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Epigenetic programming of reward function in offspring: a role for maternal diet

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Abstract Early life development, through gestation and lactation, represents a timeframe of extreme vulnerability for the developing fetus in general, and for the central nervous system in particular. An adverse perinatal environment can have a lasting negative impact on brain development, increasing the risk for developmental disorders and broader psychopathologies. A major determinant of the fetal developmental environment is maternal diet. The present review summarizes the current literature regarding the effect of poor maternal perinatal nutrition on offspring brain development, with an emphasis on reward-related neural systems and behaviors. Epigenetic mechanisms represent a likely link between maternal diet and persistent changes in offspring brain development, and these mechanisms are presented and discussed within the context of perinatal maternal nutrition.

Introduction

Fetal development requires a carefully orchestrated cascade of molecular and physiological events. The environment in which the fetus develops is determined largely by maternal physiology, outside of the combined contributions of maternal and fetal genotype to placental function. Therefore, it becomes critical to fully understand the determinants that shape an optimal maternal environment. This information is all the more essential given that the effects of an adverse maternal environment can have lifelong negative consequences for the developing fetus.

A broad array of challenges to the maternal environment can adversely affect fetal development, including poor maternal nutrition, maternal infection, or exposure to severe stressors, with well-established, profound effects on the developing central nervous system (CNS). Often, these effects increase the risk of offspring psychopathology (Bale et al. 2010) and, as we present in the case of maternal diet, specifically affect reward-related behaviors. However, the presence of maternal infection or severe stress can be unpredictable and difficult and/or impossible to prevent. In contrast, maternal nutrition represents a more readily modifiable variable that is suitable for intervention, especially in light of the barriers to acquiring balanced nutrition, such as socioeconomic status and geographic locale. Therefore, understanding the effect of maternal diet on offspring CNS development, in both a positive and a negative light, has great importance for the development of children and in ensuring their long-term health.

In an effort to understand the molecular mechanisms whereby early fetal environment can have a lasting impact on physiology in general (Gabory et al. 2011), and brain development in particular (see the excellent recent review in Kofink et al. 2013), significant interest has been focused on the role of epigenetic modifications. First, this focus is parsimonious, as epigenetic modifications are the primary mechanisms of cellular differentiation during fetal development and are therefore more vulnerable to gestational programming. As such, they allow the developing organism to readily adapt to her/his future environment, as communicated via maternal status. Second, these changes can be long-lasting and potentially heritable, promoting risk to subsequent generations. However, substantial evidence indicates that at least in the CNS, these modifications

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are continuously altered in the adult brain [see Day and Sweatt (2010) for review], raising the possibility that conditions programmed during gestation may be amenable to future rescue. There are a number of epigenetic mechanisms currently widely investigated in the CNS that could be affected by gestational nutrition; these are detailed below.

Epigenetic gene regulation

The epigenetic mechanisms that are known to play a role in CNS function via alterations in DNA accessibility range from covalent modification of DNA and post-translational modifications of chromatin, which regulate mRNA transcription, to noncoding RNA (ncRNA), which can interact with mRNA and ultimately impede translation.

DNA methylation involves the addition of a methyl group to the 5-carbon position of a base and is one of the most fundamental and widely studied epigenetic mechanisms. DNA methylation patterns are established by DNA methyltransferase (DNMT) enzymes. Canonically, DNMT1 is important in the maintenance of the methylation mark, while DNMT3a and 3b are essential to *de novo DNA* methylation. Most frequently, CpG dinucleotides are targeted methylation sites; however, very recently it was found that in the developing CNS, neurons acquire a large number of methylation sites at cytosine paired with other nucleotides (Lister et al. 2013) whose function remains unclear. DNA methylation within a promoter region of a gene is typically associated with a closed chromatin state and gene repression. However, methylated cytosine can be converted to hydroxymethylated cytosine (hmC) via the actions of Tet enzymes, and hmC appears to increase in the CNS during development and participate in transcriptional activation (Lister et al. 2013). In addition to CpG methylation within promoter regions, DNA methylation occurs throughout the genome and is referred to as genome-wide methylation. This represents methylation that typically occurs within intragenic regions of the genome. The functional consequences of changes in genome-wide methylation are less well understood, particularly in the CNS; however, global hypomethylation has been shown to lead to adverse CNS outcomes. This was demonstrated in the characterization of the *Dnmt1* forebrain-specific knockout mutant mice (Hutnick et al. 2009), which have global hypomethylation in the forebrain. These animals showed significant neurodegeneration, altered gene expression, and deficits in learning and memory.

