Introduction

Fetal programming or prenatal programming proposes that certain diseases in adulthood are primed during embryonic development (Scher, 2021). Prenatal programming integrates external or internal stimuli that modulate metabolic, hormonal, immune, and behavioral nodes during development, allowing healthy or aberrant outcomes to the infant after birth (Scher, 2021). Pregnancy is an important stage of physiological adaptations to the environment during which the fetus is exposed to the mother’s hormonal, metabolic, and immune profiles (Scher, 2021). During pregnancy and lactation, neuronal maturation, including axonal pruning, synaptic plasticity, and stable tract formation between brain structures, are selectively programmed during pregnancy and lactation (Montalvo-Martínez et al., 2018; Trujillo Villarreal et al., 2021a).

Consumption of high-sugar, high-fat, or high-sugar-high-fat diets during the prenatal stage define aberrant behavioral phenotypes in the offspring, which might be exacerbated during adulthood. While still under investigation, prenatal exposure to high-sugar-high-fat diets sets defective behaviors such as incentive-motivation behaviors leading to compulsive or mood disorders. It is believed that high-sugar-high-fat diets, defined as high-energy diets, become an aberrant stimulus that favors activation of the maternal innate immune system and alters proper fetal development. In this review, we will provide preclinical and clinical evidence that supports the contribution of prenatal programming by high-energy diets in shaping immune profiles that favor susceptibility to aberrant motivated behaviors in the offspring. We hope this review encourages future research on novel insights into the mechanisms underlying maternal programming of motivated behavior by central immune networks.

Key Words: addiction; autism; behavior; cytokines; diet; maternal immune activation; prenatal programming; sociability; trained immunity; western-diet

Search Strategy and Selection Criteria

Peer-reviewed articles were searched using PubMed database initially with no limitation on publication date. We designed a two-step strategy, for the first step, we search terms: “autism” and “prenatal programming”; “autism” and “maternal immune activation”; “social behavior” and “high-fat diet”; and “addiction” and “high-fat diet”. This first strategy allowed us to identify the role of prenatal and/or maternal programming by high-energy diets on motivated behavior including sociability or addiction. For the second step, we search terms: “western diet” and “trained immunity”; “maternal immune activation” and “cytokines”; “cytokines” and “western diet” and “behavior”; “cytokines” and “diet” and “behavior” and “addiction”; and “cytokines” and “diet” and “behavior” and “sociability”. The second step displayed reports supporting the role of high-energy diets on innate immunity, innate training and cytokines profile and their effect on social and/or addiction-like behavior.

All publications cited by the references identified in the PubMed database were selectively examined and screened for their relevance to the main topic “Prenatal programming of innate immunity on motivated behaviors after birth”.

We aimed to provide a compendious review providing evidence of prenatal triggers modulating the establishment of brain circuitry and their effects of behavior after birth.

Prenatal Programing of Motivated Behaviors in the Offspring

In nature, certain stimuli are rewarding or pleasurable and become adopted by individuals through motivated behaviors. By definition, motivated behaviors are voluntary behaviors that constantly engage in activities that provide reward or pleasure, such as drinking, eating or sex, or some social experiences. In the brain, rewards activate two main dopaminergic pathways that arise from the ventral tegmental area: the mesolimbic pathway and the mesocortical pathway. The mesolimbic pathway integrates the nucleus accumbens, central amygdala, basolateral amygdala, bed nucleus of stria terminalis, lateral septal area, and lateral hypothalamus; whereas the mesocortical pathway, the orbitofrontal and prefrontal cortices.

Ourselves and others have reported that prenatal programming by exposure to high-energy diets in dams primes aberrant motivated behavior in the offspring, including addiction-like, depression-like, and autism-like behaviors (Peleg-Raibstein et al., 2016; Camacho et al., 2017; Winther et al., 2018; Cruz-Carrillo et al., 2020; Gawlińska et al., 2021; Maldonado-Ruiz et al., 2021; Maldonado-Ruiz et al., 2021; Trujillo-Villarreal et al., 2021a, b). In particular, exposure to high-energy diets during fetal development primes addiction-like behavior in the offspring of rodents, as was determined by major lever press responses for food during
the behavioral test schedule for reinforcers (Cruz-Carrillo et al., 2020; Figure 1A and B). It seems that the offspring experience a high reward value for food that imitates the motivational and impulsive behavior for seeking synthetic reinforcers such as alcohol or drugs. On its own, clinical confirmation of prenatal programming of innate immune activation as a cause of motivated behaviors for food intake in humans is limited and largely derived from observational studies, without a proof-of-concept validation. However, some clinical reports have provided advances in the understanding of prenatal programming of food preferences (Zamboni et al., 2019). While these reports do not confirm motivated behavior for food intake in the offspring, some data documented that a greater intake of red or processed meat, low-fat snacks and desserts, and low-calorie beverages were positively associated with motivated behaviors for food, whereas consumption of whole grains, nuts, fruits, vegetables, and legumes were inversely associated with these behaviors (Lemeshow et al., 2018). Some potential limitations to the lack of consistency, reproducibility, and validation of the concept of prenatal programming by high-energy diets in mothers are in part due to pregnant women displaying episodes of cravings for palatable foods, which disturbs the accuracy of the diagnosis (Orloff and Hornes, 2014; Padmanabhan et al., 2015; Blau et al., 2020). Also, there is a lack of selective diagnostic criteria for motivation behavior for food based on the current categorization of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, which includes eating disorders such as anorexia nervosa, bulimia nervosa, or BE disorder (American Psychiatric Publishing, 2016).

