Biological Psychiatry: Celebrating 50 Years

Review

Perinatal Nutrition and Programmed Risk for Neuropsychiatric Disorders: A Focus on Animal Models

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ABSTRACT

Maternal nutrition is critically important for fetal development. Recent human studies demonstrate a strong connection between diet during pregnancy and offspring risk for neuropsychiatric disorders including depression, anxiety, and attention-deficit/hyperactivity disorder. Animal models have emerged as a crucial tool for understanding maternal nutrition's contribution to prenatal programming and the later development of neuropsychiatric disorders. This review highlights preclinical studies examining how maternal consumption of the three macronutrients (protein, fats, and carbohydrates) influence offspring negative-valence behaviors relevant to neuropsychiatric disorders. We highlight the translational aspects of animal models and so examine exposure periods that mirror the neurodevelopmental stages of human gestation. Because of our emphasis on programmed changes in neurobehavioral development, studies that continue diet exposure until assessment in adulthood are not discussed. The presented research provides a strong foundation of preclinical evidence of nutritional programming of neurobehavioral impairments. Alterations in risk assessment and response were observed alongside neurodevelopmental impairments related to neurogenesis, synaptogenesis, and synaptic plasticity. To date, the large majority of studies utilized rodent models, and the field could benefit from additional study of large-animal models. Additional future directions are discussed, including the need for further studies examining how sex as a biological variable affects the contribution of maternal nutrition to prenatal programming.

Keywords: Animal model, Behavior, Maternal diet, Neuropsychiatric disorders, Nutrition, Prenatal programming

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Neuropsychiatric disorders are a major global health concern. They are highly prevalent and lack effective prevention and treatment strategies, consequently imposing enormous societal costs (1–5). The origins and mechanisms of neuropsychiatric disorders are of great consequence to the interests of the public and the scientific community, with findings from epidemiological and animal studies indicating that early life conditions greatly contribute to risk of mental disorders (6,7). The fetal programming hypothesis posits that prenatal environmental factors influence long-term neuropsychiatric outcomes by altering epigenetic control of neural processes or disrupting neural function during critical periods of development (7,8). The prenatal environment is significantly influenced by nutrient availability, and nutritional programming specifically investigates the residual impact of fetal nutrient imbalance (9). The mother supplies offspring nutrition during gestation and lactation, and an excess or deficiency in most nutrients impacts fetal neurodevelopment (10). The placenta facilitates maternofetal nutrient exchange in utero, buffering glucose fluctuations, storing lipids, and producing a few essential amino acids (11) (Figure 1). In addition to diet, maternal metabolic conditions (e.g., maternal obesity, diabetes) alter nutrient balance and placental function (10,12); clinical and animal models implicate these conditions in increased offspring risk of neuropsychiatric disorders (13–15). Maternal nutrition and metabolic state are highly interrelated and associated with diet, making their contributions to offspring neuropsychiatric impairments difficult to differentiate.

Epidemiologic studies exploring nutritional programming are complicated by substantial variation in nutrition and limitations in modifying the diet of pregnant mothers and newborns. Animal models allow precise control of diet content and the ability to limit manipulation to critical periods of development. Notably, developmental ontogeny varies depending on the model utilized; neurodevelopmental processes that occur during late gestation in humans take place postnatally in rodents (16,17) (Figure 2). It is therefore necessary that translational efforts consider differences in nutrient transfer and demand between the intrauterine and extrauterine environments. Adopting an endophenotype approach to neuropsychiatric research, this review focuses on evidence from animal models demonstrating nutritional programming of offspring negative-valence behaviors (18,19). In humans, the negative-valence domain encompasses fear and sadness; while they are adaptive in many contexts, negative-valence behaviors are dysregulated in multiple psychopathologies (20,21). Although

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animal models are not equivalent to the complex spectrum of behavioral endophenotypes in humans, they can reliably investigate aspects of the negative-valence system via behavioral assays. Just as excessive fear and anxiety can impair a person's ability to evaluate and respond to a stressful or threatening situation, an animal's behavioral response can reveal altered appraisal and avoidance of a threatening stimulus, giving insight to potentially dysregulated defensive response (22–24) (Supplemental Figure S1). In rodents, changes in thigmotaxis (the tendency to avoid open, exposed areas) and passive coping behaviors can reliably indicate altered threat response, similar to anxiety in humans (25–29). Importantly, major components of negative-valence networks are well defined and conserved among mammals. Investigation of the corticolimbic system, which is involved in risk assessment and response, gives insight into neurobiological aspects of neuropsychiatric disorders in humans (30).

