



Published in final edited form as:

Int Rev Neurobiol. 2014 ; 115: 1–49. doi:10.1016/B978-0-12-801311-3.00001-9.

Environmental Alterations of Epigenetics Prior to the Birth

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Abstract

The etiology of many brain diseases remains allusive to date after intensive investigation of genomic background and symptomatology from the day of birth. Emerging evidences indicate that a third factor, *epigenetics prior to the birth*, can exert profound influence on the development and functioning of the brain and over many neurodevelopmental syndromes. This chapter reviews how aversive environmental exposure to parents might predispose or increase vulnerability of offspring to neurodevelopmental deficit through alteration of epigenetics. These epigenetic altering environmental factors will be discussed in the category of addictive agents, nutrition or diet, prescriptive medicine, environmental pollutant, and stress. Epigenetic alterations induced by these aversive environmental factors cover all aspects of epigenetics including DNA methylation, histone modification, non-coding RNA, and chromatin modification. Next, the mechanisms how these environmental inputs influence epigenetics will be discussed. Finally, how environmentally altered epigenetic marks affect neurodevelopment is exemplified by the alcohol-induced fetal alcohol syndrome. It is hoped that a thorough understanding of the nature of prenatal epigenetic inputs will enable researchers with a clear vision to better unravel neurodevelopmental deficit, late onset neuropsychiatric diseases, or idiosyncratic mental disorders.

Keywords

DNA methylation; Histone modification; Chromatin; Environmental hazards; Epigenetic medicine; Gene and environmental interaction; Fetal alcohol syndrome

1. INTRODUCTION

Recent progress on epigenetics begins to provide unprecedented insight how the formation of our nervous system is affected by the environmental inputs in life history dated long before birth, or even generations back (Figure 1). These environmental memories are recorded chemically in the form of epigenetic codes, deposited on the top of DNA or histones (for review see (Jaenisch & Bird, 2003; Portela & Esteller, 2010)). Evolutionarily, to avoid endless accumulation of epigenetic marks with each new cycle of life, during formation of zygotes and germ line, most of these memories are erased, but not entirely (Saitou, Kagiwada, & Kurimoto, 2012). Epigenetics codes in the form of DNA methylation, histone tail modification, or chromatin conformation can critically affect gene transcription

by e.g. altering the 3-D DNA conformation to dictate transcription factor binding. Thus, depending on how much altered epigenetic codes are retained within a generation or several generations, this epigenetic memory may affect brain development or functioning through mis-regulation of gene transcription.

There are three categorical stages of life history when epigenetics are registered--- ancestral (including parents), prenatal, and postnatal stages. Among these stages, prenatal epigenetic registration is the most eminent and profound influence on the formation or fine-tuning of the nervous system during development. Thus, environmental inputs prior to the birth have been reported to impose epigenetic entries, many of which are carried throughout the life of somatic cells, including those in the brain. This review will focus on epigenetic influences by various types of environmental factors specifically at prenatal stage. From a clinical point of view, this review advocates that many contributing factors and mechanisms of neurodevelopmental deficit, including late onset mental or psychiatric diseases (e.g. autism or schizophrenia), may have been seeded before birth beyond the default of the parental genetics.

Section 2 is devoted to eminent environmental factors including substances of abuse, prescription medications, pollutants, diets, and stress which are found to alter the epigenetics of offspring of exposed parents; the nature and types of epigenetics altered in the cells and organs will be reviewed. Section 3 elucidates how environmental factors might chemically alter epigenetics; thus leading to a better understanding of how other environmental factors might exert yet to be found influence. Section 4 elaborates that epigenetics evolved during neurodevelopment as an intrinsic program. Environmental factors, by altering epigenetics at individual genes or via the epigenetic program of differentiating neuroprogenitor cells, may alter the course of neurodevelopment. This will be demonstrated using alcohol exposure during pregnancy (fetal alcohol syndrome) as a model. The fetal alcohol syndrome is taken as an example, because it has a systemic influence of epigenetics in every forms and which has been found potentially transgenerational. Further, alcohol is one of the most abused environmental factors which affect men and women at all ages and has been dated back to pre-historical era.

We hope, in the following sections, via the illustration and discussion how the environmental factors long before our birth can be chemically recorded on DNA, histones, and other forms to alter the intrinsic epigenetic program and thereby altering gene expression in canonical neurodevelopment pathways, will increase our awareness and understanding how epigenetic memory pre-recorded prior to the birth might be a important causal predisposition to mental and neurological diseases in the life later.

2. Manifestation of Environmental Factors

This section starts with an illustration of most documented environmental factors that are found to affect epigenetic marks. They are categorized by their nature and ways of accessibility to our system and life, including addictive substances, diet, prescriptive drug, environmental pollutants, and the last but not least -- emotional stress. Their effects on altering epigenetics to affect early neural development start long ago when our parents or

ancestors were subject to aversive environmental exposure. The manifestations of aversive environmental factors are summarized in Table 1 and Figure 2 and briefly discussed below. The current listing is likely the tip of the iceberg as more candidate factors are expected to emerge in the future. Through understanding their nature, we hope to perceive what other environmental factors might be candidate epigenetic modifiers and how they may access epigenetics via common or new mechanisms.

2.1 Substance of abuses

2.1.1 Drinking—Alcohol, like sugar, has been associated with every form of life since the beginning of evolution. Life forms depend on sugar to survive. Since alcohol is not a commodity for survival, evolution has maintained tenacious alcohol-seeking behavior through other means, such as pleasure. If the hedonic propensity does not eternally maintain alcohol-seeking behavior, evolution added another layers of reinforcement -- addiction. Alcohol has been found to instill multiple marks of epigenetic change. The nature and mechanisms of how this ubiquitous molecule can alter epigenetics will be discussed in Section 3, and how alcohol epigenetic changes might affect neurodevelopment manifesting as fetal alcohol spectrum disorder (FASD) will be discussed in Section 4. The following is a list of evident alcohol epigenetic changes. Excessive alcohol drinking not only affects individuals, but has also been known to affect their offspring. Since alcohol is inseparable from life throughout evolution, and alcohol affects life throughout different stages of their development, it is likely through mutations, epimutation and natural selection, the “alcohol” trait may have been genetically incorporated as a genomic signature or recorded on the epigenome as epigenetic memory.

Alcohol exposure during pregnancy can lead to Fetal Alcohol Spectrum Disorder (FASD). Studies have demonstrated that alcohol induces a wide range of epigenetic alterations. Recent reviews illustrate that alcohol is in a unique position to alter multiple levels of epigenetics (Resendiz, Chen, Ozturk, & Zhou, 2013) (Ungerer, Knezovich, & Ramsay, 2013). In essence, excessive alcohol exposure induces DNA methylation changes in sperm, embryos, or developing brain (Garro, McBeth, Lima, & Lieber, 1991; Otero, Thomas, Saski, Xia, & Kelly, 2012; Ouko et al., 2009; Wolff, Kodell, Moore, & Cooney, 1998). At epigenomic level, alcohol induces bi-directional changes of DNA methylation at cytosine (5-methylcytosine;5mC) by both hyper- and hypo-methylation (Liu, Balaraman, Wang, Nephew, & Zhou, 2009; F. C. Zhou et al., 2011a). Alcohol further affects cellular 5mC and the recently found second form of methylation 5-hydroxymethylcytosine (5hmC) (Guo, Su, Zhong, Ming, & Song, 2011; Ito et al., 2011; Kriaucionis & Heintz, 2009; Tahiliani et al., 2009) during embryonic and brain development (Chen, Ozturk, & Zhou, 2013) And, prenatal alcohol interferes the intrinsic DNA methylation program (DMP) (see Section 4) (F. C. Zhou, 2012; F. C. Zhou, Chen, & Love, 2011). Alcohol also increases histone 3 acetylation globally (J. S. Kim & Shukla, 2006; Pal-Bhadra et al., 2007; Shukla, Lee, Park, & Arora, 2007), and alters miRNA expression in neural stem cells in a cell-type and stage specific manner (Miranda, 2012; Wang et al., 2009). Transgenerational epigenetic changes were also found with parental alcohol exposure leading to hypomethylation; specifically at imprinting gene H19 CpGs in F1 generation sperm DNA and F2 offspring brain (Knezovich & Ramsay, 2012) and non-imprinting gene proopiomelanocortin (*Pomc*) over F2 and F3

generations (Govorko, Bekdash, Zhang, & Sarkar, 2012). More studies are being conducted to validate the findings.

2.1.2 Smoking—According to recent Centers for Disease Control and Prevention (CDC)'s surveillance study, 14% of women smoke during pregnancy (Tong, 2013). Maternal smoking during pregnancy significantly affects fetal growth, preterm delivery and infants' long term health (Hackshaw, Rodeck, & Boniface, 2011). Several studies use human placenta to examine epigenetic changes in women smoking during pregnancy and identified genome-wide (Suter et al., 2011) and gene specific (J. Z. Maccani, Koestler, Houseman, Marsit, & Kelsey, 2013) alteration of DNA methylation, as well as reduced miRNA expression (M. A. Maccani et al., 2010). A separate study analyzed buccal cell samples from prenatal tobacco-exposed children and found lower methylation level in the transposable element, *AluYb8*. Alu insertions cause genome instability and has been implicated in disease pathogenesis (Ade, Roy-Engel, & Deininger, 2013; Rowold & Herrera, 2000). Therefore, it would be interesting to see if these methylation changes by nicotine alters the transcription or even transposability of *AluYb8*.

2.1.3. Cocaine—Cocaine abuse in pregnant women is prevalent in the United State and is associated with a wide variety of fetal deficits including premature birth, cardiac defects, attention deficit disorder and so on (Ackerman, Riggins, & Black, 2010; Bae & Zhang, 2005; Frassica, Orav, Walsh, & Lipshultz, 1994; Friedman, 1995; Rotta & Cunha, 2000; H. Zhang, Darwanto, Linkhart, Sowers, & Zhang, 2007). Differential methylation were detected at the CpG islands of selected genes and were correspondingly associated with altered gene expression (Novikova et al., 2008).

