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Review article

Offspring neuroimmune consequences of maternal malnutrition: Potential mechanism for behavioral impairments that underlie metabolic and neurodevelopmental disorders

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ABSTRACT

Maternal malnutrition significantly increases offspring risk for both metabolic and neurodevelopmental disorders. Animal models of maternal malnutrition have identified behavioral changes in the adult offspring related to executive function and reward processing. Together, these changes in executive and reward-based behaviors likely contribute to the etiology of both metabolic and neurodevelopmental disorders associated with maternal malnutrition. Concomitant with the behavioral effects, maternal malnutrition alters offspring expression of reward-related molecules and inflammatory signals in brain pathways that control executive function and reward. Neuroimmune pathways and microglial interactions in these specific brain circuits, either in early development or later in adulthood, could directly contribute to the maternal malnutrition-induced behavioral phenotypes. Understanding these mechanisms will help advance treatment strategies for metabolic and neurodevelopmental disorders, especially noninvasive dietary supplementation interventions.

1. Introduction

Maternal malnutrition, either overnutrition or undernutrition, significantly increases offspring risk for metabolic dysfunction and metabolic disease (Delahaye et al., 2008; Gardner et al., 2005; Hale et al., 2015; Hales and Barker, 2001; Ralevski and Horvath, 2015; Ravelli and Osmond, 1999; Ravelli et al., 1976; Roseboom et al., 2000; Spencer, 2013a; Sullivan et al., 2015). Disruptions in the endocrine system are clearly associated with this risk since maternal malnutrition affects hypothalamic circuits (Ralevski and Horvath, 2015). However, maternal diet-induced changes in cognitive behaviors that govern food preference and food intake suggest that higher order brain circuits involved in executive control and reward processing also contribute to metabolic programming (Bayol et al., 2007; Bellinger et al., 2004; Conceição et al., 2016; Palou et al., 2010; Rivera et al., 2016). Understanding how maternal diet affects cognitive control of food intake and processing of food-related reward cues is essential to understanding metabolic dysfunction in species with complex eating behaviors (e.g., humans). In addition to increasing metabolic dysfunction in the offspring, maternal malnutrition increases the risk for neurodevelopmental disorders such as autism, attention deficit/hyperactivity disorder, and schizophrenia (Brown and Susser, 2008; Buss et al., 2012; Krakowiak et al., 2012; Mina et al., 2016; Rivera et al., 2015; Rodriguez et al., 2008; Schaefer et al., 1998; Sullivan et al., 2015; Susser et al., 1996). Hallmark features of these disorders include deficits in prefrontal executive control and reward processing (Aron and Poldrack, 2005; Blum et al., 2008; Brisch, 2014; Happé et al., 2006; Kriete and Noelle, 2015; Orellana and Slachevsky, 2013; Previc, 2006; Schachar et al., 1993; Weinberger, 1987). These behavioral features overlap with maternal malnutrition-induced changes in cognitive control of food intake that can predispose offspring to metabolic disorders. We posit that these executive and reward-related behaviors programmed by maternal diet are central to the risk for both metabolic and neurodevelopmental disorders.

Maternal malnutrition can increase offspring exposure to inflammatory factors, which is suggested to play a mechanistic role in neuroendocrine and neurodevelopmental programming (Spencer, 2013b). Microglia, the resident immune cells of the CNS, are extremely active in establishing synaptic networks during the late embryonic and early postnatal period that program brain function into adulthood (Frost and Schafer, 2016; Lenz et al., 2013; McCarthy et al., 2015; Paolicelli et al., 2011; Schafer et al., 2012; Zhan et al., 2014). This microglial-mediated synaptic wiring engages unique neuroinflammatory mechanisms in the retinogeniculate system (Schafer et al., 2012), preoptic area for sex-specific behavior (Lenz et al., 2013; McCarthy and Wright, 2016; McCarthy et al., 2015), and helps establish

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prefrontal-hippocampal connectivity (Zhan et al., 2014).

It is unknown exactly if or how maternal diet influences microglial-directed neurodevelopmental processes. However, microglia respond to changes in diet (Valdearcos et al., 2014) and maternal malnutrition exposure coincides with a developmental window of increased microglial-mediated brain patterning. Microglia are actively involved in dopaminergic and cortical wiring (Squarzoni et al., 2014), suggesting that these neuroimmune cells may therefore be neuroanatomically situated to control the development of executive and reward-based behaviors through their influences on dopaminergic and cortical tracts. Furthermore, beyond this developmental window, neuroimmune signaling in adulthood can significantly affect neuronal function and modulate some of these same behaviors (Bachtell et al., 2015; Crews et al., 2011; Hutchinson et al., 2012; Northcutt et al., 2015; Vetreno and Crews, 2012; Vichaya et al., 2014), particularly in the context of peripheral inflammation.

Maternal malnutrition influences neuroimmune signaling and reward-related molecular signatures in the offspring (Bilbo and Tsang, 2010; da Silva et al., 2013; Grissom et al., 2016, 2015, Naef et al., 2013, 2011; Silva et al., 2010; Vucetic et al., 2010a, 2010b). Many of these effects are specific to brain regions that control executive function and reward behaviors (Grissom et al., 2016; McKee et al., 2017; Vucetic et al., 2010a, 2010b). Together, we propose that these neuroimmune and reward-related molecular changes share a common mechanism and impart functional changes, whereby neuroimmune signaling programs executive and reward circuits through microglial-neuron interactions in early development and/or later in adulthood. We review the evidence in the field that supports this notion, along with addressing gaps in the literature to inform future studies.