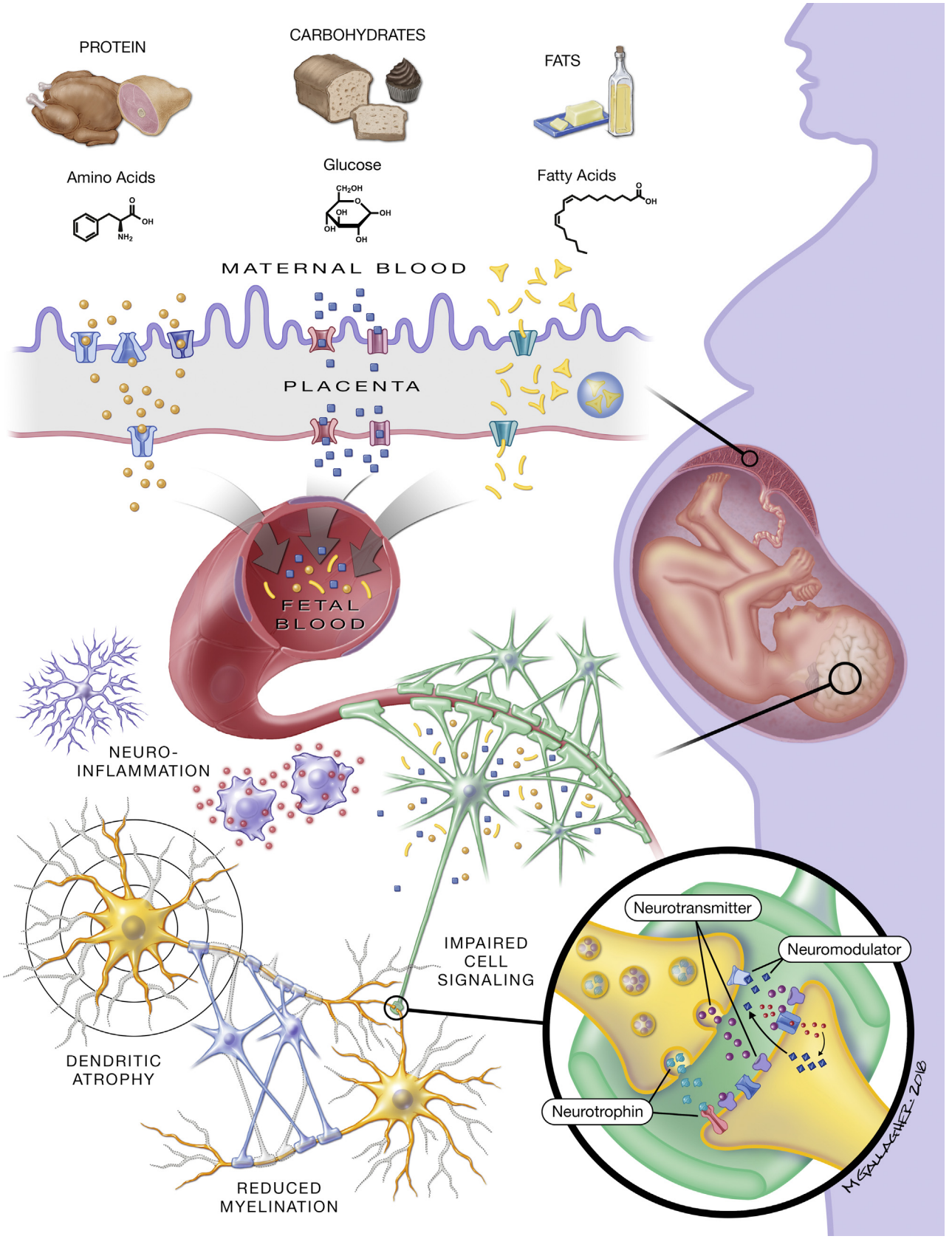
We focus on negative-valence behaviors and neural outcomes from animal models relevant to global dietary patterns and seek to investigate programming influence of maternal diet independent from metabolic disorders. This review highlights the translational aspects of animal models and so examines exposure periods that mirror the neurodevelopmental stages of human gestation (16,17). Studies are included that examine diet manipulation during gestation (conception to birth), lactation (birth to weaning), or both combined, defined here as perinatal exposure. Because of our emphasis on programmed changes in neurobehavioral development, all studies provided diet intervention (switched to control diet) by weaning. The correction of nutrient balance prior to neurobehavioral assessment in adulthood allows for the examination of long-term changes in offspring behavior. Tables are provided to supply key details for the presented behavioral studies. We concentrate on neurobehavioral differences resulting from maternal dietary manipulation of the three macronutrients: protein, fats, and carbohydrates.

