Hormones and Behavior 76 (2015) 153–161

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Maternal high-fat diet programming of the neuroendocrine system and behavior

Elinor L. Sullivan [a,b,*], Kellie M. Riper [a], Rachel Lockard [a], Jeanette C. Valleau [b]

[a] Department of Biology, University of Portland, Portland, OR, USA
[b] Division of Diabetes, Obesity and Metabolism, Oregon National Primate Research Center, Beaverton, OR, USA

ARTICLE INFO

Available online 24 April 2015

Keywords:
Maternal obesity
Anxiety
Autism
ADHD
Schizophrenia
Pregnancy
High-fat diet
Programming

ABSTRACT

This article is part of a Special Issue "SBN 2014".

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.

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 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 has increased dramatically in parallel with the rise in obesity rates (Boyle et al., 2011; Elsabbagh et al., 2012; Fombonne et al., 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.

* Corresponding author at: University of Portland, 5000 N. Willamette Blvd., Portland, OR 97203, USA. Fax: +1 503 943 7784.
E-mail address: sullivae@up.edu (E.L. Sullivan).

http://dx.doi.org/10.1016/j.yhbeh.2015.04.008
0018-506X/

Evidence from human studies suggests that maternal metabolic state and diet impact offspring's risk for behavioral disorders

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 symptomatology (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 the DSM-V criteria. This same cohort of children displayed reduced emotional regulation, with children from obese mothers having 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.

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 et al., 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