2. The consequences of maternal diet on offspring neurodevelopment and behavior

2.1. Maternal malnutrition risk for neurodevelopmental disorders

Maternal malnutrition significantly elevates children's risks for neurodevelopmental disorders. This is especially true for neurodevelopmental disorders such as autism spectrum disorders (ASD), attention deficit/hyperactivity disorder (ADHD), and schizophrenia (Brown and Susser, 2008; Buss et al., 2012; Krakowiak et al., 2012; Mina et al., 2016; Rivera et al., 2015; Rodriguez et al., 2008; Schaefer et al., 1998; Sullivan et al., 2015; Susser et al., 1996), that are increasing in prevalence and cause significant debilitation. Children of mothers exposed to nutrient deficiencies or famine are twice as likely to develop schizophrenia (Brown and Susser, 2008; Susser et al., 1996). Alternatively, high maternal body weight can triple the child's risk for schizophrenia and ASD (Schaefer et al., 1998) and can increase the risk for development of ADHD (Buss et al., 2012). Maternal obesity significantly increases the severity of ADHD and ASD symptoms in children (Buss et al., 2012; Mina et al., 2016; Rodriguez et al., 2008). Maternal conditions associated with poor diet and obesity, such as hypertension and diabetes, also increase the likelihood of a child experiencing developmental delays or being diagnosed with ASD (Krakowiak et al., 2012). These risks associated with maternal nutritional status remain after controlling for other risk factors, such as cigarette smoking, maternal age, or parity (Rodriguez et al., 2008; Schaefer et al., 1998).

ASD, ADHD, and schizophrenia have a high male prevalence (Previc, 2006) and male offspring are also more susceptible to the effects of maternal malnutrition, suggesting that sex affects offspring vulnerability to neurodevelopmental insults (Bhasin et al., 2009; Desai et al., 2005; Palou et al., 2010; Previc, 2006; Ramírez-López et al., 2016; Sugden and Holness, 2002; Whitaker et al., 2012). The mechanism(s) that underline sex differences in the prevalence of neurodevelopmental disorders is currently unknown, and therefore a topic of significant research interest. Potential mechanisms that have been identified and recently reviewed include a role of genetic sex (Arnold, 2004) or steroid hormones (Davies, 2014; Davis and Pfaff, 2014; Markham, 2012). Additionally, basic neuroimmunological sex differences are a likely candidate mechanism that contributes to the differential prevalence of neurodevelopmental disorders (Hanamsagar and Bilbo, 2016; McCarthy et al., 2017), which will be discussed in more detail in Section 3. As a whole, studying the effects of maternal malnutrition on the offspring may shed light on the etiology of ASD, ADHD, and schizophrenia. Specifically, animal models can help unravel the neurodevelopmental mechanisms that directly contribute to these debilitating disorders.

2.2. Animal models of maternal malnutrition

Maternal malnutrition has two broad categories: overnutrition and undernutrition. Malnutrition models are employed in species such as nonhuman primates, sheep, and most commonly rats and mice (Alfaradhi and Ozanne, 2011). Animal models are advantageous because researchers can manipulate maternal nutritional environment explicitly in gestation or lactation, or encompass both critical periods (Alfaradhi and Ozanne, 2011). Additionally, researchers can study the effects of specific macronutrients versus total calories.

2.2.1. Maternal undernutrition models

Maternal undernutrition models include general caloric restriction, low protein, and large litter size (Bertram and Hanson, 2001; Plagemann, 2006; Spencer, 2013a). Caloric restriction does not affect macronutrient composition but allows for varying degrees of undernutrition. This ranges from mild restriction by withholding approximately 15–30% of total calories, moderate restriction by withholding 50% of total calories, or severe restriction by withholding 70% of total calories (Bertram and Hanson, 2001). Mild restriction does not affect pup birth weight (Palou et al., 2010; Ramírez-López et al., 2016), but more moderate caloric restriction causes pups to be born small for gestational age (Delahaye et al., 2008; Desai et al., 2005).

While general caloric restriction may be relevant to extreme cases of famine, deficiencies of specific macronutrients are of issue as well, as a large proportion of the human population is deficient in protein (Morgane et al., 1978). Protein is the most expensive and least available macronutrient in even well-developed countries, causing people to fill their caloric needs with inexpensive and poor quality carbohydrates and fats (Morgane et al., 1978). Therefore, the maternal low protein (LP) model is highly relevant for studying maternal undernutrition (Stocker et al., 2005). Maternal LP diets allow for isocaloric comparisons while reducing the standard 20% protein composition to approximately 8% protein (Stocker et al., 2005; Sugden and Holness, 2002; Whitaker et al., 2012; Zambrano et al., 2006). Offspring from LP dams are small for gestational age and remain small into adulthood (Bhasin et al., 2009; Bieswal et al., 2006; Whitaker et al., 2012).

Adjustment of litter size on the first postnatal day serves as a natural model for studying maternal-offspring nutrition without manipulating dietary content (Fiorotto et al., 1991; Spencer, 2013a; Widdowson and McCance, 1960). As a model for maternal undernutrition, rearing in large litters (dams with more than 15 pups) decreases offspring growth rate. This results from naturally decreased milk supply and changes breast milk composition available to the pups (Fiorotto et al., 1991). Dams with large litters have higher milk protein ratios and their pups are smaller, leaner, and maintain lower growth rates throughout life (Fiorotto et al., 1991; Spencer, 2013a; Widdowson and McCance, 1960). This litter size model for maternal undernutrition is unique in that it exclusively manipulates the offspring postnatal window without changing the diet ingested by the mother.

2.2.2. Maternal overnutrition models

Maternal overnutrition animal models are designed to mimic nutritional patterns in modern Western society (Williams et al., 2014). These models include high fat diet, junk food diet, and small litter size