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Maternal High-Fat Diet Programming of the Neuroendocrine System and Behavior

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Abstract

Maternal obesity, metabolic state, and diet during gestation have profound effects on offspring development. The prevalence of neurodevelopmental and mental health disorders has risen rapidly in the last several decades in parallel with the rise in obesity rates. Evidence from epidemiological studies indicates that maternal obesity and metabolic complications increase the risk of offspring developing behavioral disorders such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), and schizophrenia. Animal models show that a maternal diet high in fat similarly disrupts behavioral programming of offspring, with animals showing social impairments, increased anxiety and depressive behaviors, reduced cognitive development, and hyperactivity. Maternal obesity, metabolic conditions, and high fat diet consumption increase maternal leptin, insulin, glucose, triglycerides, and inflammatory cytokines. This leads to increased risk of placental dysfunction, and altered fetal neuroendocrine development. Changes in brain development that likely contribute to the increased risk of behavioral and mental health disorders include increased inflammation in the brain, as well as alterations in the serotonergic system, dopaminergic system and hypothalamic pituitary adrenal (HPA) axis.

Keywords

Maternal obesity; anxiety; autism; ADHD; schizophrenia; pregnancy; high-fat diet; programming

I. Introduction

In the United States, one-third of women are obese and two-thirds are overweight (Ogden et al., 2012). Women with a high body mass index (BMI) are more likely to have pregnancy complications and adverse maternal and perinatal outcomes including gestational diabetes (Hedderson et al., 2012; Solomon et al., 1997), pre-eclampsia (Baeten et al., 2001; Bodnar et al., 2005), high blood pressure (Magriples et al., 2013), placental dysfunction (Hastie and

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Lappas, 2014; Higgins et al., 2013), preterm births (Cnattingius et al., 2013; Wang et al., 2011), and infants born either large or small for gestational age (Djelantik et al., 2012). The prevalence of neurodevelopmental disorders have increased dramatically in parallel with the rise in obesity rates (Boyle et al., 2011; Elsabbagh et al., 2012; Fombonne, 2011), leading researchers to examine the impact of maternal obesity, weight gain during pregnancy, and prenatal diet on offspring behavior. Obesity during pregnancy has been found to alter offspring metabolism, organ and brain development, temperament, and to increase risk for mental health and neurodevelopmental disorders. Animal studies are critical in clarifying the mechanisms by which maternal obesity programs these behavioral dysfunctions in offspring. Possible factors that have been identified thus far include elevated inflammation, decreased placental function, and dysregulation of hormones such as leptin, glucose, and insulin, which impair development of critical neurocircuitry in the developing fetus. The serotonergic system, dopaminergic system, and hypothalamus-pituitary-adrenal (HPA) axis have all been shown in animal models to be altered by maternal obesity. Evidence from human and animal studies implicates maternal obesity and perinatal high-fat diet (HFD) as risk factors for the development of attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), schizophrenia, and anxiety and depressive disorders.

In this review we will first summarize the existing human studies that examine the association between maternal obesity, weight gain during pregnancy, metabolic conditions, and maternal HFD as risk factors for ADHD, ASD, schizophrenia, anxiety, and depressive disorders. We will next review evidence from animal models that examine the impact of maternal obesity and HFD consumption on offspring behavior, and will conclude with a discussion of potential mechanisms for the association of maternal diet and metabolic state with offspring risk for behavioral disorders.

II. Evidence from Human Studies Suggest that Maternal Metabolic State and Diet Impact Offspring's Risk for Behavioral Disorders

A. Maternal Obesity and Metabolic Complications as Risk Factors for Child ADHD

Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric condition characterized by pervasive symptoms of hyperactivity, inattention, and impulsivity that impede normal functioning or development. The prevalence of ADHD has recently increased from 5.69% in 1997-1999 to 7.57% in 2006-2008, which is a 33% percent increase (Boyle et al., 2011). Children with ADHD report lower self-esteem and show an increased rate of academic failure and test anxiety. Cognitive problems such as impaired working memory and reduced executive function are also common (Dan and Raz, 2012). Adolescents with ADHD struggle with delinquency, substance abuse and numerous comorbid psychiatric disorders such as oppositional defiant disorder, conduct disorder, mood disorders, anxiety disorders, and learning disorders (Biederman, 2005). Given the considerable healthcare costs, the hardship for children and families, the negative long-term outcomes, and the substantial demands on educational and healthcare systems associated with ADHD, it is critical that future studies determine both genetic and environmental risk factors. Mothers of children with ADHD are more likely to be diagnosed with a myriad of health complications including mental health disorders (such as depression, anxiety, and