Post-translational modifications to histone proteins, including methylation, acetylation, ubiquitination, and others, are another broad category of epigenetic modifications that alter gene expression (Gräff and Tsai 2013). Histone modifications alter chromatin structure and thereby alter the accessibility of transcription factors and, consequently, can be tightly correlated to gene expression (Karlić et al. 2010). Histone modifications are maintained by histone-modifying enzymes, including histone acetyl transferases or deacetylases as well as histone methyltransferases or demethylases (Butler et al. 2012). These modifications can be highly plastic in the adult brain (Roth 2012), and these histone-modifying enzymes are known to function in concert with each other, as well as with DNMTs and other corepressor or coactivator enzymes. Therefore, these mechanisms work in concert to precisely regulate gene expression and the production of mRNA.

There are a number of additional epigenetic mechanisms that have been discovered relatively more recently. Examples include miRNAs and long noncoding RNAs, both of which have the ability to broadly alter the transcription of numerous genes and are highly responsive to environmental changes (Qureshi and Mehler 2012; Wang and Cui 2012). To date, no studies have directly examined whether changes in maternal nutrition can alter the expression of the ncRNAs in the brain. However, there are examples that clearly demonstrate that these ncRNAs are highly responsive to different environmental stimuli. In one study showing the effect of diet, consumption of conjugated linoleic acid was shown to alter the miRNA profile in adipose tissue (Parra et al. 2010). Perhaps an area that has received the most attention is how expression of these ncRNAs change in response to drugs of abuse (recently reviewed in Sartor et al. 2012). As these authors point out, miRNA regulation appears to play an important role in fine-tuning synaptic responses to environmental changes. Besides drugs of abuse, other examples include exposure to chronic stress, which was shown to alter the miRNA profile of sperm and the subsequent stress-responsive phenotype in the offspring (Rodgers et al. 2013). Therefore, dysregulation of these systems in response to suboptimal maternal diet during development is likely, though this remains to be examined directly and represents an important area for future research.

Methodological considerations in developmental programming studies

Prior to reviewing the effects of maternal diet on offspring neurodevelopmental and reward outcomes, it is important to discuss important methodological considerations involved in the studies of perinatal effects of diet on brain development. The first consideration is the timing of dietary manipulation and the implications for differences in timing when it comes to comparisons across species, specifically those of animal models that have potential

implications for humans. The majority of animal research has focused on dietary manipulations during pregnancy and/or lactation. In the rodent, significant brain development occurs postnatally [i.e., postnatal days 3–11 are thought to mirror the third trimester of a human pregnancy (Livy et al. 2003)]. So in an effort to model an entire human pregnancy, many researchers choose to extend manipulations of the maternal diet throughout the lactational period. In support of the importance of both gestation and lactation as critical periods in programming CNS development, dietary changes restricted to only gestation or lactation can lead to detrimental effects on brain development (Alexandre-Gouabau et al. 2012). Recently, it has also been shown that diet, as well as the associated maternal body weight profile prior to conception, can affect the eventual development of the offspring (Grissom et al. 2013; Nicholas et al. 2013). These data are particularly important as they extend the period of vulnerability to the timeframe even before conception.

The importance of the lactational period raises an important methodological consideration that must be addressed in developmental programming experiments. Ensuring equal access to maternal nutrition across experimental groups and between litters is crucial. In fact, manipulation of litter size is often used to model over- and undernutrition by creating small litters or large litters, respectively (Caron et al. 2012; Clarke et al. 2013; Viana et al. 2013). Therefore, studies interested in questions relating to developmental programming must keep litter size consistent across experimental groups (typically done by culling litters to a predetermined number while ideally maintaining a balance between the sexes).

Another technique that is used in developmental programming studies is the use of cross-fostering designs. This design allows for the isolation of a dietary effect to only the gestational or lactational environment. For example, pups born to dams fed a high-fat diet (HFD) during pregnancy would then be fostered by a control dam at birth. In this way, the pups would have normal nutrition and there would a normal-weight dam (to avoid the confounds associated with increased adiposity, e.g., potential gestational diabetes) during lactation. However, cross fostering is not an entirely neutral manipulation as it has been shown to change the epigenetic profile in the brain in offspring (Hager et al. 2009). Thus, the study design must be carefully considered and driven by the specific hypotheses and the experimental end points of interest.