The effects of exposure to high-energy diets exposure during prenatal programming on defective behavior were recently confirmed by our research group. We reported for the first time that mice programmed by high-energy diets experienced defects in social interaction with their peers (Maldanado-Ruiz et al., 2021; Figure 2A). Some clinical reports have confirmed the detrimental effect of exposure to high-energy diets on sociability in the descendants. However, no clear evidence has precisely confirmed the effect of high-energy diets during fetal programming on social interaction in the newborn. Recent reports documented that children diagnosed with autism spectrum disorder (ASD) display higher consumption of high-energy foods than typically developing peers, suggesting, in part, motivational behavior for food preferences (Plaza-Diaz et al., 2021). Also, maternal obesity leads to 1.59% to 1.59% of cases of ASD and a greater likelihood of having a child with ASD compared with their lean counterparts (Wang et al., 2016). While there is no direct experimental evidence to confirm an association of high-energy diets on ASD susceptibility and defective sociability, some reports have confirmed that a positive energy balance such as happened during maternal obesity does prime defective motivational behavior in people within the ASD.

High-Energy Dense Diets Activate Innate Immunity during Prenatal Programming

We have just started to decode how prenatal exposure to high-energy dense diets physiologically triggers of motivated behavior in the offspring. Randomized Controlled Clinical Trials collectively confirm that polyphenols and combinations of nutrients such as terpenoids, but not long-chain polyunsaturated fatty acids, vitamin D, specific proteins, or amino acids, impact pre- and post-nutritional performance in humans (Gutiérrez et al., 2021). Conversely, exposure to high-energy diets is thought to disrupt the physiological configuration of the reward system in rodents, which is expected to take place as early as embryonic day 13. High-energy diets refer to selective food formulas made of high-sugar, high-fat, or high-sugar-high-fat that provide most of the calories from those nutrients. However, these diets typically have little resemblance to the human Western dietary patterns in terms of macro- and micronutrient content (Hintze et al., 2018). For instance, according to the Department of Agriculture and Consumer Service (2018), the American diet formula contains 49% of its calories from carbohydrates, 35% from fat, and 16% from protein (Hintze et al., 2018). In preclinical studies, the term “Western” diet is reserved for those formulas that derive 60% to 70% of their calories from carbohydrates (high-sugar-high-fat), 30% to 60% from fats (high-fat-high-sugar or high-fat-high-sugar-high-fat) or a combination of 54% carbohydrates and 34% fat (high-sugar-high-fat). The high-fat-formula has been extensively reported as an adverse trigger of prenatal programming, affecting the establishment of brain circuitry in the offspring.

While still under investigation, prenatal programming by exposure to high-energy dense diets and the innate immune activation seems to be primed at very early stages of development. Reports confirm that mothers provide an innate priming stimulus showing interleukin (IL)-6 accumulation in plasma after ingesting a high-fat diet feeding (Bordeleau et al., 2020). In fact, increases in the mRNA levels of IL-6 have been found in the placenta of dams exposed to the high-fat diet, and it could potentially cross the placental barrier to modulate fetal development (Dahlgren et al., 2006). Notably, higher maternal IL-6 concentration during pregnancy was associated with defect in the establishment of cognitive and motor development during the early years of age (Graham et al., 2018; Rudolph et al., 2018). Finally, peripheral administration of IL-6 could induce neurovascular remodeling leading to increased permeability of the blood-brain barrier and defective behavior in mice (Menard et al., 2017). This evidence supports a causal effect of IL-6 accumulation in dams exposed to high-energy diets during pregnancy affecting the establishment of brain circuits establishment at the fetus.

Mechanistically, the high-fat diet formula has been confirmed as a trigger of innate immune activation. We and others have confirmed that the saturated lipid oleic acid, found in high-energy diets, increases concentrations of innate immunity, activates the Toll-like receptor 4 in the brain to pro-inflammatory IL-1β, IL-6, and TNF-α cytokine gene expression and released in plasma (Milanski et al., 2009; Delint-Ramirez et al., 2015). The Toll-like receptor 4/MyD88 pathway and NF-κB translocation into the nucleus subsequent production of pro-inflammatory cytokines (Kleinridders et al., 2009), and has been also reported to enhance microglial responses (Beaulieu et al., 2021). For instance, palmitic acid impairs migration and phagocytosis of microglia in response to a pro-inflammatory stimulus (West et al., 2019). Finally, palmitic acid was found to accumulate in the cerebrospinal fluid of overweight and obese subjects diagnosed with amnestic mild cognitive impairment (Melo et al., 2020). These pieces of evidence suggest that food rich in fat and sugar is perceived as an aberrant stimulus during prenatal programming, setting pro-inflammatory profiles, activating microglia, and affecting neuronal function at early stages of development.