PROTEINS

Proteins are macronutrients comprising amino acid subunits that are required for growth and the production of cellular receptors, transporters, and signaling molecules such as neurotransmitters (31). Amino acids require active transport across the placenta and blood-brain barrier. While many are produced endogenously, nine essential amino acids must be obtained from dietary sources (11). The placenta prioritizes resources to sustain fetal growth; however, animal models demonstrate that placental amino acid transport is reduced, to the detriment of fetal amino acids, when protein restriction limits maternal amino acid availability (32–37). Protein restriction is highly relevant, as millions of people worldwide consume dietary staples that are poor sources of amino acids, both in quality and in quantity (38). While the effects of gestational protein restriction on overall growth are well documented, limited animal studies investigated the effect of maternal protein restriction on offspring negative-valence behaviors (Table 1). The few animal models examining this relationship have focused on casein. Unlike the sources typically available in protein-deficient human diets, casein is a high-quality protein that provides all essential amino acids. As a rat model demonstrated that protein quality alone significantly affects offspring development (39), this discrepancy is important to note when translating findings to the human condition. Nevertheless, preclinical research provides important insights regarding the effect of inadequate dietary protein during development on offspring behavioral regulation.

Perinatal protein restriction beginning at conception consistently increased threat aversion and reduced passive coping behaviors in adult mouse offspring; female offspring further exhibited increased behavioral despair (40). When perinatal protein restriction began prior to conception, mouse offspring displayed less profound behavioral alterations, elevating only thigmotaxic response (41,42). These findings suggest that initiating protein restriction weeks prior to conception may allow maternal acclimation to the diet, potentially lessening the impact on the fetus. Additional studies in rats found that perinatal and gestational restriction similarly enhanced stress sensitivity, with female offspring demonstrating increased risk aversion and frustrative nonreward (43). In contrast, male offspring exhibited decreased threat avoidance with any exposure to maternal protein deficiency (44). Overall, perinatal protein restriction increased stress sensitivity and fear response in male and female offspring, and a single study in rats suggests sex specificity. These studies further noted increased behavioral despair in female rats only, consistent with higher rates of clinical depression in women (45). However, few studies examined depression-like responses in both male and female offspring, and the field would benefit from additional research to validate this finding.