An additional key consideration is the existence of sex differences in the offspring response during development. Nearly all studies that have examined both sexes have identified a sex difference in the offspring response to altered maternal diet, regardless of the outcome measure of interest. Identification and characterization of these sex differences are key initial steps in any developmental programming study. However, identifying the underlying mechanism that leads to the observed sex difference is more complicated. Is the difference present at birth or does it emerge only after puberty with the increased serum levels of sex-specific steroid hormones? If the sex difference exists prior to puberty, it is possible that genes expressed from the sex chromosomes play a role in the expression of the sex difference. To address this question experimentally, studies have employed the use of a 4-core genotype model (Arnold and Chen 2009). This model utilizes transgenic mouse approaches to create XX gonadal males or females and XY gonadal males or females, allowing for the discrimination of effects due to sex chromosome complement (XX vs. XY) versus effects driven by ovarian and testicular hormones.

This approach has yet to be applied to questions of developmental programming but has already been applied to complex behaviors such as social interaction (Cox and Rissman 2011); it represents a potential fruitful approach for future research. Sex differences in developmental programming of neurobehavior will continue to have important implications for understanding and correctly identifying populations at risk as a result of a suboptimal maternal environment.

While the vast majority of research has focused on maternal exposure, recent data have suggested that paternal environmental exposures can also affect phenotypes in the offspring. Undernutrition of the male can result in low-birth-weight offspring, similar to the phenotype observed in undernourished dams (Jimenez-Chillaron et al. 2009). In addition, a HFD can program body size in male and female offspring through either the female or the male germline (Dunn and Bale 2009, 2011), while paternal HFD can program ß-cell dysfunction in female offspring (Ng et al. 2010). Lastly, it has recently been shown in mice that sires exposed to cocaine had male offspring that were less motivated to consume cocaine, while the females were unaffected (Vassoler et al. 2013). Furthermore, epigenetic modifications of brain derived neurotrophic factor (BDNF) were observed only in the male offspring in the medial prefrontal cortex (mPFC). These data are intriguing, but it remains unclear by what mechanism paternal exposures can impact epigenetic function in the offspring brain, especially in most rodent models where males are not involved in rearing.

Studies of changes in maternal diet and epigenetic gene regulation have focused primarily on the hypothalamus, relating the increased risks of obesity faced by offspring of poor-quality maternal diets in both humans and animal models. This literature is extensive and has highlighted numerous alterations in hypothalamic subregions by gestational diets, including clear epigenetic mechanisms. For

instance, undernutrition in sheep has been shown to affect methylation of the glucocorticoid receptor as well as pro-opiomelanocortin (Begum et al. 2012; Stevens et al. 2010). In the converse case, neonatal overfeeding in rodents, modeled by severely reducing litter size, led to differential methylation of the *POMC* gene in the hypothalamus (Plagemann et al. 2009). Findings such as these highlight a clear role for altered hypothalamic function leading to dysfunctions in homeostatic feeding mechanisms and energy balance. However, in human environments there is an equally important role for hedonic and motivational feeding, which is supported by brain regions that are important for reward function. Additionally, dysfunction in these regions is likely to be involved in risk of psychopathology (Grissom and Reyes 2013). As such, this review focuses on what is known about epigenetic programming of reward function in the offspring as it is affected by maternal nutrient manipulations.

Maternal protein/caloric restriction and intrauterine growth restriction: impact on offspring reward function

Examination of maternal diet during pregnancy includes studies on reduction in overall caloric intake as well as those that focus on a specific macronutrient deficiency, with a significant number of studies examining the effect of protein deficiency. These maternal diets typically lead to growth restriction in the offspring; however, significant neurobiological effects have been observed with even mild maternal protein restriction that does not always impact gestational size (Resnick et al. 1982). Intrauterine growth restriction (IUGR) is a significant biomarker of a number of adverse physiological and psychological outcomes and has many causes, including maternal smoking or drug use, maternal hypertension, severe maternal obesity, and uterine or placental dysfunction, essentially anything that reduces nutrient flow to the developing fetus. As such, results from studies that examined a maternal low-protein or calorie-restricted diet may extend beyond the effects of diet deficiency to more broadly apply to other conditions that result in growth restriction.