For the effect on brain development, several studies looked at epigenetic regulation in cocaine reinforcement and identified brain-derived neurotropic factor (BDNF) as a target of epigenetic modifiers. For example, a self-administration cocaine rat model displayed increased H3 acetylation and decreased methyl CpG binding protein 2 (MeCP2) association with BDNF promoter IV in the medial prefrontal cortex (mPFC) of cocaine treated rats. This is associated with increased BDNF protein expression and *Bdnf* exon IV-containing transcripts (Sadri-Vakili et al., 2010). Whether epigenetic modification is involved in trans-generational behavior alterations is still unknown. Studies are needed to elucidate the phenotypic outcome of cocaine use on brain development. One study showed that while DNA methylation and gene expression profile changed, no phenotypic difference was observed in the hippocampus of early postnatal offspring of the control and cocaine-exposed mothers (Novikova et al., 2008). Another study demonstrated that paternal cocaine administration leads to impaired memory in the female offspring and causes hyperactivity in male offspring (He, Lidow, & Lidow, 2006).

In contrast, the impact of cocaine on fetal cardiac development is better studied. Studies show that pregnant rats exposed to cocaine results in myocardiocyte apoptosis in the term fetal heart (Bae & Zhang, 2005), and disrupted ischemic preconditioning –induced cardioprotection in adult offspring because of reduced protein kinase C ϵ (PKC ϵ) expression (K. D. Meyer, H. Zhang, & L. Zhang, 2009). The same research group further determined

the decreased PKC ϵ expression is associated with increased DNA methylation at the SP1 binding sites in the PKC ϵ promoter that reduced the recruitment of SP1 to PKC ϵ promoter.

2.1.4 Cannabis—Cannabis, the major ingredient in marijuana, is the most common abused drug in pregnant women in the US (Ebrahim, 2003). Following its recent legalization in multiple states of USA in 2013, greater population is expected to expose to this drug. In utero exposure to cannabis has been shown to restrict fetal growth, reduce head circumference (El Marroun et al., 2009), and alter fetal behavior (Day & Richardson, 1991; Huizink, 2013). DiNieri et al. demonstrated the epigenetic relevance of cannabis (DiNieri et al., 2011). They showed dopamine receptor D2 (DRD2) mRNA expression was reduced in human ventral striatum of fetus maternally exposed to cannabis. Using a rat model to further investigate this finding, they reported that decreased *Drd2* is associated with repressive chromatin marks (reduced H3K4, increased H3K9) and decreased Polymerase II binding, suggesting the long-term transcription machinery for *Drd2* was disrupted. Since DRD2 involves in regulation of addiction (Thanos, Michaelides, Umegaki, & Volkow, 2008), this study provides a link between prenatal drug exposure and adulthood addiction through the retention of epigenetic memory.

2.1.5 Opioid—Opium, an old analgesic medication that is highly addictive, has proliferated into many chemical forms and is widely used today. A wide range of drugs fall into the category opioid, including hydrocodone, oxycodone, morphine, tramadol and so on (Abuse, 2011). According to a US multicenter study, approximate 10.7% of 8,527 infants screened were exposed to cocaine or opioid (Lester et al., 2001). It has been shown that prenatal opioid exposure causes more severe phenotype than cocaine exposure on the offspring nervous system (Das, Poole, & Bada, 2004). So far, there is no published report on the epigenetic effect of prenatal exposure to opioid. However, it has been reported that sperm DNA from opioid addicts have increased methylation at the *Opioid receptor, mu1 (OPRM1)* promoter region (Chorbov, Todorov, Lynskey, & Cicero, 2011). *Oprm1* is important for controlling drug dependence through regulating the dopamine pathway (Chefer, Denoroy, Zapata, & Shippenberg, 2009). Taken together, opioid influence could be potentially transmitted through sperm to the next generation.

2.1.6 Methamphetamine (METH)—Methamphetamine (METH) is a stimulant and one of the major abused drugs worldwide. The United Nations Office on Drugs and Crime (<http://www.unodc.org/wdr/en/ats.html>) reported that, globally around 33.8 million people aged 15–64 had used Amphetamine-type stimulants (ATS) in 2011, in which, methamphetamine accounted for 71% of ATS. According to study, 5.2% of women in high METH prevalent region of the US used METH during pregnancy (Arria et al., 2006). Prenatal exposure to METH has been determined to lead to oxidative stress in embryonic brain and postnatal neurodevelopmental, cognitive and behavioral defects (Jeng, Wong, Ting, & Wells, 2005; Kwiatkowski, Roos, Stein, Thomas, & Donald, 2013). Recently, it is demonstrated that differential methylated region (DMR) in hippocampal DNA of adolescent offspring resulted from both prenatal METH exposure and differential maternal care (Itzhak, Ergui, & Young, 2014). The hypermethylated DMRs are enriched for “cerebral cortex GABAergic interneuron differentiation” gene ontology, and the hypomethylated DMRs are

highly associated with “embryonic development”. Furthermore, the exposed F1 male displayed enhanced response to cocaine-conditioned reward and increased locomotion activity, while both F1 male and female show less response to conditioned fear. Together, these data suggest prenatal METH exposure could alter the DNA methylation profile of offspring and lead to abnormal behavior.

2.2. Diet and nutrition

Dietary and nutrition disparity during fetal stage has long been considered as a critical environmental factor, which may exert long lasting effect on development. Emerging evidence indicated that ancestral dietary and nutrition disparity can influence progeny phenotype through epigenetics. Gaining evidence shows specific dietary factors can alter DNA methylation globally and at specific gene levels (demonstrated below). A major entry point to epigenetics is the involvement of these dietary factors in pathways that interact with methyl donor. These factors include alcohol, as previously discussed. Additional elements include folic acid, caffeine, polyphenols, phytoestrogen genistein, and flavonoids. Here, we will discuss folic acid and caffeine as examples and discuss the outcome of maternal folate deficiency and/or caffeine exposure on fetal epigenetics.

2.2.1 Folic acid—Dietary folic acid is recommended for women during pregnancy because of its profound effect on reduced the risk of fetal neural tube defects (Berry et al., 1999; Centers for Disease, 1991). It has been reported that an estimated 50% of women before and 66% during pregnancy have folic acid supplementation (Hoyo et al., 2011). The direct influence of folic acid on epigenetics is through the methionine pathway that generates methyl donor for DNA and histone methylation. Nevertheless, folic acid deficiency has been also related to increased histone deacetylase (HDAC) (Akchiche et al., 2012) and decreased expression of miRNAs that are involved in apoptosis and cell proliferation (Tryndyak, Ross, Beland, & Pogribny, 2009). Gueant *et al.* provided a comprehensive review on folate and fetal epigenetic programming (Gueant, Namour, Gueant-Rodriguez, & Daval, 2013).

2.2.2 Caffeine—Caffeine is the most popular psychoactive substance that can be found in coffee, tea, soft drink, and energy drinks (Frery, Johnson, & Wang, 2005). It is well known that heavy maternal consumption of caffeine is linked to spontaneous abortion, intrauterine growth restriction (IUGR) (Kuczkowski, 2009), as well as fetal neurodevelopmental and behavioral deficits (Browne, 2006; Nehlig & Debry, 1994). Recent studies have started to look at its impact on epigenetics Xu et al. (2012) showed that DNA methylation was increased in the *11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD-2)* promoter in fetal hippocampal neuron from a rat model *in utero* exposure to caffeine. An increase of *11 β -HSD-2* methylation is correlated with reduced *11 β -HSD-2* expressions. *11 β -HSD-2* is known to catalyze the conversion of cortisol to cortisone. Reduced levels of placental *11 β -HSD-2* may lead to an increased exposure of glucocorticoid in fetus. Therefore, these data suggested that cocaine retards fetal development through epigenetic programming of the hypothalamus-pituitary-adrenal (HPA) via the *11 β -HSD-2* gene.

2.3. Prescriptive medicine

A number of prescriptive medications have been found to have the side effect of directly changing epigenetics, and through which to affect development, particularly neurodevelopment. Many of them are no longer used in clinic practice, but medications with similar chemical and physical properties are being introduced by pharmaceutical industry. It is important to raise awareness in this category.

2.3.1 Valproic acid (VPA)—Valproic acid is a widely used antiepileptic drug for the treatment of seizures and bipolar disorder (Loscher, 2002). Several studies demonstrated higher risks with VPA (~10% infant growth defect) than use with other drugs (2.8%) during the first trimester of pregnancy (Wyszynski et al., 2005), indicating the potency of VPA on fetal development. It is also an inhibitor of histone deacetylase (HDAC) (Gottlicher et al., 2001). Due to this effect, VPA treatment in human embryonic stem (ES) cells caused global genomic increase of H3 acetylation, while genes disrupting acetylation were down-regulated. Furthermore, VPA inhibited ES cell differentiation into neuronal precursor cell (Balmer et al., 2012), suggesting early neural fate decision is disturbed.

2.3.2 γ -hydroxybutyrate (GHB)—GHB is an endogenous inhibitory transmitter in human (Nelson, Kaufman, Kline, & Sokoloff, 1981) and is used in anesthesia, insomnia, and depression treatment (Mamelak, Scharf, & Woods, 1986). Despite its medical application, GHB has been abused for more than 20 years and commonly known as a “date-rape drug” or a “party drug” (O’Connell, Kaye, & Plosay, 2000). To date, teratogenic effect has not been reported for GHB. A woman addicted to GHB gave birth to a healthy full term baby (Buonocore, Bracci, & Weindling, 2010). However, several studies have revealed its function in regulating epigenetic modification (C. Klein, Kemmel, Taleb, Aunis, & Maitre, 2009; Q. Lu et al., 2004). GHB has been shown to inhibit histone deacetylase, leading to accumulation of acetylated histones in adult rat brain after administration of pharmacological dose of GHB (C. Klein et al., 2009). Studies are needed to determine the effects of GHB prenatal exposure on fetal epigenetic, postnatal neurodevelopment and behavior change.