Preclinical behavioral outcomes are supported by evidence that maternal protein restriction is detrimental to offspring neural functions related to the negative-valence system. Two models investigated the effects of perinatal protein restriction on neurotransmitter systems important in behavioral regulation, finding that mouse offspring displayed a hyperactive dopaminergic system attributed to hypomethylation (46) and that rat offspring displayed desensitization of serotonergic receptors (47). While global alterations were observed in rat offspring, including decreased brain weight and protein levels, hippocampal neurogenesis appears to be particularly disrupted by gestational or perinatal protein deficiency (48,49). These disturbances are highly relevant to negative-valence behaviors; the hippocampus is a crucial part of the limbic system and fear circuitry, and impaired hippocampal neurogenesis is a potential contributor to neuropsychiatric impairment in humans (50–52). Rat offspring that had protein-restricted diets in the perinatal or gestational period displayed evidence of impaired hippocampal development, exhibiting reduced brain-derived neurotrophic factor (BDNF) levels, brain volume, and neuron population (48,49). Neurotrophic growth factors such as BDNF and insulin-like growth factor are important for healthy neurodevelopment (53,54) and are decreased in mice and rats exposed to maternal protein deficiency (34,35,48). Preclinical evidence suggests that decreased hippocampal BDNF levels could reflect elevated stress hormones that are due to protein restriction (43,44,55,56), as altered BDNF in this region is specifically associated with prenatal stress-induced methylation changes (57,58).


PROTEIN
CARBOHYDRATES
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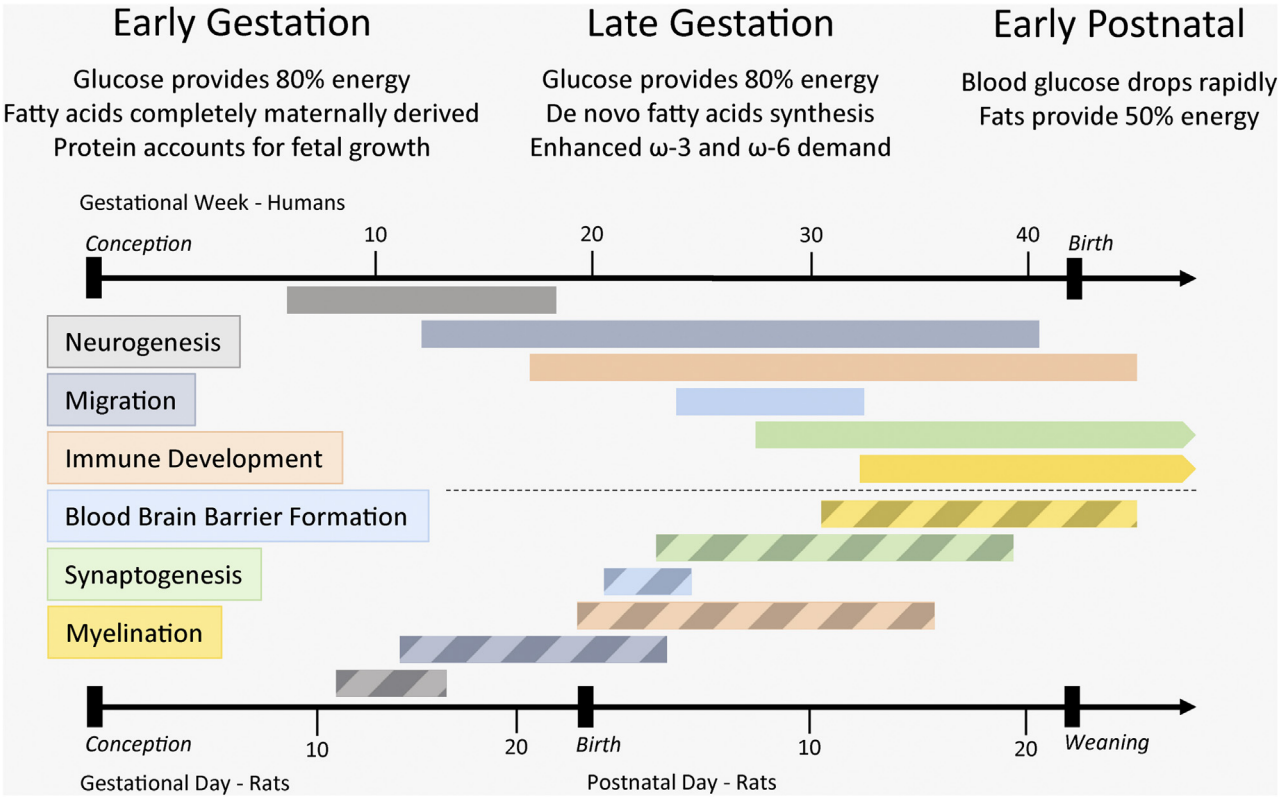

