have also been shown to stably modify DNA methylation of the glucocorticoid receptor (GR) and estrogen receptor alpha (ER-alpha) genes such that it alters their gene transcription throughout the lifespan (Champagne, et al., 2006;Weaver, et al., 2004).

In light of our BDNF methylation results, we reasoned that if the observed gene deficits were due to DNA methylation, then a drug capable of reversing DNA methylation levels

should reverse the deficits in BDNF gene expression. To address this hypothesis, we took adult rats that had experienced adverse conditions during infancy and treated them with a demethylating agent called zebularine, a drug recognized for its remarkable ability to reverse DNA methylation in the treatment of cancer (Cheng, et al., 2003; Marquez, et al., 2005). We found that after a 7-day treatment with zebularine, both the aberrant DNA methylation and gene expression patterns incited by early-life adversity had been reversed. Interestingly, we found no effects of the treatment in control animals, indicating a specific interaction with early-life experience.

As discussed in an earlier section, there is ample evidence that early-life adversity produces aberrant BDNF gene activity that is correlated with lasting changes in behavior. We thus aimed to determine whether our early-life experience regimen had likewise affected behavioral outcome. We found that females with a history of infant adversity (maltreated-females) showed the same types of abusive behaviors toward offspring that they themselves had experienced as infants. Lastly, in one final series of experiments, we sought to determine whether the epigenetic modifications could be transmitted across a generation. We found that indeed eight-day-old offspring (both males and females) derived from the maltreated-females had significant methylation of BDNF DNA in their prefrontal cortex and hippocampus in comparison to offspring derived from normal-treated females. Strikingly, cross-fostering experiments (where offspring born to maltreated-females were cross-fostered to normal females and vice versa) allowed us to determine that the transgenerational inheritance was not simply a product of the postnatal experience, but likely reflected some unidentified prenatal component.

In sum, our results demonstrate a remarkable robustness to the experience-driven changes in BDNF DNA methylation by early-life adverse experiences. First, our data indicate that adverse social interactions and environmental conditions during the first week of life can alter cortical BDNF gene expression through epigenetic mechanisms. Second, and perhaps most intriguingly, our results have highlighted an epigenetic molecular mechanism potentially underlying not only lifelong but transgenerational effects incited by early-life adverse conditions. Finally, our results with zebularine indicate that the effects of early-life adversity are potentially modifiable. These latter results dovetail those where HDAC inhibitors have been used successfully to modify epigenetic effects of maternal care on the GR gene (Weaver, et al., 2004, 2005, 2006).

Early-life adversity and epigenetic modifications to other genes

Recent studies have also indicated the ability of early-life adversity to epigenetically mark the DNA of other genes. For example, periodic separation of an infant from the caregiver (3 hr daily; ELS) during early-life induces hypomethylation of the arginine vasopressin (AVP) gene, an effect that coincided with increased corticosterone secretion both at basal conditions and in response to stress, as well as an attenuated memory capacity (Murgatroyd, et al., 2009). A chronic, variable daily stress regimen to pregnant mice during early gestation has been shown to produce a depressive-like phenotype in adult offspring that parallels hypomethylation of specific cytosines with the regulatory regions of the corticotropin-releasing factor (CRF) gene in both the hypothalamus and amygdala (Mueller and Bale, 2008). Finally, hippocampal samples derived from suicide victims with a history of childhood maltreatment (abuse and/or neglect) have decreased levels of GR mRNA that are correlated with increased cytosine methylation (McGowan, et al., 2009). Altogether, evidence continues to mount that both DNA methylation and demethylation at specific gene loci are involved in the neurobiological consequences of adverse early-life experiences (Figure 2). Though the effect of these experiences on histone modifications remains to be

determined, it is likely the case that there is a combination of DNA methylation and histone modifications contributing to the long-term effects.

Concluding remarks

In the previous sections we discussed the data demonstrating that experiences in the immature animal produce lasting changes in behavior, BDNF gene activity, and epigenetic marking of the BDNF gene. The question remains unanswered whether these epigenetic alterations have directly caused the cognitive manifestations of early-life adversity. However, a growing body of literature continues to link epigenetic gene regulation, especially of the BDNF gene, with brain plasticity and cognitive function (Bredy, et al., 2007; Hunter et al., 2009; Levenson, et al., 2006; Lubin, et al., 2008; Tian, et al., 2009; Tsankova, et al., 2006). If epigenetic regulation of genes plays an active process in regulating an animal's ability to respond to and form memories of its environment and experiences, then epigenetic modifications made to genes early in development could have the capacity to subsequently affect cognition. More studies are certainly necessary to provide a definitive link between early-experience-driven gene DNA methylation and behavioral outcome. In addition, as clinical work continues to indicate that there is an interaction between early-life stress, genotype (particularly for BDNF), and neurobehavioral outcome (e.g. Casey, et al., 2009; Caspi, et al., 2002, 2003; Gatt, et al., 2009), it is likely the case that to be in a position to fully understand how early experiences promote long-term changes in brain function and behavior, genetic polymorphisms with experience-driven epigenetic changes will need to be the focus of future work. A better understanding of their interaction holds promise of intervention strategies aimed at reducing the cognitive dysfunction and risk for psychiatric disorders associated with early-life stress and trauma. As a final point, since the effects of stressful and traumatic experiences on neurotrophins are not limited to early development (Alleva and Francia, 2009; Cirulli and Alleva, 2009; Duman and Monteggia, 2006), the characterization of stress-induced epigenetic modifications at these gene loci beyond infancy could provide valuable clues concerning the link between neurotrophins, later-life stress, and psychiatric disorders.

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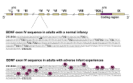

Figure 1.
Epigenetic marking of the BDNF gene by early-life adverse experiences. Top panel – Schematic describing the organization of the rodent BDNF gene, which contains nine non-coding exons and a common coding exon (Aid, et al., 2007; Timmusk, et al., 1993). Asterisks designate promoters, tan boxes represent untranslated regions, and purple boxes represent protein coding regions. Bottom panels – Sequencing analysis in the prefrontal cortex of adults that had experienced favorable social interactions and environmental conditions during infancy revealed little or no cytosine methylation across 12 CG dinucleotide sites examined for BDNF exon IV (sites are numbered and in bold). Conversely, sequencing analysis of adult animals that had been maltreated as infants revealed significant cytosine methylation across the targeted region. Data recreated from Roth, et al., 2009.

Figure 2.

Chromatin remodeling and its proposed role in governing the neurobiological consequences of early-life adverse experiences. Recent evidence indicates that adverse social interactions and stressful experiences early in development epigenetically mark genes in the CNS. Documented epigenetic changes include experience-driven DNA demethylation of the arginine vasopressin (AVP) and corticotropin-releasing factor (CRF) genes, and DNA methylation of the brain-derived neurotrophic factor (BDNF) and glucocorticoid receptor (GR) genes. These changes, along with those presumably occurring at histones, produce a unique epigenetic signature in the CNS that regulates transcription of the genome and influences behavioral output.