2.4. Environmental toxins and pollutants

This category of environmental factors represents the largest group, and ever-increasing candidates are being found.

2.4.1 Arsenic—Arsenic is one of the major pollutants in drinking water worldwide, especially in Bangladesh, India, China and Taiwan (Meharg, 2005). It has been linked with multiple types of cancer by epidemiologic evidence (Celik et al., 2008; Straif et al., 2009). Several studies identified Arsenic effect on epigenetics in somatic cells. A detailed review of these studies can be found in Reichard and Puga (Reichard & Puga, 2010). It is now known that the epigenetic influence by arsenic can be transmitted to the next generation. Fetal brain samples of prenatal arsenic exposed mice showed global reduction of acetylation at H3K9, while adult exposure displayed impaired memory and fear conditioning performance. (Cronican et al., 2013). Cord blood samples from arsenic exposed human maintained higher amounts of arsenic and revealed aberrant DNA methylation in a gene specific manner (Kile

et al., 2012; Koestler, Avissar-Whiting, Houseman, Karagas, & Marsit, 2013). Furthermore, miRNAs with increased expression associated with higher urine arsenic have been identified (Rager et al., 2013). However, how these epigenetic changes correlate with previously identified disrupted fetal neuronal development (Chattopadhyay, Bhaumik, Nag Chaudhury, & Das Gupta, 2002) still needs to be explored.

2.4.2 Lead—Lead toxicity causes significant health problems in the US and worldwide. More than 250,000 children age before 5 years have higher blood lead levels than the CDC reference level based on a 2012 report from the CDC (Kuehn, 2012). Prenatal exposure to lead interrupts neuronal development plasticity, especially to the rapid growing neonatal brain (Bellinger, 2005; T. Sanders, Liu, Buchner, & Tchounwou, 2009; White et al., 2007). Therefore, it is important to know the mechanisms for lead neurotoxicity. The effects of lead on epigenetics is mostly associated with aberrant DNA methylation and altered expression of methylation-associated enzymes such as DNMTs and MECP2 (Bihaqi, Huang, Wu, & Zawia, 2011; Pilsner et al., 2009; Schneider, Kidd, & Anderson, 2013) although the reason still needs to be elucidated. Senut et al. provided a detailed review on lead exposure and epigenetics of fetal brain development (Senut et al., 2012).

2.4.3 Cadmium—Cadmium exposure is mostly through consumption of vegetables, drinking water, seafood, and through tobacco smoking that has severe impacts on global human health (Olsson et al., 2002). Prenatal exposure to cadmium has been shown to lead to altered thymocyte development (Hanson, Brundage, Schafer, Tou, & Barnett, 2010), aberrant immune response (Holaskova, Elliott, Hanson, Schafer, & Barnett, 2012), and decreased birth weight in a sex-specific manner (Kippler et al., 2013). The sex-specific toxicity is also correlated with differential methylation between girls and boys based on cord blood sample from exposed newborns and blood from 4–5 year children of Bangladesh (Kippler et al., 2013). A similar study conducted in the US also identified differential methylated genes in leukocytes from mother-baby pairs (A. P. Sanders et al., 2013). Interestingly, those genes set were largely distinct between maternal and fetal DNA, indicating different pathways are misregulated between mother and children.

2.4.4 Methyl mercury—Human exposure to methyl mercury (MeHg) is mostly through the consumption of ocean fish (Mergler et al., 2007). Therefore, high levels of MeHg exposure can be found in fish-eating population throughout the world, including people in the United States, Japan, Germany, (Pirrone & Mahaffey, 2005). For example, about 5–10% of women of childbearing age in the US have exceeding levels of MeHg (McDowell et al., 2004), and 73.7% of women in Japan of this age are exposed to high levels of MeHg (Yasutake A, 2004). It is known that MeHg can be transferred from the mother to fetus via neutral amino acid transportation across the placenta (Kajiwara, Yasutake, Adachi, & Hirayama, 1996). Neonatal and infants expose to MeHg by intake of milk from the mother. Prenatal exposure to MeHg lead to severe fetal neurological disorders including cerebral palsy, mental retardation, primitive reflexes, dysarthria, and hyperkinesia (Harada, 1995; Marsh et al., 1980; Myers & Davidson, 1998). Several studies have been performed to tease out the effects MeHg exposure on fetal epigenetics. An animal study exposed mice to MeHg from embryonic day 7 (E7) to postnatal day 7 (P7) found the offspring at 12-week old

exhibited repressed chromatin marks (DNA hypermethylation, decreased histone acetylation, increased H3K27 trimethylation) at the *Bdnf* promoter IV (Onishchenko, Karpova, Sabri, Castren, & Ceccatelli, 2008). This altered epigenetic states was associated with decreased *Bdnf* expression and depression like behavior. Furthermore, they showed that fluoxetine (an antidepressant) treatment altered depression behavior, restored *Bdnf* expression, and increased H3 acetylation (Onishchenko et al., 2008). A different study revealed MeHg inhibited neural stem cell proliferation and induced senescence-associated markers. This decreased cell proliferation phenotype was confirmed in the subgranular zone in the hippocampi of adult mice prenatally exposed to low doses of MeHg (Bose, Onishchenko, Edoff, Janson Lang, & Ceccatelli, 2012). In addition, global DNA methylation and *Dnmt3b* expression were decreased in the parental NSC exposed to MeHg and in the daughter cell under MeHg free condition.

2.4.5 Bisphenol A (BPA)—Bisphenol A is widely used for plastic bottle, protective lining of metal-based food and beverage containers. Laboratory studies showed that adulthood BPA exposure affects normal neurodevelopment, sexually dimorphic behaviors, and hyperactivity disorder (Palanza, Gioiosa, vom Saal, & Parmigiani, 2008; vom Saal et al., 2007). Prenatal exposures to low doses of BPA lead to acceleration of neurogenesis and aberrant neuronal migration (Nakamura et al., 2006). From the epigenetic perspective, prenatal BPA exposure altered DNA methylation both gene-specifically (Yeo et al., 2013) and globally, but in a dose dependent manner (J. H. Kim et al., 2014). Yeo et al. showed that BPA induced MECP2 association and reduced H3K9 acetylation at the potassium chloride cotransporter 2 (*Kcc2*) promoter, which is associated with decreased *Kcc2* expression and leading to delayed perinatal chloride shift in the cortical neurons. Their result provides a possible explanation for the epigenetic mechanism of neurotoxicity due to BPA exposure.

Many new environmental hazards have suspected to affect biological response through altering epigenetics, including nickel (Zoroddu et al., 2010), chromium (X. Zhou, Li, Arita, Sun, & Costa, 2009), plastic derived endocrine disruptor [Bis(2-ethylhexyl) phthalate, dibutyl phthalate] (Manikkam, Tracey, Guerrero-Bosagna, & Skinner, 2013), but their prenatal effects particularly in neurodevelopment still need to be elucidated.

E. Stress and Aversive Life Experience

Parental emotional stress has been known to impact the emotional abnormality and behavioral development of offspring. For example, studies show that maternal post-traumatic stress disorder (PTSD) can be transmitted across generations (Yehuda & Bierer, 2008; Yehuda, Schmeidler, Wainberg, Binder-Brynes, & Duvdevani, 1998) and is associated with dysregulation of neurobiological systems, such as the hypothalamus-pituitary- adrenal (HPA) axis (Boscarino, 1996; Mason, Giller, Kosten, Ostroff, & Podd, 1986; McGowan, 2013). Stress is implicated in the development of mental disorders and other adverse outcomes such as low birth weight (Reed, 2012), poor maternal-infant bonding (Muzik, Marcus, & Flynn, 2009), and infant sleep and behavioral problems at 18 months (Hairston et al., 2011).

Maternal PTSD (McGowan, 2013), maternal separation (Lewis, Staudinger, Scheck, & Olive, 2013), depression (Dalton, Kolshus, & McLoughlin, 2014; Heim & Binder, 2012), maternal care (Champagne & Curley, 2009), childhood adversity or early life stress (Franklin et al., 2010; Murgatroyd et al., 2009; Roth, Lubin, Funk, & Sweatt, 2009), and paternal stress (Rodgers, Morgan, Bronson, Revello, & Bale, 2013), are environmental inputs that have been shown to affect the epigenetic profile of the offspring. The most prominent mechanism for trans-generational epigenetic regulation in response to prenatal stress is via the hypothalamic-pituitary-adrenal (HPA) axis. It is known that changes in glucocorticoid levels influence the HPA axis as well as alter fetal brain development. In addition, altered cortisol levels are associated with changes in glucocorticoid receptor activity (Matthews, 2002). Indeed, glucocorticoid receptor (GR) gene (*Nr3c1*) has altered DNA methylation and gene expression in several human studies and animal models after prenatal exposure to stress (Hompes et al., 2013; McGowan et al., 2009; Oberlander et al., 2008; Tyrka, Price, Marsit, Walters, & Carpenter, 2012). Epigenetic changes in genes other than *Nr3c1* have also been reported. For example, increased *miR-16* expression (Bai et al., 2012) and increased promoter DNA methylation of *BDNF* (Roth et al., 2009) were found in separate studies, but both changes result in a reduction in brain derived neurotrophic factor (*BDNF*) mRNA expression, suggesting *BDNF* may play a role in regulating offspring behavior in response to prenatal stress exposure.

3. Mechanisms of Environmentally Induced Epigenetic Changes

In this section, the epigenetic mechanisms mediated by prenatal exposure to environmental deleterious factors is discussed based on epigenetic categories (Figure 3), as well as giving examples of altered genes associated with epigenetic changes (Table 2).