Figure 2. Neurodevelopmental ontogeny and nutrient requirements. Nutritional requirements for developing offspring change in accordance with physiological demand. During in utero development, glucose provided by circulating maternal glucose is the main source of energy for the developing fetus. The availability of energy and amino acids determines the rate of protein synthesis, and protein accretion is critical to sustaining fetal growth in early and late gestation. During advanced gestation, demands for omega-3 (ω-3) and omega-6 (ω-6) essential fatty acids increase, and the fetus is capable of some de novo fatty acid synthesis to assist in lipid accumulation. Immediately following birth, blood glucose drops rapidly as the continual source of maternal glucose via the placenta is replaced with nutrition provided by nursing. Lipids account for a substantial source of energy in the early postnatal stage as fat accumulation continues. The importance of these nutritional changes across development is conserved across animal models, but the timing varies according to developmental rate. Presented are paired neurodevelopmental timelines for humans (above, in gestational weeks [weeks post conception]; solid bars) and rats (below, in gestational days [days post conception] and postnatal days [days after birth]; striped bars) (similar in mice). Different brain regions have asynchronous development; therefore, the general stages of brain development are presented in this image. Discordant schedules of neurodevelopment are evident between the two species. In particular, processes that occur during late gestation in humans take place postnatally in rats. Weaning in rodents is triggered naturally by sexual maturity around 3 weeks of age, marking the beginning of adolescence/adulthood. It is important to note that different rat and mouse species have innately varied timelines, and for some of the animal models discussed in this review, weaning occurred at the natural point for that species, which may be a number of days before or after postnatal day 21.

Demonstrating the complexity of nutritional programming, nutrient changes due to protein restriction are not limited to amino acids. Gestational protein restriction decreased maternal lipid availability in rats, lowering fetal brain fatty acid levels and potentially contributing to the long-lasting reductions in myelin produced by early-lactation protein restriction (59,60). Clinical studies show that myelin deficits are associated with neuropsychiatric disorders, and both clinical

Figure 1. Maternal diet and fetal macronutrient availability. Food sources rich in protein, carbohydrates, and fats increase the presence of amino acids, glucose, and fatty acids in maternal circulation. These nutrients enter fetal circulation via different methods of placental transport. Amino acids provided by dietary protein require active transport across the placenta, and the placenta can produce select amino acids such as glutamate that it then delivers into the fetal circulatory system. The transport of glucose (derived from sugars and grains) across the placenta is facilitated by glucose transport proteins, causing changes in fetal blood glucose concentrations that closely mirror maternal levels. Fatty acids derived from triglycerides that are present in dietary fats such as butter and oil can freely diffuse across the placental boundary, and fatty acid transport proteins provide additional energy-dependent transfer. While many fatty acids directly enter fetal circulation, the placenta can convert the fatty acids back to triglycerides for storage in lipid droplets. After entering fetal circulation, macronutrients traverse the blood-brain barrier via mechanisms similar to placental transport. As described throughout this review, nutritional programming results in altered neural function and development (depicted in gray). Discussed mechanisms include elevated neuroinflammation, dendritic atrophy and instability, and delayed glial maturation resulting in reduced myelination. Many of the reported studies investigated altered expression, production, and function of cell signaling molecules and receptors. Inadequate fetal nutrition is associated with changes in neurotrophin (e.g., brain-derived neurotrophic factor signaling), neurotransmitter (e.g., dopamine), and neuromodulator systems (e.g., endocannabinoid signaling).