The majority of protein restriction protocols limit maternal protein intake by half as compared to control-fed animals. One of the most consistent findings across studies utilizing maternal protein restriction is the effect on reward-related behaviors. In one study in which dams were exposed to a protein-restricted diet throughout pregnancy and lactation, male offspring showed an increase in speed to retrieve a food reward. This altered behavior was accompanied by an increase in c-Fos + neurons (a generic marker of neuronal activation) in the amygdala and caudate putamen in response to the intake of a palatable diet (da Silva et al. 2013). Another study that examined low-protein exposure restricted to either pregnancy or lactation found opposing results depending on the exposure time. Protein restriction through pregnancy and lactation decreased female offspring responding in an operant task; however, if the protein restriction occurred only during lactation, the effect was to increase motivation. Interestingly, in both these studies, offspring from protein-restricted dams were significantly impaired in learning the task. After a more severe protein restriction (6 % vs. 25 % casein) in rats 5 weeks prior to and throughout pregnancy, male offspring were found to be more responsive to reward, demonstrating greater response in an operant paradigm for sucrose (Tonkiss et al. 1990). Collectively, these studies indicate that reward-related behaviors represent one area of vulnerability within the context of limited protein during development and/or secondary to growth restriction in utero.

Our own work with mice has shown that offspring from dams fed a low-protein diet through pregnancy and lactation have a reduced preference for sucrose (Vucetic et al. 2010b). In addition, these animals have an altered locomotor response to cocaine, reaching a similar peak 30 min after cocaine administration but taking significantly longer to recover to baseline levels of locomotor activity. Furthermore, the animals from the low-protein-diet pregnancies also had significantly more c-Fos + cells in the nucleus accumbens in response to cocaine injection.

In addition to behavioral characterizations, a number of studies have investigated how the underlying neurotransmitter system might be altered by the maternal low-protein diet. We have shown that offspring from low-protein-fed dams have significant increases in dopamine (DA)-related gene expression within the reward circuitry (VTA, Nac, and PFC), as well as alterations in DA content (Vucetic et al. 2010b). Simultaneously, however, these offspring display decreased gene expression related to opioid function (Grissom and Reyes 2013). Other groups have also reported changes in the DA system as a result of maternal low-protein diet during pregnancy, including reports of increased whole-brain DA levels (Chen et al. 1997; Marichich et al. 1979), tyrosine hydroxylase (TH) activity (Marichich et al. 1979), and altered DA receptor binding in the striatum (Marichich et al. 1979; Palmer et al. 2008). Beyond DA, altered glutamatergic signaling has also been observed in the PFC of offspring from protein-restricted dams (Guest et al. 2012). Additionally, restriction of total maternal food by 50 % from embryonic day 144 through postnatal day 21 in the rat affected cell proliferation in hypothalamus and hippocampus in a complicated pattern, depending on the age at which the animals were examined (Coupé et al. 2009). Furthermore, protein restriction in rats confined to just gestation or gestation and lactation (to alter

the postnatal growth rate) affected metabolic pathways within the hypothalamus resulting in changes in local energy supply (Alexandre-Gouabau et al. 2012). These alterations are likely to contribute to the impact of maternal protein restriction via interactions with DA and opioids regulating reward and consummatory behavior, and, furthermore, they highlight the diverse abnormalities that might be expected to occur due to CNS-wide epigenetic programming.

Maternal protein/caloric restriction and intrauterine growth restriction: impact on offspring CNS epigenetics