3.1. On DNA methylation

Alterations in DNA methylation are the most common type of epigenetic change that is found upon prenatal exposure to hazardous environmental agents. One of the key causal reasons is availability of methyl donor within the cellular environment. Alcohol, dietary folate, and arsenic directly regulate methylation through the alteration of the methionine pathway. Methionine is the precursor of an active methyl donor, *S*-adenosylmethionine (SAM). Alcohol has been shown to have multiple effects on methionine synthesis through inhibiting metabolic enzymes (Halsted et al., 1996), and methionine adenosyltransferase (MAT) (S. C. Lu et al., 2000). Dietary folate is a cofactor of methionine synthase, which converts homocysteine to methionine. Moreover, arsenic, which is a widespread source of contamination in drinking water, consumes SAM and glutathione to produce dimethylarsenic acid for detoxification and facilitating excretion (Drobna et al., 2005). The second causal alteration of DNA methylation is through regulating the expression of DNA methyltransferases (DNMTs). This has been found in a number of studies that exposed fetus to lead (Bihaqi et al., 2011) (Schneider et al., 2013), MeHg (Bose et al., 2012), and alcohol (Govorko et al., 2012; Perkinsa, Lehmann, Lawrence, & Kelly, 2013).

Alterations of DNA methylation are dynamic and stage dependent, and they occur both globally and gene specifically. For example, Novikova *et al.* used a mouse model to demonstrate the effects of maternal cocaine exposure during the second and third trimester

and showed that global DNA methylation was decreased in hippocampal pyramidal neurons at postnatal day 3 (P3) but increased at P30 of the male offspring exposed to cocaine (Novikova et al., 2008). When examining gene specific methylation change, they found more CGI (CG island) and repetitive elements were hypomethylated at P3 and less CGI-associated promoters showed altered methylation state at P30. These results suggest that maternal cocaine exposure affects the offspring not only at the newborn stage but persists into prepubertal period, although the effect may be reduced during development.

The DNA methylation changes recorded in the epigenome can be carried in germ cells and if escaped from erasure can be transmitted to next generation. A well-documented case reported that the DNA methylation and disease states caused by the insecticide Vinclozolin were transmitted across 3–4 generations through sperm epigenetic mechanisms (Anway, Leathers, & Skinner, 2006; Skinner, Anway, Savenkova, Gore, & Crews, 2008). Another study looked at early life stress and its transmissible impacts and provided evidence that stress-induced epigenetic memory is retainable across generations (Franklin et al., 2010). This study showed that maternal separation in F0 animals leads to altered promoter methylation of *Mecp2*, *CBI*, and *Crfr2* in the F1 and F2 sperm, and in F2 female brain as well as persistent behavioral change. The altered methylation was also associated with changes in gene expression (Franklin et al., 2010).

3.2. On Histone modification

The second most common altered epigenetic mark is histone modification. This includes histone acetylation, methylation, and other types of modification on different residues of histone subunits. Histone acetylation is generally considered as an open chromatin mark, while histone methylation could be either an open or condensed mark depending on the residue of methylation. For example, H3K4 methylation is considered as a gene activation signal, whereas H3K9 and H3K27 methylation is correlated with transcription repression (Y. Zhang & Reinberg, 2001).

Many of the environmental factors affect chromatin structure through direct interaction with enzymes that modified histone codes. The most prominent one is inhibition of histone deacetylase (HDAC) or histone acetyl transferase (HAT). For example, Valproic acid (VPA) and Trichostatin A (TSA; antifungal antibiotic) are well-known histone deacetylase (HDAC) inhibitors (Gottlicher et al., 2001; Vigushin et al., 2001). Previously, γ -hydroxybutyrate (GHB), which is structurally related to VPA and TSA, has also been classified as a HDAC inhibitor by increasing histone acetylation and reducing HDAC activity (C. Klein et al., 2009). Not only do these HDAC inhibitors lead to a global increase of H3 acetylation, but also indirectly increase the ratio of H3K4me3/H3K27me3, and to down-regulate genes that suppress acetylation (Balmer et al., 2012; Gurvich et al., 2005; C. Klein et al., 2009). The third mechanism is the alteration of synthesis of the enzymes that modify histone code. For example, alcohol has been shown to reduce the level of histone acetyltransferase and lead to decreased H3 and H4 acetylation in a rat FASD model (W. Guo et al., 2011).

3.3. On miRNA and other non-coding RNA

Other than DNA methylation and histone code, differential expression or methylation of miRNA and long non-coding RNA (ncRNA) has also been associated with prenatal exposure to alcohol, nicotine, arsenic and emotional stress (Dalton et al., 2014; M. A. Maccani et al., 2010; Rager et al., 2013). However, the direct causal mechanism on changes to these non-coding RNA is largely unclear. The known causes are alterations of DNA methylation on non-coding regions (Chen, Shin, Thamocharan, & Devaskar, 2014; Laufer et al., 2013) or alterations of RNA methylation on these non-coding RNAs (Xhemalce, Robson, & Kouzarides, 2012). For example, Laufer et al. identified ncRNAs that harbor differential DNA methylation and have altered ncRNA expression resulting from fetal alcohol exposure. Interestingly, some of these ncRNAs colocalize with imprinting regions that are related to neurological disorders (Laufer et al., 2013). It is proposed that increased promoter methylation for these ncRNAs link to decreased expression of ncRNAs (Vrba, Munoz-Rodriguez, Stampfer, & Futscher, 2013), similar to the general central dogma of gene regulation by DNA methylation. Additionally, a class of miRNAs contains upstream RE1 silencing transcription factor (REST) elements to regulate the miRNA expression (Fineberg, Kosik, & Davidson, 2009). Furthermore, some of the REST containing miRNAs also reciprocally target the REST complexes such as MeCP2 (Conaco, Otto, Han, & Mandel, 2006). Therefore, miRNAs and the REST complexes form a feedback loop to regulate each other (M. E. Klein et al., 2007; Yamakuchi & Lowenstein, 2009). For instance, MeCP2 induces *miR-132* transcription by activating the neurotropic factor (BDNF), which promotes *miR-132* expression. However, *miR-132* also targets the long 3'UTR of MeCP2 transcripts, which is specifically present in differentiated neural tissue but not other tissues (M. E. Klein et al., 2007). Therefore, *miR-132* regulates the translation of MeCP2 and their interaction control the balanced production at both sides in a tissue-specific manner.

3.4. On Transposable elements

Transposable elements (TEs) are repetitive and movable DNA sequences that are also called “jumping genes” for their ability to move and insert into the genome (Ade et al., 2013; Chenais, Caruso, Hiard, & Casse, 2012; Rowold & Herrera, 2000). Two of the most abundant transposable elements are the non-Long terminal repeat element Long Interspersed Elements-1 (LINE-1) and the nonautonomous Short Interspersed Elements Alu elements, which account for 42% of all TEs in the human genome (Lander et al., 2001). The richness of LINE-1 and Alu elements commonly lead to non-allelic homologous recombination that further induce genomic instability such as deletion/insertion, translocation, inversion or duplication (Konkel & Batzer, 2010).

Similar to non-coding RNA, one known mechanism for regulating transposable element is through DNA methylation (Chenais et al., 2012; Reiss, Zhang, Rouhi, Reuter, & Mager, 2010). Indeed, alterations of LINE-1 and Alu at methylation levels have been reported in several studies of prenatal exposure to deleterious factors such as alcohol (Wilhelm-Benartzi et al., 2012), smoking (Breton et al., 2009) and arsenic (Intarasunanont et al., 2012). For example, human placenta of maternal alcohol and nicotine-exposed fetus harbor differential methylation on *LINE-1* and *AluYb8* elements (Wilhelm-Benartzi et al., 2012). The reason why differential methylation of TEs is measured with fetal alcohol versus smoking exposure

is still unknown. However, it has been shown in plants that methylation of TE inhibits transposition (Hollister & Gaut, 2009). Therefore, is it possible that TE methylation in response to prenatal environmental exposure alters genomic stability introduced by TE transposition. This altered genomic stability further determines the intrinsic genetic regulation response to external exposure.

4. Effect of Epigenetic Alterations on Neurodevelopment

4.1. Epigenetic Functional Concerns

How environmental factors change epigenetics to alter the neurodevelopment and function of the nervous system are core interests of biologists and clinicians. It should be noted first that many of the epigenetic changes may remain silent. However, epigenetic alteration can be accumulated over life, thus inherited and acquired epigenetic changes can reach the critical mass that tips the balance of DNA methylation or histone modification, leading to compaction or relaxation of the 3-D DNA conformation and changing the accessibility of the transcription factors. This may be relevant clinically to late onset disease, or idiosyncratic psychiatric disorders. Second, it is still yet to be elucidated what level and what loci of the epigenetic changes entail a transcriptional transformation, e.g. how may CpG methylation changes and their distance to the transcription action center affect gene expression. Current attention focuses in promoter regions where particularly functional transcription factors or other collaborative epigenetic complexes reside. However emerging understanding of the distribution and role of the epigenetic marks expand the horizons of the epicenters, such as enhancer, silencer, and alternative splicing determination sites. Further, new epigenetic functional roles are derived from the recent understanding of dynamics and diversity of the two DNA methylation forms. Although 5mC's association with suppression of transcription is well accepted, the role of recently found 5hmC was ambivalent at the time of discovery (Bhutani, Burns, & Blau, 2011) and was considered an intermediate state of demethylation. We have recently reported that 5hmC is not an intermediate product but remains throughout life in the brain (Chen, Damayanti, Irudayaraj, Dunn, & Zhou, 2014). Recent research has begun to shed some light on the potential role of 5hmC. It has been found that 5mC and 5hmC, are diversely distributed in the genome where 5mC occurs preferentially in the promoter/enhancer regions, while 5hmC is increased in the intragenic gene body regions of genes undergoing active transcription in mouse embryonic stem (ES) cells (Stroud, Feng, Morey Kinney, Pradhan, & Jacobsen, 2011; Wu et al., 2011; Yildirim et al., 2011) and mouse cerebellum (J. U. Guo et al., 2011; Pastor et al., 2011; Wu et al., 2011). 5mC and 5hmC are also distributed in proximity to different categories of histone codes respectively, in ES cells (Pastor et al., 2011; Stroud et al., 2011; Williams et al., 2011; Y. Xu et al., 2011). We further demonstrated that 5mC and 5hmC are differentially associated with euchromatin versus heterochromatin. During neural development in early brain formation, 5mC preferentially binds to MBD1 and MeCP2 colocalizes with histone H3K9 trimethylation (H3K9me3) and H3K27me3, and is ultimately packed into heterochromatin during and after neural differentiation. 5mC is likely to organize a more selective transcription during differentiation (Chen, Damayanti, et al., 2014). In contrast, 5hmC preferentially binds to MBD3, colocalized with the euchromatin histone H3K4me2, and gradually translocates to the euchromatin, which demonstrates a transition to transcription

