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Review

Maternal high fat diet consumption during the perinatal period programs offspring behavior

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HIGHLIGHTS

- Maternal diet and metabolic status have a long-term impact on offspring behavior.
- Obesity is associated with increased inflammatory cytokines, nutrients, and hormones.
- Increases in circulating factors impact the environment of the developing offspring.
- Offspring exposed to maternal obesity during development are at increased risk for mental health disorders.

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ABSTRACT

The environment that a developing offspring experiences during the perinatal period is markedly influenced by maternal health and diet composition. Evidence from both epidemiological studies and animal models indicates that maternal diet and metabolic status play a critical role in programming the neural circuitry that regulates behavior, resulting in long-term consequences for offspring behavior. Maternal diet and metabolic state influence the behavior of offspring directly by impacting the intrauterine environment and indirectly by modulating maternal behavior. The mechanisms by which maternal diet and metabolic profile shape the perinatal environment remain largely unknown, but recent research has found that increases in inflammatory cytokines, nutrients (glucose and fatty acids), and hormones (insulin and leptin) affect the environment of the developing offspring. Offspring exposed to maternal obesity and high fat diet consumption during development are more susceptible to developing mental health and behavioral disorders such as anxiety, depression, attention deficit hyperactivity disorder, and autism spectrum disorders. Recent evidence suggests that this increased risk for behavioral disorders is driven by modifications in the development of neural pathways involved in behavioral regulation. In particular, research indicates that the development of the serotonergic system is impacted by exposure to maternal obesity and high fat diet consumption, and this disruption may underlie many of the behavioral disturbances observed in these offspring. Given the high rates of obesity and high fat diet consumption in pregnant women, it is vital to examine the influence that maternal nutrition and metabolic profile have on the developing offspring.

Contents

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1. Introduction

The majority of infants born in the United States and other western countries are exposed to maternal obese or overweight metabolic status and high fat diet (HFD) consumption during perinatal development. In the U.S., data from latest National Health and Nutrition Examination Survey (compiled from 1999–2010) indicates that 69% of adults are overweight or obese [1]. This increased risk of obesity is thought to be due to hyperphagia [2] and decreased physical activity [3]. At this time, about one third of pregnant women in the U.S. are obese [4], and this metabolic state has persistent implications for both the women and their children. Mammals encounter two environments during neural development: the intrauterine and early postnatal environments. Both of these are highly influenced by maternal diet and metabolic status. Animal models provide strong evidence that perinatal nutrition has an enduring impact on numerous aspects of offspring physiology and behavior, including a higher likelihood of developing mental health disorders [5,6], impairments in social behaviors [7], decreased cognitive abilities [6,8,9], enhanced response to stress [10,11], and altered reward-based behaviors [12]. The metabolic profile of the mother has an additional impact on the developing offspring. Factors associated with maternal obesity, such as inflammation [13], hyperlipidemia, lipotoxicity, hyperglycemia, and insulin resistance, have each been demonstrated to have a long-term effect on the developing offspring and are associated with increased risk of mental health disorders including anxiety and depression [5,6,14], attention deficit hyperactivity disorder (ADHD) [15], and autism spectrum disorders (ASD) [16–18].

With the current prevalence of obesity in western nations, it is vital to examine the impact that this may have on the behavior and physiology of future generations. In animal models, a HFD is commonly used to promote maternal obesity. In the majority of these studies, most of the females consuming the HFD become obese, and so it is difficult to determine which outcomes are due to factors associated with maternal obesity (e.g., hyperlipidemia, hyperglycemia, and hyperinsulinemia) versus the consumption of a HFD. Furthermore, maternal HFD consumption and obesity often co-occur in humans, making it difficult to discriminate the effects of the HFD itself from the maternal metabolic profile. Our group has developed a nonhuman primate (NHP) model of maternal obesity, and an important advantage of this model is that approximately one third of the females consuming the HFD are resistant to weight gain in response to the diet. These animals have body weights similar to control animals, and this allows us to distinguish the effects of HFD intake from maternal obesity. As the majority of studies examine maternal obesity induced by HFD consumption, this review will therefore discuss the effects of both factors and will assume that consumption of a diet high in fat results in obesity. In addition, we will highlight studies that are able to distinguish between the effects of maternal HFD consumption and maternal obesity on offspring.

2. Co-morbidity between obesity and mental health disorders

In humans, the obese state itself is associated with increased risk of developing mental health disorders, including anxiety [19], depression [19], and ADHD [20]. Obesity also increases susceptibility to neurodegenerative disorders such as Alzheimer's disease [21–23] and Parkinson's disease [24,25]. When combined with obesity, factors like socioeconomic status, ethnicity, and maternal attitudes further increase the propensity for children to develop problems with internalization and social interaction [26]. Conversely, anxiety and depression are known to influence human obesity risk by impacting ingestive behavior, food preference, and physical activity level. Mood disorders like anxiety and depression are associated with enhanced desire for palatable energy-dense foods [27] and decreased levels of physical activity [28]. Reward-based eating has been shown to decrease feelings of stress in human patients [29], and has been described as an addiction or a type of self-medication with comfort food [30]. This effect is supported by animal studies that show that consumption of a palatable diet decreases anxiety in the short-term [31] and decreases anxiety and depression-like symptoms in rats exposed to perinatal stress [32]. Evidence from rodent studies indicates that the observed reduction in anxiety-like behaviors is linked to an increase in glucocorticoid receptor mRNA expression in the hippocampus, providing support to the idea that palatable diet consumption influences the endocrine system to alleviate anxiety [32]. Perinatal exposure to a HFD has been demonstrated to alter the development of key pathways implicated in regulating mood and behavior such as the serotonergic [33] and dopaminergic [2,34] systems.

3. HFD consumption impacts offspring behavior by modifying maternal behavior

When diet affects the behavior of mothers, it indirectly results in changes in the behavior of the offspring. In rodent models, naturally occurring individual differences in maternal care during early postnatal life are associated with the programming of differences in offspring behavior and stress response [35–37]. Mothers that display decreased grooming and a lack of attentive behavior towards their offspring have offspring with increased anxiety-like behavior, and mothers who are attentive have offspring who are less anxious and better suited to handle stressful situations [38,39]. Offspring from attentive mothers have improved hippocampal plasticity during stress and enhanced contextual fear conditioning [37]. In addition, male offspring of rat dams that exhibited a high frequency of licking and grooming behavior towards their pups display decreased aggression towards their peers [35]. All of these measures indicate that the nature of the interaction between mother and offspring influences the behavior of the offspring.

There is also evidence that experiencing maternal rejection or separation has a long-term impact on offspring behavior. NHP offspring experiencing maternal rejection are reported to be more prone to anxiety-like behaviors [40]. Female rodent offspring exposed to maternal separation displayed increased anxiety-like behavior in social situations [41]. However, other studies find that early maternal rejection increases offspring independence and decreases infant stress behaviors [42]. Therefore, the behavioral outcome appears to be influenced by the time period when the offspring experiences the maternal separation or rejection. For example, monkeys separated from their mother at one week of age showed increased self-comforting behaviors (such as thumb sucking), whereas those

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