As stated, prenatal programming modulates metabolic, hormonal, immune, and behavioral nodes during development, all of which are targeted and negatively disrupted by high-energy diets. However, it is not totally clear how these nodes are interconnected and behave throughout high-energy diets during the prenatal stage, setting aberrant behaviors in the offspring, and this is a major future perspective for research.

Defining the Contribution of Innate Immune Activation to Defective Motivated Behaviors

We have focused our research on the hypothesis that exposing dams to high-energy diets favors the activation of the innate immune system during prenatal programming, which affects brain circuits and leads to aberrant motivated behaviors in the offspring. Reports have shown that central and peripheral immune cells interact with each other and coordinate major pathways of synaptic refinement and proper connectome establishment during neurodevelopment. In this context, experimental evidence has confirmed that the central nervous system is not an “immunologic privileged” organ, but that peripheral immune cells infiltrate the brain and coordinate neurodevelopment by central-peripheral cross-talk (Carenza et al., 2018). Comprised of fetal and maternal immune factors, the innate cross talk develops neurodegenerative susceptibility in murine models (Stephenson et al., 2018). Physiologically, the innate system includes macrophages, neutrophils, basophils, eosinophils, and natural killer cells, and among these, microglia, the brain’s resident macrophage, the most relevant immune cell in the brain.

The most evident evidence confirming the role of innate immune activation favoring aberrant motivated behavior in the offspring came from mothers exposed to infection during pregnancy. Substantial preclinical and clinical reports have documented that maternal innate immune activation increases susceptibility to neuropsychiatric disorders in the offspring, including schizophrenia, attention-deficit/hyperactivity disorder, Tourette syndrome, bipolar disorder, and ASD (Brown and Meyer, 2018). Preclinical studies have provided some advances for characterizing biological traits linked to maternal immune activation for studies about aberrant motivated behavior in the offspring. Prenatal exposure to pro-inflammatory agents (such as lipopolysaccharide or poly(I:C)) reduces social interaction in murine models and nonhuman primates. Notably, defects in sociability correlate with an increase of pro-inflammatory cytokines INF-γ, IL-6, IL-17A, and TNF-α in plasma, and high expression of IL-6, toll-like receptor-4, and monocyte chemoattractant protein-1 (MCP-1) in the fetal brain (Careaga et al., 2017), which has been also documented in ASD subjects. Deficiencies that maternal immune activation by Poly I:C disrupts cortical microstructure in rodent offspringshowing defects which depends on the IL-17A signaling (Shin Yim et al., 2017). In this context, we have reported that asocal offspring born from murine dams exposed to high-energy-diets shows high expression of pro-inflammatory cytokines INF-γ, IL-6, IL-17A, and MCP-1, and also, volume brain alterations and reactive microglia and gliosis (Maldanado-Ruiz et al., 2021; Trujillo-Villarreal et al., 2021a; Figure 2A–D). Notably, we discovered that systemic MCP-1 inhibition by an MCP-1 antibody increases the brain volume of the primary somatosensory cortex whereas decreases the brain volume of lobe X of cerebellum in the offspring of control and cafeteria subjects (Figure 2C and D). Accordingly, microglia, as the major innate immune cell in the brain, is sensitive to high-energy-diets and altered establishment of neuronal circuits during development by affecting myelination (Bordeleau et al., 2021), synaptic pruning (Smith et al., 2020), and potentially by modulating blood-brain barrier and neurovascular unit (Cheng et al., 2016; Shen et al., 2020) or neuronal activity (Badimon et al., 2020). These pieces of evidence open a new research field suggesting that systemic chemokines might modulate microglial function and brain volume changes assisting motivated behaviors.

Together, exposure to high-energy diets activates the innate immune system during prenatal programming, leading to aberrant behaviors in murine brain abnormalities which are reminiscent of brain abnormalities found in ASD subjects.
Conclusion and Future Perspectives

Prenatal programming by high-energy diets highlights the in-utero environment and its critical role in prime susceptibility to aberrant motivated behaviors after birth. A particularly important point to consider is the fact that prenatal programming primes diverse behavioral outcomes coded by the activation of the reward circuit. Despite robust preclinical evidence supporting persistent long-term effects of prenatal programming on aberrant motivated behaviors, evidence in humans is limited and largely derived from observational studies thus, causality or proof of concept of selective physiological traits cannot be inferred.

A major perspective for future research focuses on cell type characterization of innate immune cell infiltration into the brain during physiological and pathological scenarios. In a remarkable report, Jonathan Kipnis and his group identified that a selective population of innate immune cells in the brain came from skull bone niches under homeostatic and pathological conditions (Cugurra et al., 2021). This provides a potential route of innate immune cells infiltration, which might be regulated during prenatal stages of development, modulating the establishment of brain circuitry. In any case, major and active direct-target technological approaches would improve and define how high-energy diets contribute to the infiltration of selective innate immune cells into the brain and the establishment of brain circuits that assist aberrant motivated behaviors after birth.

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