neurosis), immune related disorders, and obesity (Ray et al., 2009). A growing body of evidence from epidemiological studies suggests that exposure to maternal obesity increases risk of developing ADHD and severity of ADHD symptoms (Buss et al., 2012; Chen et al., 2014; Rodriguez, 2010; Rodriguez et al., 2008). Obese mothers are reported to have a 2.8-fold increased risk of having a child with ADHD than their non-obese counterparts (Buss et al., 2012). In addition, children of obese and overweight mothers show more severe teacher-rated inattention, but not hyperactivity symptoms than those of normal weight mothers (Rodriguez, 2010). However, in a similar study this link did not hold under a sibling-comparison model, suggesting there may be familial environmental factors affecting this association (Chen et al., 2014). Though several studies show an association between maternal BMI and the severity of the child's ADHD symptomology (Buss et al., 2012; Chen et al., 2014; Rodriguez, 2010; Rodriguez et al., 2008), a study by Brion et al. failed to show this association in a cross-cohort model when adjusting for socioeconomic status (Brion et al., 2011). Despite this study, the majority of current publications agree that a high maternal weight status increases the likelihood of having a child with heightened ADHD symptoms.

In addition, an elevated pre-pregnancy BMI has been shown to negatively impact child brain function and behavior. Buss et al. found that high pre-pregnancy BMI impaired executive functioning in children and that these impairments were potential mediators of the association between maternal obesity and ADHD severity (Buss et al., 2012). In a Swedish cohort, children of obese and overweight mothers had a two-fold increased risk for inattention symptoms as reported by teachers using DSM-V criteria. This same cohort of children displayed reduced emotional regulation, with children from obese mothers having a greater difficulty dealing with sadness, fear, and anger (Rodriguez, 2010). Overall, mounting recent evidence indicates that maternal obesity is a risk factor for the child developing ADHD and increases the severity of ADHD symptoms.

The data examining the impact of elevated weight gain during pregnancy on child ADHD risk is limited and inconsistent. A 2008 study found that women that were overweight and gained a large amount of weight during pregnancy showed a two-fold increase in the risk of the child displaying ADHD symptoms (Rodriguez et al., 2008). This association was not observed in women who were normal weight or underweight at the beginning of pregnancy and had elevated weight gain during pregnancy (Rodriguez et al., 2008). Conversely, another study that followed 174 mother-child pairs receiving obstetric care in California from early gestation to childhood concluded that excessive gestational weight gain was not associated with an increase in child ADHD symptoms in mothers from any BMI category (Buss et al., 2012). Given the limited evidence and the conflicting findings of studies examining maternal weight gain and child ADHD risk, it is important that future studies carefully track maternal weight gain during pregnancy in a large population of women with varying initial metabolic states.

Very few studies have investigated the link between child ADHD symptoms and maternal metabolic diseases such as diabetes. One study determined that offspring exposed to gestational diabetes mellitus (GDM) had higher mean inattention scores at baseline compared to unexposed children, but no difference in hyperactivity/impulsivity scores. However, none of these GDM exposed children had an increased risk of ADHD by 6 years

of age (Nomura et al., 2012). Two studies found that low socioeconomic status and exposure to GDM are associated with increased ADHD symptomatology in children (Nomura et al., 2012; Schmitt and Romanos, 2012). Currently, no evidence exists that demonstrates an increased risk of ADHD in mothers with GDM when socioeconomic status is controlled for. Large population based studies are needed to examine the association between exposure to GDM and other metabolic conditions and risk for ADHD.

Studies rarely identify ADHD subtype (inattentive or hyperactive), severity, or discuss their potential link with child IQ score. It is possible that children with ADHD and high IQ scores associate with maternal factors differently than affected children with low IQ scores. Karalunas et al. identified “Mild,” “Surgent,” and “Irritable” as three ADHD subgroups based on temperament, and validated the subgroups with physiological measures and clinical outcomes (Karalunas et al., 2014). Future studies would benefit from deeper analysis into ADHD subtypes, which may explain some of the discrepancies present across current literature.

B. Maternal Obesity and Metabolic Complications as Risk Factors for Child Autism Spectrum Disorders

Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders that include a broad range of symptoms and levels of impairment, but are primarily characterized by social impairment, communication difficulties, and repetitive behaviors (American Psychiatric Association, 2000). The prevalence of ASD and developmental delays (DD) has increased dramatically in the past decade (Boyle et al., 2011; Elsabbagh et al., 2012; Fombonne, 2011) during the same time as the rising rates of obesity in the adult population. This recent surge in the occurrence of ASD is a major public health concern and has prompted investigation into environmental factors such as maternal obesity that are potential mediators of this increase in ASD prevalence.