Table 1. Protein Studies

Source	Model	Strain/ Species	Subject Sex	Diet Manipulation	Diet Exposure Period	Behavioral Assays	Testing Age	Significant Outcomes
Reyes-Castro *et al.*, 2012 (44)	Rat	Wistar	Male	10% protein (control: 20%)	Gestation, lactation, perinatal	OFT, EPM	10 weeks	Gestational, lactational, and perinatal restriction impaired risk assessment (EPM)
Reyes-Castro *et al.*, 2012 (43)	Rat	Wistar	Female	10% protein (control: 20%)	Gestation, lactation, perinatal	OFT, EPM, operant conditioning, PR	12–22 weeks	Perinatal and gestational restriction increased thigmotaxis (EPM, OFT) Gestational restriction decreased motivation (PR)
Crossland *et al.*, 2017 (41)	Mouse	C57BL/6J	Male	8% protein (control: 20%)	Preconception and perinatal	OFT, EPM, light/ dark transition, forced swim test, TST, fear conditioning	8–12 weeks	Increased thigmotaxis (EPM)
Belluscio *et al.*, 2014 (40)	Mouse	CF-1	Male and female	9% protein (control: 20%)	Perinatal	OFT, EPM, TST, CE	3–9 weeks	Decreased motivation (CE), increased thigmotaxis, and decreased rearing and head dipping (OFT, EPM) Increased behavioral despair in females only (TST)
Pillay *et al.*, 2016 (42)	Mouse	African striped mouse	Male and female	10% protein (control: 19%)	Preconception and perinatal	OFT	10–11 weeks	Increased thigmotaxis (OFT)

Diet manipulation values presented as percent of g/kg.
CE, cage escape; EPM, elevated plus maze; OFT, open field test; PR, progressive ratio; TST, tail suspension test.

and preclinical evidence supports the importance of sufficient brain fatty acids for neurobehavioral health (60,61). Clearly, altering maternal protein content triggers multiple compensatory changes as the body attempts to optimize both maternal and fetal health. In addition to the aforementioned associations with offspring neural health, maternal fatty acids, steroid hormones, and growth factors regulate placental amino acid transport, alluding to the complex interrelation of mechanistic components (32). Future research expanding on the presented findings should consider these potential mechanisms and additionally investigate the impact of protein quality on offspring neurobehavioral health. Importantly, casein is the standard protein utilized in laboratory animal chow, so a casein diet is consistent with other models of dietary manipulation, such as Western-style diets.

WESTERN-STYLE DIETS

Considerable attention has been given to the neurobehavioral impacts of developmental exposure to highly palatable dietary patterns. These diets are calorically dense, provide increased calories from fat, and incorporate sugar as a noteworthy source of carbohydrates. When consumed consistently, this dietary pattern, referred to as Western-style diet (WSD), can produce metabolic impairments, including obesity, disrupted glucose and insulin homeostasis, and altered metabolic hormones. The WSD and resulting metabolic disorders have considerable global prevalence, and reviews of clinical and preclinical research demonstrate that each contributes to increased risk of offspring neuropsychiatric disorders (13–15,62–64). Small-animal models of WSD-induced obesity report alterations in maternal oocyte quality and placental function that independently influence fetal nutrient availability and neurodevelopment (65,66). However, findings from long-term maternal WSD models are rarely able to distinguish between the effects of diet and metabolic state. A recent study in nonhuman primates showed that influences such as perinatal WSD exposure and maternal obesity, but not maternal insulin resistance, differentially impaired offspring behavioral regulation (67). While maternal WSD models are fairly common, there is limited literature investigating the long-term effects on neurobehavioral development in the absence of maternal obesity.

To examine diet-induced changes without metabolic impairments, we focus on acute models of maternal WSD consumption: those that begin diet exposure a maximum of 2 weeks preconception and do not produce differences in maternal body weight before conception (Table 2). A rat model indicated that WSD during lactation decreased risk aversion and elevated exploratory activity at weaning, consistent with disinhibition (68). In adulthood, rat offspring exposed to lactation WSD likewise demonstrated impaired risk assessment in male offspring but conversely increased inhibition in male and female offspring (69). A similar disconnect between avoidance and inhibition resulted from a perinatal WSD model in Oldfield mice, with female offspring exhibiting increased freezing behaviors (70). Unlike typical laboratory strains, both control and WSD offspring exhibited an atypical preference for exposed areas, complicating the interpretation. Another rat model investigating sustained threat response found that WSD during lactation shortened threat evasion but did not increase immobility, suggesting altered risk aversion but not conclusively behavioral despair (71). While mouse offspring with gestational WSD exposure exhibited similarly reduced risk aversion (72), fear responses in rats were not altered in investigations of gestational and perinatal WSD exposure (69,73).