needed for differentiation. Thus, 5mC and 5hmC are each functionally unique in the epigenetic landscape. This additional layer of complexity in the epigenome is more efficient when driving the complex journey of development, as well as more responsive to environmental inputs (Chen et al., 2013; Resendiz et al., 2013; F. C. Zhou, 2012). Perhaps the most conclusive evidence that we have observed is the co-localization of 5hmC with *Po/III* in the euchromatin regions throughout neuronal differentiation, and the transient and complete dissociation of 5mC and *Po/III* throughout chromatin in nucleus (Chen, Damayanti, et al., 2014).

4.2. Intrinsic Epigenetic Program

DNA methylation, throughout development, is not static or random, but rather “orderly” with a clear pattern. This orderly pattern is preserved over evolutionary time. Such an evolving epigenetic pattern that constitutes a “memory” (Bird, 2002) may be a way for maintenance of stable cellular identities (De Carvalho, You, & Jones, 2010; Deaton & Bird, 2011). The DNA methylation dynamics are observed as early as zygote formation by starting with global demethylation to the entire genome except the silenced X chromosome (Saitou et al., 2012), and from here a new wave of DNA methylation re-establishes methylation selectively among house keeping and tissue specific gene cohorts. This orderly methylation of gene cohorts has been hypothesized as a driving force for directing cellular restriction spatiotemporally in tissue and organ development. This orderly DNA methylation transformation during tissue or organ development is referred to here as *DNA methylation program* (DMP) [reviewed see (F. C. Zhou, 2012)].

During early neural tube development, the DNA methylation and demethylation are dynamically progressing along with neural differentiation (Figure 4). Many of the neuroprogenitor cells near the ventricle bear low level of DNA methylation marks. The neural tubes expand their cell number through proliferation but with absence of DNMTs. Thus, new born cells do not bear much DNA methylation in actively proliferating ventricular zone and dorsal neural tube (F. C. Zhou et al., 2011). They acquire DNA methylation of both 5mC and 5hmC when the proliferation ceases, to begin their restriction (cell fate progression), and head for migration. The 5mC and 5hmC within the nuclei are initially distributed diffusely, but gradually polarize as the precursor cells differentiate and migrate. The 5mC-rich chromatin and 5hmC-rich chromatin become mosaic and correspond to the heterochromatic (DAPI-dense) and the euchromatic (DAPI-sparse) compartments respectively, within the nuclei (Chen, Damayanti, et al., 2014). The DNA methyltransferase 1 and 3 (DNMT1 and 3) escalate in parallel with these DNA methylations. The appearance of 5hmC and demethylation are accompanied with the enzyme ten-eleven transferase (Tet1/2). The DNA methylation binding protein e.g. MBD1 appears 1–2 days (in mouse) after the arrival of 5mC and 5hmC (F. C. Zhou et al., 2011). The demethylation into 5-carboxylcytosine (5caC) and 5-formylcytosine (5fC) were also found days (in mouse) after the 5hmC. Thus, at neurulation-stage, 5mC, 5hmC, MBD1, and DNMT1 exhibited a distinct temporal DMP pattern that coincided with neural differentiation in the neural tube (F. C. Zhou et al., 2011). In spatial pattern, as the neural tube develops in the AP-axis, the brainstem differentiation progresses first and progresses rostrally and caudally -- the DMP follow the progression of the neural axis. In the dorsoventral division, the ventralis

differentiates earlier than the dorsalis, so as the DMP. DNMT is similarly distributed to 5mC spatiotemporally in neural axial and dorso-ventral patterns (F. C. Zhou et al., 2011). MBD1 shows a similar dorso-ventral pattern to that of 5mC but appears a day late in gestation. The progression of the DMP is demonstrated genome-wide. During neural stem cell differentiation, a signature epigenomic program is diversification of DNA methylation, in which many moderately methylated genes became hypo- and hyper-methylated (F. C. Zhou et al., 2011a). This is consistent with the understanding that many multipotent genes were turned off, e.g. *Oct 4*; and many cell specific genes were turned on, e.g. *MAP2* (F. C. Zhou et al., 2011a).

As the neural tube vesicles turn into brain regions, the cellular 5mC and 5hmC are highly correlated with the neural progenitor cells and their progression during differentiation throughout brain regions. Similar to the neural tube, throughout developing brain where neuroprogenitor cells are differentiating, 5mC appears first followed by 5hmC. As the DMP progresses further, many of the differentiating neurons containing a high level of DNA methylation will lose their 5mC and 5hmC after arriving in target regions of the brain when transitioning to active wiring and synaptogenesis. It is also apparent that the DNA demethylation marks, 5caC and 5fC, have existed along with the brain formation. This methylation and demethylation cycle can repeat over the progression of differentiation. The progression of DMP is cell stage-dependent. Thus, within a brain region, the late differentiating neuroprogenitor cells initiate the early DMP while the more differentiated neurons advance further in DMP. This is demonstrated in the hippocampus during early development where newly arrived neurons are distributed in orderly layers (Chen et al., 2013). This indicates that DMP includes DNA methylation and demethylation, which are prevailing throughout brain development. This likely explains the active repression, e.g. cell cycle genes, or multipotent genes *Nanog* and *Oct4*, and activation of neural determining or differentiation gene cohorts, e.g. *Ascl1*, *Ngn1*, and *Sox1*.

5hmC also demonstrates an epigenomic change in the developing hippocampus and cerebellum. When comparing early postnatal and one-year-old mice, it was found that the acquisition of 5hmC was developmentally programmed (Szulwach et al., 2011). As elucidated earlier, the correlation of 5hmC to activation of transcription is gaining more support. Furthermore, the 5hmC levels were inversely correlated with methyl-CpG-binding protein 2 (MeCP2) in the cerebellum and hippocampus during early postnatal development (Szulwach et al., 2011). Thus, the DMP includes 5mC and 5hmC dynamics, and methylation-demethylation transition spatiotemporally during development.

The cellular patterning of histone codes, as indicated in Section 4.2 is closely synchronized with DNA methylation during neural development (Chen, Damayanti, et al., 2014). 5mC is progressively associated with H3K9me3 and H3K27me3 in heterochromatin, and 5hmC is progressively associated with H3K4me2 in euchromatin as the neuroprogenitor cells claim their neural fate and migrate toward target sites. Together methylcytosines determine the 3-D conformation of the DNA to accommodate the binding of TF onto specific NT binding sites. The histone complex is also organized by the epigenetic regulator. Polycomb group (PcG) proteins associated with gene repression recruit H3K27me3 and H3K9me3 to maintain multipotency of the neuroprogenitor cells and inhibit differentiation, while

trithorax group (TrxG) proteins associated with gene repression recruit H3K4me3 mark. Their interplays switch the bivalent states of proneuronal genes and multipotency genes such as neurogenins (Ngns), *Pax6*, *Sox*, *Nkx2.2* and *Ascl1* (Mikkelsen et al., 2007; Prozorovski et al., 2008) [review see (Nakashima, 2004)] and subsequently determine the fate and differentiation of the neuroprogenitor cells in the neuroepithelial layer. Epigenetic regulation of neurodevelopment is also regulated by small non-coding RNAs such as microRNAs (miRNAs) that are known to regulate neural stem cell fate by targeting mRNA at post-transcription level and chromatin-remodeling pathways during embryonic and adult neurogenesis [review see (Lopez-Ramirez & Nicoli, 2013)]. The timing and regulation of the miRNA formation in the neuroepithelial cells relevant to neuronal differentiation remain allusive. Advance in this area will greatly increase our understanding of how miRNA mediate the orderly evolving neuron.

4.3. Alcohol Drinking, Epigenetics Phenotypes, and FASDs

The altered epigenetics reaching critical mass has been demonstrated to affect wide-spectrum of tissue and organ development including the brain, their functions, and long lasting consequence. Since parental alcohol drinking, among many aversive environmental agents, induces epigenetic alterations and these epigenetic consequences have been studied in depth, the exemplifications below serve as a model for analyses of other environmental agents. As indicated above, parental or prenatal alcohol exposure results in a wide range of epigenetic changes including DNA methylation, histone modification and miRNA in the growing offspring. These epigenetic alterations affect multiple level and stage of the development.

4.3.1 Effect on germ line and placenta—First, prior to the conception, alcohol exposure is reported to increase DNA demethylation at normally hypermethylated imprinting control sites of the H19 locus in sperm (Ouko et al., 2009), and during pregnancy alcohol affects placenta DNA methylation (Haycock, 2009), which are likely to contribute to altering the critical gene expression dosages required for normal prenatal development and placenta supportive functions. Furthermore, the early alteration of DNA methylation may interfere with the default histone coding and chromatin conformation required during normal development (Knezovich & Ramsay, 2012).