The majority of studies that examine the relationship between high maternal BMI and child diagnosis of ASD find a significant association (Bilder et al., 2013; Krakowiak et al., 2012; Maimburg and Vaeth, 2006; Moss and Chugani, 2014; Reynolds et al., 2014; Suren et al., 2014). Krakowiak et al. demonstrated a relationship between a maternal obesity and diagnosis of the child with ASD and/or developmental disabilities (Krakowiak et al., 2012). Reynolds et al. divided their mother-infant cohort into obese and non-obese mothers and also found that maternal obesity was a strong predictor for diagnosis of autism in toddlers (Reynolds et al., 2014). Dodds et al. showed that ASD participants were more likely to have mothers who had a pre-pregnancy weight of greater than 90 kg (Dodds et al., 2011). Another study showed a weak association with overweight and obese mothers and child ASD diagnosis, but these associations were stronger when the link between maternal weight and infant birth weight was analyzed (Moss and Chugani, 2014). Maternal obesity and maternal underweight are both associated with very low birth weight infants (Moss and Chugani, 2014). Children with very low birth weight are more than twice as likely to be diagnosed with ASD as children born at a normal weight (Moss and Chugani, 2014). Additional studies have also found a link between very low birth weight and increased ASD diagnoses (Abel et al., 2013; Moss and Chugani, 2014; Pinto-Martin et al., 2011). This has been confirmed in

twin studies, as the twin with the lower birth weight is at higher risk for an ASD diagnosis that the larger twin (Losh et al., 2012). Children born prematurely are also at increased risk for ASD (Abel et al., 2013; Limperopoulos et al., 2008; Moss and Chugani, 2014). Abel et al. demonstrated in a large Swedish population that poor fetal growth and extremely high fetal growth are both associated with higher risk of ASD with or without intellectual disability (Abel et al., 2013). This suggests that maternal obesity indirectly increases risk for autism by increasing the occurrence of other prenatal risk factors. As the majority of human studies provide evidence for an association between maternal obesity and risk for ASD it is critical that future studies examine the mechanisms for this association and identify potential therapeutic strategies to mitigate the increased risk of ASD due to exposure to maternal obesity.

There is also some evidence that excess pregnancy weight gain increases risk for ASD (Bilder et al., 2013; Dodds et al., 2011), though not all studies demonstrate this (Stein et al., 2006). One longitudinal cohort study found that maternal obesity and weight gain during pregnancy played a larger role in those with low genetic susceptibility, as defined by having a sibling with ASD or a mother with psychiatric or neurological disorders (Dodds et al., 2011). Additional large population based studies to examine this association within different ASD subpopulations are needed to further clarify the role of pregnancy weight gain.

Several maternal metabolic conditions are associated with ASD risk and developmental delay (Krakowiak et al., 2012), including maternal type-2 diabetes and GDM. Most studies find an association between GDM and increased risk of ASD (Dodds et al., 2011; Krakowiak et al., 2012; Lyall et al., 2012). Pre-eclampsia is also found to be positively associated with ASD risk (Glasson et al., 2004; Mann et al., 2010; Wallace et al., 2008). Higher rates of pre-eclampsia are found in the prenatal history of ASD patients as compared to unaffected siblings and a population of typically developing children (Glasson et al., 2004). Pregnancies complicated by pre-eclampsia also demonstrated increased risk of pervasive developmental disorder-not otherwise specified and Asperger's Syndrome (Glasson et al., 2004). There is also a positive correlation between pre-eclampsia and severity of social/communication symptoms and repetitive behaviors within an ASD population (Wallace et al., 2008). Hypertension is another maternal factor that is positively associated with offspring ASD diagnosis (Dodds et al., 2011; Krakowiak et al., 2012; Wallace et al., 2008; Lyall et al., 2012). Metabolic conditions that obese women are more likely to develop during pregnancy than lean women such as diabetes, pre-eclampsia, and hypertension are all associated with increased risk of ASD and other developmental delays in offspring.

There are several other diet and metabolic factors that could benefit from further investigation in regards to offspring ASD risk. One study found that paternal obesity increased risk for ASD (Suren et al., 2014). This is the only study to examine paternal obesity and ASD risk. As it showed that paternal obesity is also a potential risk factor in ASD development, further examination of this association is warranted. Nutritional composition during pregnancy is another factor that has rarely been looked at in regards to ASD risk, but Lyall et al. found that diets rich in omega-3 and omega-6 fatty acids during gestation reduce risk of the offspring developing ASD. As ASD includes a broad range of

symptoms and severity of impairment, the etiologies are likely different dependent on these factors. Examining large cohorts and dividing them into subgroups according to symptoms, level of impairment, and level of genetic susceptibility will help clarify the role of maternal metabolic factors in the development of ASD.