Given the numerous behavioral abnormalities and subsequent alterations in function in multiple neurotransmitter systems induced by maternal nutrient or protein restriction, the next question is whether epigenetic modifications may represent a link between the maternal diet and persistent changes in gene expression in the offspring brain. Using a model of protein restriction through pregnancy and lactation in mice, we have shown global hypomethylation (Grissom and Reyes 2013) in the brain as well as promoter-specific changes in DNA methylation in cyclin-dependent kinase inhibitor 1C, which is critical for dopaminergic neuron development (Vucetic et al. 2010b). In rats, 50 % protein restriction only during lactation led to a decrease in hydroxymethylcytosine content in the rat CNS (Penn 1976). A low-protein diet can also affect the expression of genes that are important in DNA methylation, e.g., *Dnmt1* (Grissom and Reyes 2013). In addition, a 50 % low-protein diet in the last half of gestation in mice led to altered miRNA expression and differential methylation of genes in the renin–angiotensin system in the fetal brain (Goyal et al. 2010). A 50 % calorie reduction in late pregnancy led to sex-specific changes in global methylation and differential methylation of miRNAs in placental samples (Chen et al. 2013). A low-protein diet in pigs increases expression of miRNAs that regulate adipose deposition (Pan et al. 2013). These findings, combined with others that have shown a link between early life environment and epigenetic modifications in other organ systems (Pinney and Simmons 2010), identify epigenetic modifications as an important link between maternal undernutrition and persistent changes in gene expression.

Maternal high-fat diet and overnutrition: impact on offspring reward function

On the other end of the spectrum from IUGR are offspring that are born large for gestational age (LGA). Maternal obesity prior to and during pregnancy can significantly increase the risk for the offspring to be born LGA in both humans and animal models. In animal models, offspring develop in an environment in which nutrition exceeds what is required for adequate development, either in total calories or an unbalanced diet that provides too much fat or sugar; these dams in this environment typically gain excessive weight during gestation. The most frequently used manipulation is to introduce a HFD either before gestation or at the beginning of pregnancy.

Many investigators have demonstrated that the offspring of maternal overnutrition have an increased tendency to overconsume rewards. Rat offspring exposed perinatally to a HFD showed increased nicotine self-administration behavior during fixed-ratio schedules and an increase in breakpoint using progressive-ratio testing for responding to nicotine. Perinatal exposure to a HFD increased the vulnerability of the offspring to excessive nicotine use by enhancing its reward potential (Morganstern et al. 2013). A HFD during pregnancy has been found to increase HFD and alcohol intake in female offspring (Bocarsly et al. 2012), while offspring exposed to HFD during the last week of gestation and throughout lactation display blunted locomotor response to amphetamine (AMP) and reduced sensitization to the drug compared to offspring of control - diet dams (Naef et al. 2008). Whether and how these behaviors relate to the risk profile for addictive disorders in children born LGA remains to be determined and is an important area for future epidemiological research. Also, these offspring show increased operant response for a fat-enriched reward (Naef et al. 2011). In a related model that administers a "junk food" diet to the dams (high fat and sugar), offspring exhibit greater fat intake in both male and female offspring (Ong and Muhlhausler 2011). We have shown in mice from dams fed a 60 % HFD through pregnancy and lactation that there is an increased preference for fat and sugar (Vucetic et al. 2010a) as well as an exaggerated locomotor response to cocaine, with a larger peak response and longer time to recover (Grissom and Reyes 2013). This increased preference for natural rewards (fat and sugar) seen in offspring born to HFD-fed dams likely contributes to the offspring's increased risk for obesity (Tamashiro and Moran 2010) through increased intake of rewarding, calorie-dense foods.

As with the maternal undernutrition models, DA appears to be sensitive to dysregulation in response to early life exposure to HFD. In offspring from dams fed a HFD, attenuated DA release in the NAc in response to AMP was observed, as well as increased activity of the NAc DA transporter and decreased ventral tegmental area (VTA) D(2) receptor mRNA levels (Naef et al. 2011). In the "junk food" diet model, the offspring demonstrated alterations in the expression of μ-opioid receptor and dopamine transporter within the reward circuitry (Ong and Muhlhausler

2011). In our model of HFD through pregnancy and lactation, we have observed alterations in DA and opioid gene expression (Vucetic et al. 2010a) within the reward circuitry.