These results indicate that early developmental exposure to WSD, particularly during lactation in rat models, impairs risk assessment and modulates later-life stress sensitivity. The

Table 2. Western-style–Diet Studies

Source	Model	Strain/ Species	Subject Sex	Diet Manipulation[a]	Diet Exposure Period	Behavioral Assays	Testing Age	Significant Outcomes
Wright *et al.*, 2011 (69)	Rat	Wistar	Male and female	Chow and cafeteria diet: DAC 9.53 g fat (control: 2.70 g), 5.71 g sucrose (control: DAC 2.70 g fat, 1.75 g sucrose)	Gestation, lactation, perinatal	OFT, EPM	10 weeks	Lactational WSD decreased risk aversion in male rat offspring (EPM, OFT) Lactational WSD decreased activity and passive coping behaviors in male and female rat offspring (OFT, EPM)
Janthakhin *et al.*, 2017 (73)	Rat	Wistar	Male	Chow: 45% energy lard, 17.5% energy sucrose (control: 0% lard, 0% sucrose)	Perinatal	OFT	3–5 months	No differences
Speight *et al.*, 2017 (68)	Rat	Wistar	Male and female	Chow and cafeteria diet: DAC 11.63 g fat, 5.95 g sucrose (control: DAC 3.325 g fat, 1.97 g sucrose)	Lactation	OFT, EPM, home-cage activity	3 weeks	Decreased risk aversion and increased activity and rearing (OFT, EPM)
Giriko *et al.*, 2013 (71)	Rat	Wistar	Male	Chow: 18% ration lard, 2% ration sucrose (control: 0% lard, 0% sucrose)	Lactation	FST, foot-shock, OFT[b]	8–14 weeks	Decreased climbing and swimming (FST) and increased aggressive response (foot-shock)
Johnson *et al.*, 2017 (70)	Mouse	Oldfield	Male and female	Chow: 15% ration lard, 20% ration sugar (control: 0% lard, 10% sugar)	Preconception and perinatal	EPM, voluntary wheel running, home-cage activity	12 weeks	All animals had an increased number of entries into open arms compared with closed arms Increased immobility in females (EPM) Decreased head dipping but increased rearing in male mouse offspring (EPM) Decreased activity (home-cage)
Ribeiro *et al.*, 2018 (72)	Mouse	Swiss	Male and female	Chow and cafeteria diet[c]	Gestation	LDT, OFT[b]	4 weeks	Decreased risk aversion in male and female mouse offspring, exaggerated in male offspring (LDT)

DAC, daily average consumption, calculated experimentally; EPM, elevated plus maze; FST, forced swim test; LDT, light/dark transition; OFT, open field test; WSD, Western-style diet.

[a]Studies that used cafeteria diets provided a variety of food products in addition to nutritionally complete chow. Cafeteria diet compositions varied depending on the model, but they typically were an assortment of candy and chips. Nutritional or energy intake was not available from Wright *et al*. (69), so reported averages were taken from a different publication from the same group (135).

[b]Open field tests that did not consider zone differences were used to assess activity only, not threat response.

[c]Ribeiro *et al*. (72) did not report macronutrient content comparable to other cafeteria dietary models. See (72) for additional information regarding component products' energy and nutritional content for WSD and control diet.

importance of this exposure window could be due to the changing nutrition requirements of neonates. Mother's milk is extremely lipid dense, mostly in saturated fats like those elevated in WSD, suggesting that nursing offspring are more susceptible to maternal WSD effects (74). Additionally, during the early postnatal period, rodents undergo important neurodevelopmental processes that, if disrupted, could be responsible for the observed perturbations in behavior (75). Rat and mouse offspring provided evidence that perinatal or lactation WSD exposure resulted in dendritic atrophy and spine instability in the amygdala, hippocampus, and prefrontal cortex (73,76,77), with abnormal dendritic environments implicated in various psychopathologies (78). A porcine model also demonstrated hippocampal disturbances, as perinatal WSD reduced hippocampal volume and altered neurogenic mechanisms (79,80). The dopamine system contributes to attentional and impulse control, and several studies of perinatal WSD in rats demonstrate persistent impairments in dopamine transmission (81–83). The impairments in fear and anxiety circuits observed in animal models provide strong evidence that maternal WSD exposure disrupts neurobehavioral development in a manner highly translatable to human neuropsychiatric disorders.