C. Maternal Obesity and Metabolic Complications as Risk Factors for Schizophrenia

The majority of studies that demonstrate that maternal metabolic state impacts offspring risk of developing schizophrenia have come from instances of famine. For example, gestational malnutrition during the Dutch Hunger Winter of 1944-1945 has been reported to double risk of the offspring developing schizophrenia (Kyle and Pichard, 2006). In Western nations the primary nutritional problem is that of nutritional excess, and thus many studies have examined maternal overnutrition as a risk factor for offspring developing neurodevelopmental deficits. Exposure to maternal obesity was associated with increased risk of developing schizophrenia in adulthood in two large birth cohort studies (Jones et al., 1998; Schaefer et al., 2000). One cohort included over 19,000 births in California within the Kaiser system between 1959 and 1967, and found that mothers with a BMI of 30 or greater were three times as likely to have a child diagnosed with schizophrenia as an adult (Schaefer et al., 2000). This result remained significant when adjusted for maternal age, ethnicity, education, and cigarette smoking, as well as parity and offspring gender. Another study, using a Finnish cohort, which included all births in 1966, reported rates of schizophrenia among children of mothers with a BMI of 29 or greater to be twice that of the reference group (Jones et al., 1998). However, this association was no longer significant when offspring gender, social class, and maternal age at conception were included as covariates. A Japanese study found that a one unit increase in BMI was associated with a 24% increase in the odds of having a child with schizophrenia during early pregnancy and a 24% increase in late pregnancy (Kawai et al., 2004). Additional studies are needed to fully elucidate the important relationship between maternal obesity and offspring schizophrenia risk.

The impact of exposure to maternal metabolic complications during gestation on schizophrenia risk in offspring has been largely understudied. The strongest association surrounding obstetric complications is between pre-eclampsia and offspring schizophrenia risk (Eide et al., 2013). Mothers with gestational pre-eclampsia are reported to have 2.5 times the risk of having a child with schizophrenia than an unaffected mother (Dalman et al., 1999). Sorensen et al. did not observe an increased risk of schizophrenia associated with maternal pre-eclampsia. However, they did report a link between hypertension during pregnancy and schizophrenia risk. Interestingly, mothers treated for hypertension with diuretics during the third trimester of pregnancy showed a four-fold increase in child schizophrenia risk. Yet, maternal hypertension in the absence of diuretic treatment did not hold this association (Sorensen et al., 2003). It is not clear whether these results indicate a drug-associated risk, or if this association emerges because only severe cases of hypertension warranted diuretic treatment. Exposure to maternal diabetes has also been reported as a risk factor for schizophrenia. A recent meta-analysis of various obstetric complications and offspring schizophrenia risk report a shocking 7.78-fold increased risk in children of mothers that are diabetic (Cannon et al., 2002). However, this result is based on the findings of two studies, neither of which specified the type of maternal diabetes (i.e. type

1 versus type 2 diabetes mellitus). Although a few studies provide evidence that exposure to maternal pre-eclampsia and diabetes increase risk for the development of schizophrenia in adulthood, much more evidence is needed to fully understand their contribution to the etiology of schizophrenia.

D. Maternal Obesity and Metabolic Complications as Risk Factors for Anxiety and Depression

The impact of maternal obesity and diet on offspring's risk of depression and anxiety disorders is largely unstudied, in part because these disorders often do not develop until adolescence or adulthood. Maternal obesity prior to pregnancy has been reported to increase the risk for children to have difficulty regulating emotions such as fear and sadness (Rodriguez, 2010). Maternal pre-pregnancy BMI has also been found to be correlated with elevated internalizing problems in children, which include emotional difficulties such as withdrawal and depression (Van Lieshout et al., 2013). This finding first emerged when the children in the study were eight years old, and increased throughout late childhood and adolescence.

Maternal obesity can only be indirectly linked to offspring risk of anxiety and depression. Maternal obesity is associated with increased rates of infants born small or large for gestational age (Djelantik et al., 2012; Gavard and Artal, 2014; Nohr et al., 2008), and these infants have a higher likelihood of anxiety and depression during adolescence (Colman et al., 2012). Risk of childhood and adult obesity is also increased by exposure to maternal obesity and diabetes. Childhood obesity is associated with anxiety, depression, and social problems (Rizzo et al., 1997). Female infants with a high birth weight or a ponderal index, a measure of weight to height ratio similar to BMI, in the top 10% are more likely than those of normal birth weight and ponderal index to be depressed as adults (Herva et al., 2008). Even in non-obese children, a higher BMI is associated with depression and anxiety (Rofey et al., 2009). Adult obesity is also associated with increased risk of anxiety and depressive disorders (Simon et al., 2006). Interestingly, the association between obesity and depression and anxiety is stronger in females than males (Desai et al., 2009). Women are also more prone to these disorders than men (Desai et al., 2009; Zhao et al., 2009), but this relationship holds true for average or overweight women, but not underweight women (Zhao et al., 2009). This is likely an interaction between sex hormones and hormones produced by adipose tissue. There appears to be a connection between maternal obesity, child obesity, and anxiety and depression, particularly in female offspring, which requires further study.