Maternal high-fat diet and overnutrition: impact on offspring CNS epigenetics

Our group has expended significant effort investigating epigenetic modifications in response to maternal HFD. Offspring born to dams fed a HFD through pregnancy and lactation demonstrate a number of alterations in DNA methylation (Vucetic et al. 2010a). Within the reward circuitry, a maternal HFD resulted in a reduction in DNA methylation in the promoter regions of μ-opioid receptor and preproenkephalin, and subsequent overexpression of these genes. In addition to these promoter-specific changes in DNA methylation, we also observed a decrease in global methylation across all regions of the brain examined, including the reward-related regions: VTA, NAc, and PFC. We were interested in whether we could reverse this global decrease in DNA methylation by providing additional methyl donors to the maternal diet; therefore, methyl donor supplementation was added to both the control diet and the HFD during pregnancy and lactation. This supplementation was able to reverse global hypomethylation in some of the examined regions (though notably not in the VTA) and some of the gene expression changes and the increased preference for fat (though notably not sucrose). This experiment showed that supplementation of the maternal diet with methyl donors has the ability to normalize some of the HFD-driven phenotypes (Carlin et al. 2013), highlighting the importance of altered DNA methylation in contributing to the effects of maternal HFD on brain development. Beyond the CNS, epigenetic changes have also been observed in the placenta in response to HFD in early life. The placenta is a key interface between the maternal environment and the fetus. A HFD in the first half of pregnancy leads to differential methylation within the placenta and this varies by sex (e.g., global hypomethylation seen only in females) (Gallou-Kabani et al. 2010). Also, maternal HFD was shown to alter the expression of epigenetic-related genes in the placenta (Gabory et al. 2012).

Future directions

The significance of gestation and the perinatal period in the development of the CNS in offspring, combined with the prevalence of poor nutrition (limited access to affordable, high-quality protein coupled with ready access to high-fat, high-sugar processed foods) has made the investigation of the influence of maternal diet on offspring neurodevelopment one of rapidly increasing interest. However, even as the field continues to identify CNS abnormalities resulting from gestational dietary insults, there remain a number of unanswered questions and underexplored mechanisms.

There has been a great deal of interest recently surrounding the question of whether epigenetic modifications that are observed in response to environmental insults can be passed on to future offspring, representing transgenerational inheritance (Bohacek et al. 2013; Grossniklaus et al. 2013; Lim and Brunet 2013). True transgenerational inheritance via the matriline requires a phenotype to be passed onto the F3 generation, which is the first generation that is truly unexposed to the original insult (i.e., the germ cells in the exposed F1 animals become the F2 generation). In contrast, paternal transmission can be observed if the phenotype is observed in the F2 generation. While there are an increasing number of reports that show the transgenerational inheritance of a phenotype, whether epigenetic mechanisms underlie this phenomenon is not yet clear. In a recent article, paternal obesity in the F0 generation was found to increase the risk for obesity in both F1 and F2 offspring. Additionally, analysis revealed a significant change in the miRNA expression profile in the testes and the sperm of the F0 obese males as well as global hypomethylation (Fullston et al. 2013). These data strongly suggest that the CNS could also be impacted; however, given the impact of maternal care on offspring CNS development, future experiments to investigate these effects would want to disentangle purely molecular alterations from altered maternal care in F1 and F2 generations.

As mentioned earlier, there are a number of potential epigenetic mechanisms that are likely to be involved in the gestational programming of offspring neurodevelopment. Thus far, however, investigations have been largely limited to DNA methylation. In some respects this is the ideal starting point, as DNA methylation is a fundamental mechanism for cell fate specification and development, starting from the earliest stages of embryogenesis through to the switch from neurogenesis to astrogliogenesis in the postnatal rodent brain. Furthermore, as mentioned above, DNA methylation interacts with chromatin modifications to regulate gene expression and, therefore disruptions, in DNA methylation imply wide-scale alterations in histone modifications, for example. However, the impact of maternal diet on chromatin modifications has yet to be widely elucidated. Furthermore, miRNA mechanisms are also likely to be disrupted as transcription of miRNAs are likely to be regulated by alterations in DNA accessibility, with wholly unknown effects on mRNA transcription and translation. Further investigation into these mechanisms is likely to prove fertile ground for understanding how the maternal diet can program offspring reward-related

behavior and, more broadly, how gestational insults alter the development of the CNS.

It is now clear that a poor maternal diet during pregnancy and lactation, and even prior to conception, can adversely affect offspring brain development. Reward-related neurotransmitter systems and behaviors are vulnerable to dysregulation that persist throughout the animal's lifetime. Epigenetic modifications, primarily DNA methylation, have been identified as one link between maternal diet and offspring brain development. A broader appreciation of the underlying mechanisms that lead to altered DNA methylation and investigations into additional epigenetic alterations (e.g., histone modifications, ncRNAs) are important future directions for the field.

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