4.3.2 Effect on embryonic and early brain development—The effect of prenatal alcohol-induced epigenetics alterations on development at embryonic stage is richly demonstrated in the literature. A high-throughput DNA-methylation immunoprecipitation analysis indicated that a binge-like alcohol exposure alters the methylation profile of over a thousand genes at early neural development (Liu et al., 2009; F. C. Zhou et al., 2011a). These alterations were further shown to be associated with a change in the expression of several genes, including those required for neural specification and neural growth (F. C. Zhou et al., 2011). Genomic analysis of neural stem cells (NSC) has revealed that alcohol retards moderately methylated genes from going toward hypermethylation and hypomethylation necessary for differentiation, indicating alcohol's disruption of the neuroprogenitor DNA methylation program (F. C. Zhou et al., 2011a; F. C. Zhou et al., 2011). The evidence of altered phenotypes associated with alcohol's DNA methylation was

demonstrated by the use of agouti viable-yellow (A^{vy}) mouse mutant, which contains a methylation-sensitive element within the A^{vy} locus to dictate coat color dynamics (Duhl, Vrieling, Miller, Wolff, & Barsh, 1994; Wolff et al., 1998). It was found that parental alcohol exposure resulted in modification of DNA methylation and increase coat color diversity from yellow (unmethylated) to pseudoagouti (highly methylated) in the offspring (Kaminen-Ahola et al., 2010).

A key effect of maternal alcohol exposure on embryonic development is the perturbation of intrinsic DMP. Alcohol exposure during early fetal development (at mid-gestation), which is known to cause fetal alcohol spectrum disorders, altered the density and distribution of the DNA methylation marks. The alcohol exposure delayed the temporal and spatial cellular DNA methylation program in the neural tube that parallels with the retarded neural tube growth and decreased neuronal formation. The embryonic growth retardation is similar to direct inhibition of DNA methylation with 5-aza-cytidine (5-AZA). (F. C. Zhou et al., 2011). The prenatal alcohol exposure also continues to retard the DNA methylation program of 5mC and 5hmC dynamics in developing brain. As normal development proceed in mouse E15 to first week of life, the characteristic DMP, including 5mC, 5hmC and their binding proteins MBD1 and MBD3, lead the hippocampal neuronal differentiation and maturation spatiotemporally as indicated by their phenotypic marks in the Cornu Ammonis area 1 and dentate gyrus at perinatal stage. Alcohol hindered the acquisition and progression of methylation marks, and altered the chromatin translocation of these marks in the nucleus, which was correlated with developmental retardation (Chen et al., 2013).

Alcohol abuse profoundly affects histone modification in adult stage (D'Addario et al., 2013; Shukla & Aroor, 2006; Shukla et al., 2008). Parental alcohol exposure also impacts the emotional stress regulation system via histone modifications, as evidenced by altered histone 3 methylation and acetylation of POMC cells (Govorko et al., 2012). Excessive ethanol at a level attained by alcoholics was found to suppress the expression of four miRNAs, *miR-9*, *21*, *-153*, and *-335*; whereas a lower ethanol concentration, attainable during social drinking, induced *miR-335* expression (Balaraman, Tingling, Tsai, & Miranda, 2013; Sathyan, Golden, & Miranda, 2007). These miRNA can mediate apoptosis (e.g. *miR-21*), regulate neural progenitor cell, or cell cycle genes (e.g. *miR-21*, *-153*, and *-335*).

4.3.3 Potential late onset effect—Derived from fetal alcohol syndrome, we recently advocated the conception of “Epigenetic Medicine” which prescribes that many of the prenatal alcohol-induced abnormalities are not manifested or recognized until later life (Resendiz et al., 2013), such as mood disorders, schizoaffective disorders (Burd, Klug, Martsof, & Kerbeshian, 2003; Famy, Streissguth, & Unis, 1998; O'Connor et al., 2002), epilepsy (Bonthius et al., 2001; O'Malley & Barr, 1998), and cancer (Murugan, Zhang, Mojtahedzadeh, & Sarkar, 2013; Polanco, Crismale-Gann, Reuhl, Sarkar, & Cohick, 2010). These late onset phenotypes may be activated as further accumulated epigenetic alterations beset by the initial environmental insult, reach their threshold. A major challenge in delineating the epigenetic background of these phenotypes is that they are not easily defined in a genetic context. Nonetheless, preliminary advances have been made in the epigenetic examination of stress regulating genes and their ties to anxiety disorders in adulthood. Similarly, though not yet validated in fetal alcohol models, promising epigenetic gene

targets have emerged for schizophrenia (Kirkbride et al., 2012), depression (Sabunciyar et al., 2012), and various cancers (Murugan et al., 2013; Polanco et al., 2010).

4.3.4 Transgenerational effect—The transgenerational heritability of epigenetic traits that contribute to the phenotypes of disease states in the offspring is documented by the insecticide Vinclozolin which was transmitted across generations through sperm epigenetic mechanisms (Anway et al., 2006; Skinner et al., 2008). FASD features in the absence of maternal alcohol consumption where the fathers were alcoholics are being reported (Abel, 2004). Rats with chronic drinking were found to have lower than normal DNMT mRNA levels in sperm (Bielawski, Zaher, Svinarich, & Abel, 2002). As indicated earlier, parental alcohol can change DNA methylation in sperms (Haycock, 2009; Ouko et al., 2009). Another study reported hypomethylation specifically at H19 CpGs in F1 generation sperm DNA and F2 offspring brain (Knezovich & Ramsay, 2012). Prenatal alcohol has also been linked to inherited epigenetic aberrations on non-imprinted genes. Neurons containing POMC-derived peptides have been functionally compromised in patients with a family history of alcoholism, raising the possibility that the alcohol effects on the POMC system may be transmissible across generations (Zimmermann et al., 2004). In animal models, parental alcohol exposure increased the POMC DNA methylation of basal and stress paradigm of both males and females of the F1 generation, and further persisted in the F2 and F3 progeny of the established male germline (Govorko et al., 2012). These studies point to the potential heritability of alcohol-induced epigenetic abnormalities and associated gene functionality across generations. More studies are needed to confirm the genetic site, nature, and stability of reprogrammed epigenetics in the distant offspring. The outcomes could prove useful in furthering our understanding of many late-onset diseases or diseases of unknown etiology and their treatments.

Acknowledgments

The work is supported by the M. W. Keck Foundation, National Institute of Health AA016698, P60 AA07611, and Indiana University Collaborative Research Grant to FCZ. We like to thank Dr. Stephen Mason for editing the manuscript.

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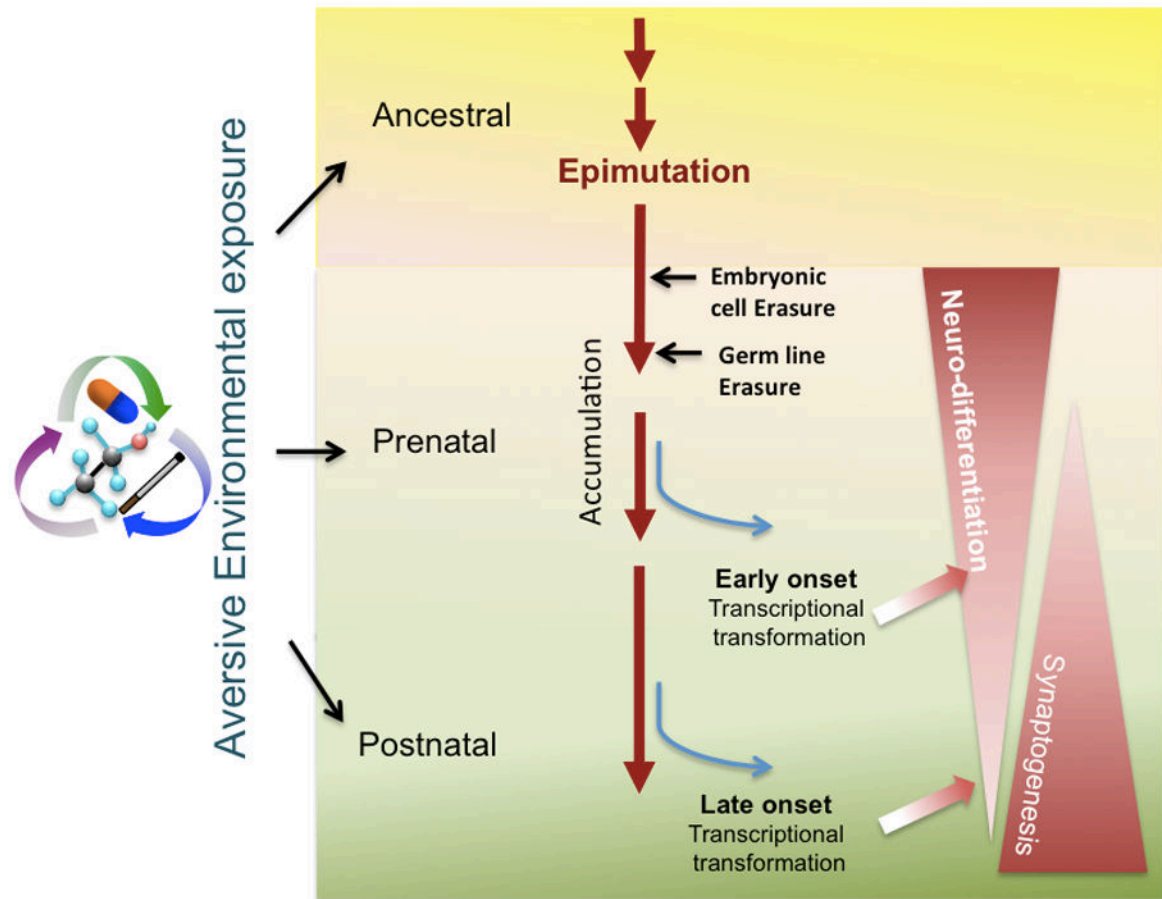


Figure 1.