III. Mechanisms by which Maternal High-Fat Diet Consumption and Obesity Program Offspring Neurocircuitry and Behavior

Evidence from both epidemiological studies and animal models provides insight into the impact of maternal obesity and HFD consumption on the development of the neurocircuitry critical to behavioral regulation. Rodent models are widely used to study the effects of maternal HFD consumption and obesity on offspring. These studies provide a high level of environmental control and mechanistic insights that cannot be obtained in human studies. Rodent studies have clarified several mechanisms by which maternal HFD consumption can

influence offspring behavior, including maternal inflammation altering offspring neurocircuitry. Nearly all studies on maternal obesity in rodents use a HFD to induce obesity, and therefore obesity and diet are not examined separately. An exception to this is a study using an embryo transfer design in which obese or control dams had their embryos implanted into obese or control females (Grissom et al., 2014). This study demonstrates that obesity before pregnancy can alter the offspring brain, as shown by altered expression of opioid receptors (Grissom et al., 2014). As rodent brain development extends into the early postnatal period, maternal diet exclusively during lactation has also been studied. When rat dams were placed on a HFD during lactation, their offspring were developmentally delayed and had increased depressive and aggressive behaviors compared to controls (Giriko et al., 2013), showing that nutrition during lactation is also important in offspring development and behavior. Very few studies examine the effects of maternal diet or obesity on offspring behavior using nonhuman primates or other large mammals. More of these studies are needed, as large animal models benefit from the environmental controls possible in rodent studies, but are similar to humans in the timing of brain development, placental structure, and complex behavioral patterns.

A. Neuroendocrine Mechanisms

Glucose and Insulin—Maternal obesity exposes the developing fetus to increased levels of nutrients and endocrine agents such as fatty acids, glucose, triglycerides, leptin, and inflammatory cytokines. Both maternal obesity and maternal diabetes are associated with elevated blood glucose (Leung and Lao, 2000), and, as glucose can penetrate the blood-placenta barrier, the developing fetus is exposed to hyperglycemia. These metabolic disorders are also associated with elevated insulin levels; however, because insulin does not cross the placenta (Oken and Gillman, 2003), the pancreas of the fetus secretes increased insulin in response to the hyperglycemia. Considering insulin's important role as a growth factor in brain development (Simerly, 2008), this exposure to hyperinsulinemia during prenatal period may alter the development of brain circuitry critical in regulating behavior.

Leptin—Leptin is also elevated in obese and diabetic mothers (Hauguel-de Mouzon and Shafrir, 2001; Lepercq et al., 2002). In humans, leptin receptors are distributed in many brain regions critical in behavioral regulation such as the cortex, hippocampus, amygdala, thalamus, and hypothalamus (Couce et al., 1997; Meister, 2000). Moreover, leptin and its receptors are widely distributed in the HPA axis (Roubos et al., 2012), which plays an important role in regulating the stress response and is implicated in emotional disorders such as anxiety and depression (Arborelius et al., 1999; Lamers et al., 2012; Raadsheer et al., 1994). Leptin can also act indirectly to influence fetal development, by increasing inflammatory cytokines in both maternal circulation and in the placenta (Lappas et al., 2005).

Elevated leptin has been studied in association with ASD within human populations. Children with ASD have higher levels of leptin than age matched controls, particularly those with early onset autism (Ashwood et al., 2008). This remains significant when medicated state, IQ, and BMI are controlled for. In a study examining children with ASD without comorbid disorders, leptin levels were higher than in control children (Blardi et al., 2010).

Leptin levels also increased at a higher rate in children with ASD than in the control population (Blardi et al., 2010). A postmortem study examining brain tissue showed that leptin and inflammatory cytokines were elevated in the anterior cingulate gyrus of patients with autism compared to controls (Vargas et al., 2005) Increased leptin likely contributes to the immune dysfunction and increased inflammatory cytokines found in ASD.

Inflammation—Obesity is associated with elevated inflammatory cytokine production, due to increased adiposity, and is considered a state of chronic inflammation (Visser et al., 1999). Exposure to inflammation during gestation is associated with premature birth, low birth weight (Blackmore et al., 2011), and neurodevelopmental disorders such as ADHD (Donev and Thome, 2010), ASD (Angelidou et al., 2012), and schizophrenia (Buka et al., 2001). Inflammatory factors readily cross the blood placental barrier and impact fetal brain development. Rodent studies indicate that administration of the proinflammatory cytokine interleukin-6 impacts cortical gene expression and behavior (Smith et al., 2007). Evidence from both rodent (Bilbo and Tsang, 2010) and nonhuman primate (Grayson et al., 2010; Sullivan et al., 2010) models indicate that maternal HFD consumption causes elevated levels of inflammatory markers in the brain, which has a long-term impact on behaviors such as anxiety and learning. In rodents, consumption of a HFD during pregnancy resulted in increased markers of microglial activation and proinflammatory cytokines in the hippocampi of offspring (Bilbo and Tsang, 2010). The offspring were weaned onto a control diet at P21, but male offspring demonstrated increased anxiety-like behavior in adulthood (P85-95), as shown by spending less time in open arms compared to the closed arms of an elevated plus maze. In research examining gender differences in rodent offspring, female offspring from HFD fed dams have increased proinflammatory cytokines and microglial activity, along with social impairments and increased anxiety-like behavior (Kang et al., 2014), mirroring results from nonhuman primate studies. These behaviors were demonstrated by a social interaction test to observe how long a mouse spent alone versus in the same chamber as another mouse, and an open field assay to see how much time the mouse spent in the brightly lit center versus along the perimeter and how much distance was traveled (Kang et al., 2014). Male offspring from HFD mothers exhibited elevated hyperactivity compared to control offspring. In this study, a dietary intervention during lactation ameliorated brain inflammation and social deficits, and partially ameliorated anxiety-like behavior in females, but did not alter hyperactivity in the males (Kang et al., 2014).

Exposure of the developing fetus to inflammatory cytokines results in behavioral abnormalities consistent with ASD (Buehler, 2011; Onore et al., 2012). A case-control study found that mothers of children with ASD had increased inflammation during pregnancy (Goines et al., 2011). Immune dysfunction occurs in pregnancy which is complicated by maternal HFD consumption, infections, or illness; and all of these have been found to increase the risk of ASD in offspring (Onore et al., 2012). Also, immune dysfunction is highly correlated with ASD, with greater immune dysfunction associated with increased impairment in patients with ASD (Ashwood et al., 2011; Onore et al., 2012). Evidence from animal models and human studies indicates that the development of many neural systems that are critical in behavioral regulation, such as the serotonergic system, the dopaminergic

system, and the HPA axis, are sensitive to circulating cytokine levels (Das, 2001; Ishikawa et al., 2007; Jarskog et al., 1997).

B. Neural systems

Serotonin and Behavior—The serotonergic system is very important in regulation of emotion and psychological disorders. Animals treated with the proinflammatory cytokine interferon-alpha have decreased serotonergic axon density in the ventral medial prefrontal cortex and amygdala (Ishikawa et al., 2007). In rodents, offspring of mothers consuming a HFD had alterations in the hippocampus, including increased brain-derived neurotrophic factor (BDNF) in the dorsal hippocampus, and increased 5-HT1A receptors in the ventral hippocampus (Peleg-Raibstein et al., 2012). These offspring had increased anxiety behaviors, but normal conditioned fear responses and normal exploratory behavior (Peleg-Raibstein et al., 2012). A suppression of serotonin synthesis is well documented in humans diagnosed with ADHD (Oades et al., 2008) and other neurodevelopmental disorders, such as ASD (Challier et al., 2008; Chugani et al., 1999), and anxiety and depressive disorders (Laucht et al., 2009; Spindelegger et al., 2009; Sullivan et al., 2006). All of these disorders are commonly treated with selective serotonin reuptake inhibitors. Consequently, a possible mechanism by which maternal obesity increases risk for the neurodevelopmental disorders is by the suppression of the brain serotonin system in response to exposure to increased inflammation.

Using a nonhuman primate model, our group has demonstrated that maternal HFD consumption impairs the development of the serotonergic system resulting in a reduction of serotonin synthesis and increased anxiety behaviors (such as increased latency to touch novel objects) specifically in female offspring (Sullivan et al., 2010). Further data has shown that increased anxiety behaviors persists in juvenile female offspring from HFD mothers whether they remain on a HFD or are switched to a control diet after weaning (Sullivan and Valleau, in press). Hyperactivity and repetitive pacing behavior is also increased in HFD offspring at this later age, particularly in males (Sullivan and Valleau, in press). Our nonhuman primate model also demonstrates that mothers on a HFD during pregnancy have increased placental inflammation (Frias et al., 2011), and their offspring have increased inflammation in the hypothalamus (Grayson et al., 2010), again suggesting that maternal inflammation found in obesity suppresses offspring serotonin thereby increasing risk for behavioral abnormalities. As human development and physiology is so similar to that of other primate species, the same mechanisms are likely responsible for the increased psychological disorders seen in human offspring from obese and metabolically impaired mothers.

Dopamine and Behavior—Dopamine dysregulation is another potential mechanism by which HFD offspring develop abnormal behavior. Rat offspring from mothers fed a HFD during late gestation and lactation had elevated mesocorticolimbic dopamine (DA) in the nucleus accumbens, leading to decreased DA sensitivity, demonstrated by decreased locomotor activity in response to psychostimulant administration (Naef et al., 2008). Additionally, HFD fed rat dams have offspring with increased DA responses to acute stress, but not the sensitized DA and ACTH responses to repeated stress that is observed in control

animals (Naef et al., 2013). A mouse model of maternal HFD-induced obesity showed dopamine dysregulation in the offspring, including changes in methylation and gene expression (Vucetic et al., 2010). Maternal inflammation itself has been found to effect offspring dopamine, as maternal leptin and interleukin-6 increase the activity of dopamine neurons in the nucleus accumbens of adult offspring, as well as increasing locomotor response to amphetamines (Aguilar-Valles et al., 2012). Maternal inflammation has been previously shown to cause offspring deficits in latent and prepulse inhibition, along with decreased social and exploratory behavior (Smith et al., 2007), which are associated with dopamine dysfunction and mental health disorders such as schizophrenia and ASD. The increased inflammation that accompanies maternal HFD consumption likely impacts the dopaminergic system of offspring, causing increased risk of psychopathology as changes in the dopaminergic system are associated with disorders such as ASD(Bowton et al., 2014; Hamilton et al., 2015; Staal, 2014), ADHD (Hasler et al., 2015; Pan et al., 2015; Tong et al., 2015), schizophrenia (Howes et al., 2015; Slifstein et al., 2015; Sumiyoshi et al., 2014), anxiety (Agius et al., 2014; Lee et al., 2015), and depression (Clausius et al., 2009; Dunlop and Nemeroff, 2007).