The aversive environment exposure (e.g. alcohol, nicotine, air pollution) can be recorded in the form of epigenetics throughout ancestral (including parental), prenatal, and postnatal stages. These altered epigenetics (epimutation) on the top of DNA or histone can be accumulated over time but can also be erased twice in a lifetime during zygotic stage and germ line maturation. The persisting epimutation when reached a critical threshold may alter gene transcription to affect the neural development. Depending on stage of life, the earlier onset may affect neural differentiation and brain formation. The continuous increment of epimutation or lasting influence of epigenetic changes may further affect synaptogenesis and together affect the brain function and neuropsychiatric disease at given time of the life.

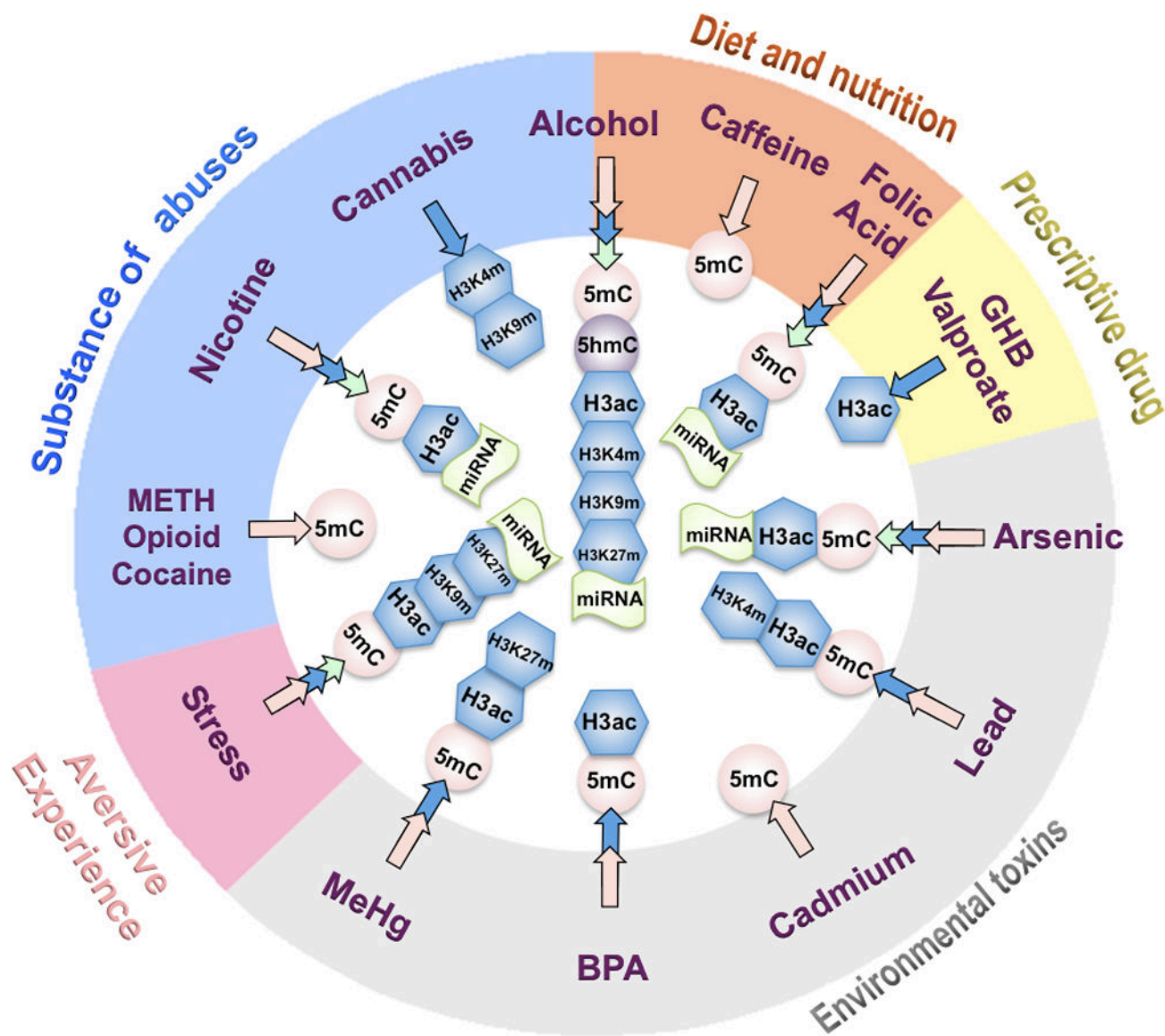


Figure 2. Epigenetic entry of aversive environmental factors. This figure provides information for the epigenetic modifications that have shown to be altered by different types of environmental factors prior to birth. These factors are divided into five categories depending on their nature and ways of access, including substance of abuse, diet and nutrition, prescriptive drugs, environmental toxins and stress. Some factors may cross the categories, e.g. Alcohol belongs to both substance of abuses and diet. The effected epigenetic marks including DNA methylation (5mC, 5hmC) and histone modification (H3ac, H3K4me, etc...) are illustrated. For subtypes altered miRNAs, see Table 1.

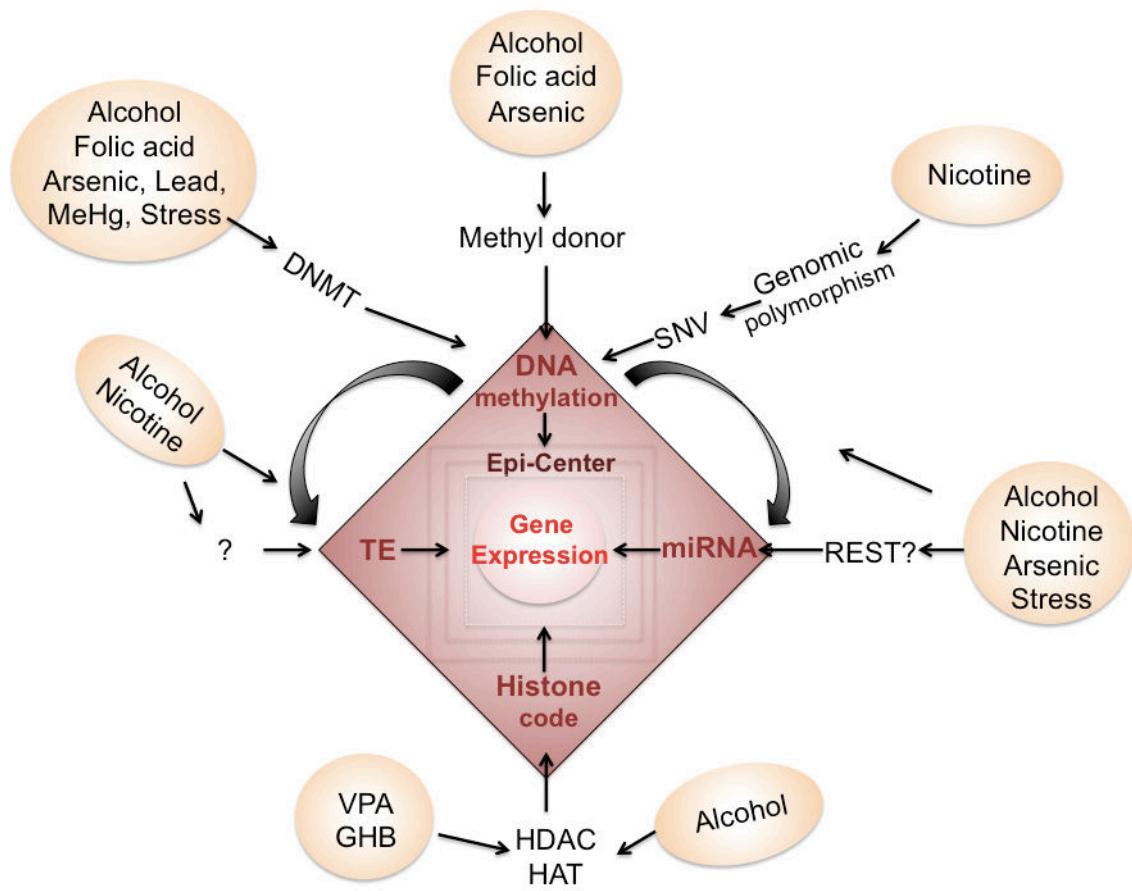


Figure 3.

Mechanism of converting epigenetic marks. Each aversive environmental factor take specific entry to alter the epigenetics, e.g. through altering DNA methyltransferase (DNMT) and changing methyl donor availability to affect DNA methylation, changing histone deacetylase (HDAC) or histone acetyltransferase (HAT) to alter histone code, or through altering DNA methylation on regulatory regions of transposon element (TE) or on miRNA to affect TE and miRNA. To this date, there are missing information how environmental factors might directly affect the TE or miRNA. The RE1 silencing transcription factor (REST), which regulates the expression of miRNA, may be a potential pathway. Finally, the genomic polymorphism or C-T mutation resulted single nucleotide variant (SNV) can also affect the CpG methylation.

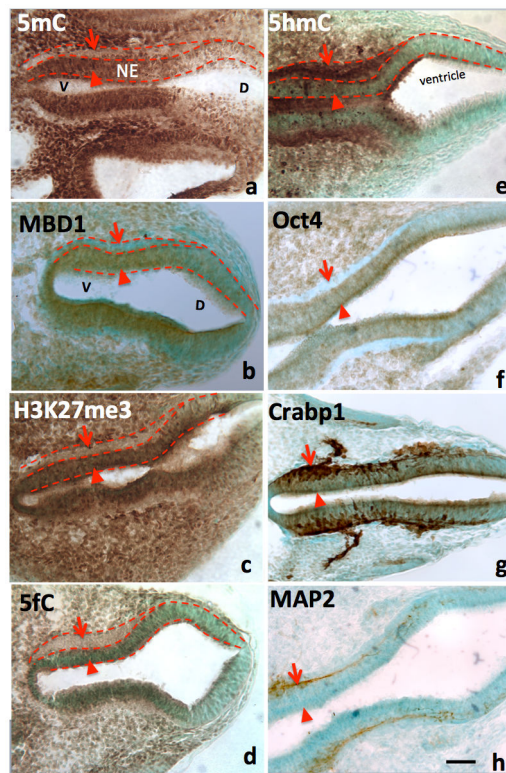


Figure 4.