Hypothalamic-Pituitary-Adrenal Axis and Behavior—The hypothalamic-pituitary-adrenal (HPA) axis and extrahypothalamic corticotropin-releasing hormone (CRH) expressing neurons play an important role in regulating stress response and behavioral response to stress. In human populations, HPA hyperactivity is commonly associated with depressive and anxiety disorders (Stetler and Miller, 2011). Thus, examination of the impact of maternal obesity and HFD consumption on the development of the HPA axis is critical. The peptide hormones CRH and arginine vasopressin are synthesized in the paraventricular nucleus (PVN) of the hypothalamus in response to stress. CRH and vasopressin are released into the hypothalamo-hypophyseal portal system where they stimulate the corticotroph cells in the pituitary gland to produce adrenocorticotropic hormone (ACTH). ACTH is released into systemic circulation and acts on the adrenal cortex to trigger release of glucocorticoids (primarily cortisol in humans and nonhuman primates and corticosterone in rodents). The glucocorticoids in turn regulate HPA axis activity by acting on the pituitary, hypothalamus, hippocampus, and amygdala. It is important to note that during the basal state, ACTH release is regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus and thus both ACTH and cortisol exhibit diurnal variation (Sage et al., 2001). Several studies indicate the response of the HPA axis to stress also exhibits a circadian rhythm. (Sage et al., 2001) A second distinct population of CRH expressing neurons is located in the amygdala and lateral bed nucleus of the stria terminalis (Schulkin et al., 1998). This population is not directly regulated by glucocorticoids and is thought to regulate fear and anxiety. Maternal obesity and diet impact both the HPA axis and extrahypothalamic CRH neurons, which can contribute to human mental health disorders. Rats fed a HFD starting mid-pregnancy were reported to have male offspring with increased basal corticosterone levels at postnatal day 10 (D'Asti et al., 2010). This HPA axis dysregulation was associated with reduced hypothalamic and hippocampal phospholipid-derived arachidonic acid (D'Asti et al., 2010). In mice, basal blood corticosterone level negatively correlates with the change in corticosterone level and anxiety behaviors during chronic stress (Kim et al., 2013). In another study, rat dams consuming a HFD during pregnancy and lactation had offspring

with decreased basal corticosterone levels, but a heightened response to stress with a slower restoration of baseline corticosterone levels in adulthood, along with increased anxiety-like behaviors (Sasaki et al., 2013). These animals also had increased glucocorticoid receptors in the amygdala and altered inflammatory gene expression in the hippocampus and amygdala (Sasaki et al., 2013). Glucocorticoids act on glucocorticoid receptors in the amygdala to regulate CRH expression and anxiety-like behavior (Schulkin et al., 1998). In contrast to the findings in adult offspring, the researchers observed decreased anxiety behaviors in adolescent offspring exposed to a perinatal diet high in fat along with increased glucocorticoid receptors expression in the hippocampus. These age-dependent behavioral changes may be due to differences in the stress response profile of adults and adolescents such as that found in human studies, in which impulsivity in adolescents is associated with anxiety in adults (Sasaki et al., 2014). In both human and animal studies, offspring exposed to maternal obesity-induced inflammation display alterations in the HPA axis and extrahypothalamic CRH expression. This is a plausible mechanism by which maternal obesity can increase the risk of anxiety-related disorders in offspring.

C. HFD Consumption Modifies Maternal Behavior

It is well documented that maternal behavior towards her infant during the perinatal period has a long-term influence on the behavior of the offspring. Recent data indicates that diet may affect the behavior of mothers towards their infants, thereby indirectly altering offspring behavior. Rodent studies provide substantial evidence that differences in maternal care during the early postnatal period have a persistent impact on offspring behavior and stress responsivity (Caldji et al., 2011; Parent and Meaney, 2008). A reduction in grooming and maternal attention during the early post-natal period is associated with increased anxiety-like behavior in adult offspring (Parent and Meaney, 2008; Walker, 2010). Mothers who are attentive have offspring with less anxiety and are better able to regulate their response to stress (Walker, 2010; Weaver et al., 2006). Moreover, maternal attentiveness is associated with improved plasticity in the hippocampus in response to stress and enhanced contextual fear conditioning (Bagot et al., 2009). In rodent models, maternal HFD consumption increases nursing behaviors (Bertino, 1982; Connor et al., 2012; Purcell et al., 2011), and some evidence suggests that it decreases grooming behaviors (Connor et al., 2012). In our nonhuman primate model, we also see an increase in nursing and decrease in grooming behaviors among our HFD fed mother-infant pairs (Sullivan et al., in preparation). In humans, postpartum depression influences maternal behavior and increases the risk of mental health disorders in offspring later in life (Verbeek et al., 2012). Consumption of an unhealthy Western style diet increases the risk of postpartum depression, and consumption of a healthy diet can improve symptoms (Okubo et al., 2011). By altering maternal behavior, maternal HFD consumption can indirectly modify offspring psychology and behavior. It is important for future studies to explore the diet composition that optimizes maternal infant interactions and thus, decreases the risk of offspring experiencing mental health and neurodevelopmental disorders. Also, more research is needed in order to differentiate the impact of prenatal nutrition from the impact of diet on maternal behavior that subsequently influences offspring behavior.

IV. Conclusion

The perinatal environment has a substantial impact on the development of offspring brain neurocircuitry and behavioral regulation. Factors such as maternal obesity, metabolic state, and diet during gestation can all impact the developing offspring. Mounting evidence from human studies implicates maternal obesity as a risk factor for neurodevelopmental disorders such as ADHD and ASD. Also, two studies report that maternal obesity increases the risk of schizophrenia. Currently, there are no human studies that provide direct evidence that maternal obesity increases the risk of offspring developing anxiety or depression. However, maternal obesity has been linked to impairments in child emotional regulation and to increased risk factors for anxiety and depression such as high or low birth weight, childhood obesity, and adult obesity. Increased gestational weight gain has also been examined as a potential risk factor. Currently a limited number of studies have examined gestational weight gain as a risk factor for neurodevelopmental and mental health disorders and the data that does exist is inconsistent. A few studies demonstrate that increased pregnancy weight gain is associated with greater risk of ASD and ADHD in offspring. However, elevated gestational weight gain has not been shown to influence risk for schizophrenia or anxiety and depression. Maternal metabolic conditions such as diabetes, hypertension, and pre-eclampsia have been examined as potential risk factors for neurodevelopmental and mental health disorders. Exposure to these metabolic conditions during pregnancy is associated with increased risk of ASD and developmental delays in offspring. There is also limited evidence that maternal diabetes mellitus increases risk for ADHD. Additionally, a few studies indicate that exposure to maternal pre-eclampsia and diabetes increase risk for schizophrenia. Currently, there are no studies that have examined gestational metabolic conditions and anxiety and depression risk. Overall, there is substantial evidence that maternal obesity may be a risk factor for neurodevelopmental disorders. The impact of maternal diet, metabolic state, and gestational weight gain are understudied and need to be examined in future studies. Moreover, the mechanisms by which maternal obesity impacts offspring risk for neurodevelopmental disorders remain unclear. Thus, it is critical that future studies examine the mechanisms for this association and identify potential therapeutic strategies to mitigate the increased risk of neurodevelopmental disorders due to exposure to maternal obesity during development.

Evidence from animal models supports the epidemiologic studies and demonstrates that maternal HFD-induced obesity impacts behavioral programming of offspring resulting in impairments in social behavior, increased anxiety and depressive behaviors, reduced cognitive development, and hyperactivity. Maternal obesity, metabolic conditions, and HFD consumption during gestation are associated with placental dysfunction and exposure of the developing fetus to increased circulating levels of leptin, insulin, glucose, triglycerides, and inflammatory cytokines. Exposure to increased inflammatory factors during fetal development leads to increased inflammation in several brain regions, as well as impairments in the development of the serotonergic system and dopamine. These impairments in the development of neural circuitry critical in behavioral regulation appear to be persistent and contribute to the increased risk of neurodevelopmental and mental health disorders in offspring exposed to maternal obesity. Many of the same systems that regulate

behavior also regulate food intake and metabolism, such as serotonin, dopamine, and the HPA axis. So, in addition to increased risk of mental health disorders, children of obese mothers are also at higher risk of becoming obese themselves (Sullivan and Grove, 2010). It is well established that individuals who are obese or who have metabolic syndrome are at higher risk for a multitude of comorbid mental health disorders (Carpiniello et al., 2012). Maternal obesity and metabolic issues can therefore directly and indirectly increase the risk of mental health disorders by disrupting the development of this neural circuitry. Considering the pervasiveness of maternal obesity and HFD consumption and its marked impact on fetal development, the prevalence of neurodevelopmental and mental health disorders will continue to rise in future generations. In light of the substantial societal impact of these disorders it is critical that future studies identify interventions that are effective in diminishing the effects of maternal obesity and HFD consumption during gestation on offspring behavior and brain development.

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Highlights

- Maternal obesity increases risk for neurodevelopmental disorders
- Maternal metabolic conditions increase risk of neurodevelopmental disorders
- In animals maternal high-fat diet disrupts behavioral programming of offspring
- Maternal obesity results in increased hormones, nutrients and inflammatory factors
- Maternal high-fat diet and obesity impact offspring brain development