From Chen et al., *Frontiers in Genetics* (Chen, Damayanti, et al., 2014). The differential role of 5mC versus 5hmC in the DNA methylation program is inferred by their association with phenotypic marks during the making of neural tube. At early neurulation (E10), a sequential escalation of 5mC and 5hmC occurred, where 5mC appeared first at neuroepithelial (A, NE) layer (arrowheads) to prepare the differentiation, and faded as the NE cells differentiated and migrate away from ventricle (A, arrows). At this time, the distribution of the DNA methylation binding protein, MBD1, has exactly the same pattern as that of 5mC (B). Its function is depicted by the suppressive histone mark, H3K27me3, which distributed (C) similar to that of 5mC and MBD1. The demethylated metabolite 5fC also matched with 5mC. In contrast, the 5hmC appeared at differentiating neurons (E, arrowheads) and continued to increase in differentiated neurons (E, arrows). This program also occurred at ventro- (left) dorsal (right) gradation (A–H) where 5mC (A) preceded 5hmC (E). The role of 5mC and 5hmC on neural tube cell differentiation is further depicted by the differentiation phenotypic markers in a spatially precise manner. The role of the 5mC is demonstrated by the appearance of the Oct4 in the NE layer (F, arrowhead) and the loss of Oct4 in differentiated neurons (F, arrow). The role of 5hmC is noted by the stage-wise neuronal marker Crabp1 (G) and MAP2 (H) distributed in a spatially correlated manner. V: ventral; D: dorsal.

Table 1

Epigenetic Change and Phenotype after Prenatal Exposure to Environmental Agents

Agent	Change in Epigenetics			Offspring phenotype correlated with epigenetic change
	DNA methylation	Histone modification	miRNA	
Alcohol	5mC (Garro et al., 1991; Otero et al., 2012; Ouko et al., 2009; Wolff et al., 1998) 5hmC (Chen et al., 2013)	H3Kac (Pal-Bhadra et al., 2007, Shukla et al., 2007) H3K4me, H3K9me, (Pal-Bhadra et al., 2007); H3K27me (Subbanna et al., 2013)	miR148, miR152 (Kutay et al., 2012), miR21, miR153, miR335 (Sathyan et al., 2007)	Delayed maturation and reduced size of hippocampus (Chen et al., 2013) Reduced neuron cell number, cortical plate, thickness, delayed formation in the neural tube, forebrain, hindbrain (F. C. Zhou et al., 2011)
Nicotine	5mC (Breton et al., 2009; J. Z. Maccani et al., 2013; Suter et al., 2010; Suter et al., 2011)	H3ac (Levine et al., 2011)	miR16, miR21, miR146a (M. A. Maccani et al., 2010)	Birth weight reduction (Suter et al., 2011) Increased aggression, locomotion in adult male (Yochum et al., 2014)
Cannabis	N/A	H3K4me, H3K9me (DiNieri et al., 2011)	N/A	Increased opiate reward sensitivity in adult (DiNieri et al., 2011)
Cocaine	5mC (Bae & Zhang, 2005; K. D. Meyer et al., 2009; Novikova et al., 2008; H. Zhang et al., 2007)	N/A	N/A	Increased apoptosis in the term fetal heart; cardiac remodeling (K. Meyer, H. Zhang, & L. Zhang, 2009)
Opioid	5mC (Chorbov et al., 2011)	N/A	N/A	N/A
Methamphetamine	5mC (Itzhak et al., 2014)	N/A	N/A	Enhanced cocaine reward and hyper-locomotion; reduced conditional fear (Itzhak et al., 2014)
Folic acid (Deficiency)	5mC (Gueant et al., 2013)	H3ac (Akchiche et al., 2012)	miR124(Kerek et al., 2013) miR302a (Liang et al., 2012)	Growth retardation, reduced brain size(Kerek et al., 2013)
Caffeine	5mC (Buscariollo et al., 2014; D. Xu et al., 2012)	N/A	N/A	Growth retardation (D. Xu et al., 2012) Altered cardiac function and morphology in adult mice (Buscariollo et al., 2014)
Valproic acid (VPA)	N/A	H3ac (Balmer et al., 2012; Monti, Polazzi, & Contestabile, 2009)	N/A	Reduced birth rate; reduced sociability and social preference (K. C. Kim et al., 2011)
γ-hydroxybutyrate (GHB)	N/A	H3ac (C. Klein et al., 2009)	N/A	N/A
Arsenic	5mC (Intarasunanont et al., 2012; Kile et al., 2012; Pilsner et al., 2012; Xie et al., 2007)	H3ac (Cronican et al., 2013)	let 7a, miR16, miR17, miR20a, miR20b, miR26b, miR96, miR98, miR107, miR126, miR195, and miR-454 (Rager et al., 2013)	Impaired spatial and episodic memory, as well as fear conditioning performance (Cronican et al., 2013)
Lead	5mC (Bihagi et al., 2011; Pilsner et al., 2009; Schneider et al., 2013)	H3ac, H3K4me (Bihagi et al., 2011)	N/A	Enhanced neurodegeneration in primate (Bihagi et al., 2011)

Agent	Change in Epigenetics			Offspring phenotype correlated with epigenetic change
	DNA methylation	Histone modification	miRNA	
Cadmium	5mC (Castillo, Ibanez, Guajardo, Llanos, & Ronco, 2012; Kippler et al., 2013; A. P. Sanders et al., 2013)	N/A	N/A	Reduced birth weight and height (Castillo et al., 2012)
Methyl mercury	5mC (Bose et al., 2012; Onishchenko et al., 2008)	H3ac, H3K27me (Onishchenko et al., 2008)	N/A	Depression like behavior (Onishchenko et al., 2008);
Bisphenol A	5mC (Yaoi et al., 2008)	H3ac (Yaoi et al., 2008)	N/A	Delay the perinatal chloride shift in cortical neurons (Yeo et al., 2013)
Stress	5mC (Champagne & Curley, 2009; Darnaudery & Maccari, 2008; Heim & Binder, 2012; Szyf, 2013)	H3ac, H3K9me H3K27me (Dalton et al., 2014; Reus et al., 2013)	miR16 (Bai et al., 2012), miR9, miR29a, miR124, miR132, miR212 (Uchida et al., 2011)	Induces depressive-like behaviors; altered response to aversive environments (Champagne & Curley, 2009; Franklin et al., 2010)

Table 2

Genes altered by environmental agents

Gene	Gene name	Epigenetic change	Agent	Reference
BDNF	Brain derived neurotropic factor	DNA methylation ↑ at whole gene	Alcohol	(Maier, Cramer, West, & Sohrabji, 1999)
		DNA methylation ↑ at promoter VI	Nicotine	(Toledo-Rodriguez et al., 2010)
		MECP2 expression ↓ No change in methylation level	Lead	(Stansfield, Pilsner, Lu, Wright, & Guilarte, 2012)
		DNA methylation ↑; H3K27me3 ↑; H3ac ↓ at promoter IV	Methyl mercury	(Onishchenko et al., 2008)
		DNA methylation ↑ at promoter IV & IX	Stress	(Roth et al., 2009)
RUNX3	Runt-related transcription factor 3	Site specific change in DNA methylation	Nicotine	(J. Z. Maccani et al., 2013)
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1	DNA methylation at XRE (transcription factor) binding site ↓	Nicotine	(Suter et al., 2010)
DRD2	Dopamine receptor D2	H3K9me2 ↑ H3K4me3 ↓ RNApol II binding ↓	Cannabis	(DiNieri et al., 2011)
DRD4	Dopamine receptor D4	DNA methylation ↑	Alcohol	(H. Zhang et al., 2013)
11b-HSD-2	11β-hydroxysteroid dehydrogenase type 2	DNA methylation at promoter ↑	Caffeine	(D. Xu et al., 2012)
		In the placenta: promoter methylation ↑, <i>Dnmt3a</i> ↑; In fetal hypothalamus: promoter methylation ↓, methylation at exon1 ↑; no change in fetal cortex	Stress	(Jensen Pena, Monk, & Champagne, 2012)
OPRM1	Opioid receptor, mu 1	DNA methylation ↑	Alcohol	(H. Zhang et al., 2013)
		DNA methylation at promoter ↑	Opioid	(Chorbov et al., 2011)
PAX6	Paired box 6	H3K4me3/H3K27me3 ratio <1 (silenced chromatin)	Valproic acid	(Balmer et al., 2012)
KCC2	Potassium chloride cotransporter 2	MECP2 binding ↑ H3K9ac ↓	Bisphenol A	(Yeo et al., 2013)
MAOA	Monoamine oxidase A	DNA methylation ↑	Alcohol	(Philibert, Plume, Gibbons, Brody, & Beach, 2012)
GABRB3	GABA A receptor B3	DNA methylation ↑	Alcohol	(H. Zhang et al., 2013)
NR2B	NMDA receptor subunit 2b	CpG Site specific hypomethylation H3K9Ac ↑, H3K9Me ↓	Alcohol	(Qiang, Denny, Lieu, Carreon, & Li, 2011; H. Zhang et al., 2013)
H19/GF2		DNA methylation ↓	Alcohol	(Haycock & Ramsay, 2009)
NEUROD6	Neuronal differentiation 6	Promoter methylation ↑	Alcohol	(Liu et al., 2009)
POMC	Pro-opiomelanocortin	Promoter methylation ↑	Alcohol	(Govorko et al., 2012)