There are a number of physiological pathways by which maternal WSD alters the course of offspring neurobehavioral development, including inducing neuroinflammatory response and altering the microbiotic environment (77,79). Major

confounding factors of the current WSD literature are the limited models investigating programmed WSD effects independent from maternal metabolic state and the considerable disparity in diet formulation. While this is true with any investigation of diet-derived outcomes, it is particularly pronounced in WSD models, as the experimental manipulation is designed to emulate a multifaceted dietary pattern and not a single targeted factor. In fact, the three main aspects of the WSD (caloric density, increased fat, and increased sugar) have each been individually associated with altered offspring neurobehavioral outcomes. The following sections discuss how specific alterations in maternal carbohydrate and fat sources each independently alter offspring neurobehavioral development.

CARBOHYDRATES

The WSD is associated with increased consumption of simple carbohydrates and sugars, typically in the form of sucrose or fructose-derived sweeteners. Sucrose is a dimer of glucose and fructose, both becoming freely available in the blood following a meal. Glucose has enhanced importance during gestation; the fetus derives 80% of its energy from glucose, with fetal blood glucose mirroring maternal fluctuations (11). Unlike glucose, fructose is not regulated by insulin and produces unique metabolic consequences as it is slowly converted to glucose by the liver. Despite the body of metabolic programming research investigating the impact of gestational diabetes on offspring risk of neuropsychiatric disorders (84), there is limited mechanistic insight regarding how glucose/insulin homeostasis or fructose influences offspring neurobehavioral development, particularly in the absence of metabolic disorders. Maintaining our focus on maternal nutrition, we identified models of moderate sugar intake without gestational diabetes. Importantly, these studies did not alter maternal weight gain or induce diabetes in offspring. To date, only one preclinical source investigated the influence of maternal sugar intake on offspring behavioral programming (Supplemental Table S1).

Choi *et al.* (85) examined the effect of added sugar during gestation on behavior of male mice. Gestational sucrose exposure impaired risk assessment, induced hyperactivity, and decreased spontaneous alternation behavior (suggesting inattention or behavioral inflexibility). Aberrant attentive control and impulsivity were associated with altered striatal dopamine transport and receptor expression, despite normal dopaminergic neuron density. Changes in striatal dopamine function are believed to be key to attention-deficit/hyperactivity disorder pathology; in humans, striatal dopamine transporter activity is associated with trait impulsivity (86), but not conclusively with attention-deficit/hyperactivity disorder (87). Nonetheless, the outcomes from Choi *et al.* (85) suggest that maternal sugar consumption may contribute to the pathophysiology of dopamine-related neurobehavioral abnormalities.

Despite limited behavioral research, the few neural studies evaluating maternal sugar consumption indicate several mechanisms of impaired hippocampal neurogenesis. One group found that gestational exposure to sucrose-sweetened beverages accelerated neurodegeneration, with decreased central insulin-like growth factor levels in sucrose-exposed rat offspring suggesting that impaired neuroprotection contributed to hippocampal atrophy (88,89). Increased maternal plasma glucose could contribute to the uninhibited apoptosis, as preclinical models of gestational diabetes demonstrated that maternal glucose and insulin levels directly influence fetal plasma insulin-like growth factor and neural insulin-like growth factor expression in neonates (90,91). The involvement of neurotrophic factors is supported by a rat model of elevated maternal fructose consumption, with increased histone modification suppressing BDNF production (92). Evidence of fructose-induced epigenetic modification is shown in a study with adult mice demonstrating that fructose consumption alters transcript abundance and other epigenetic controls, including DNA methylation (93). Yet another group found that perinatal fructose exposure modulated expression of several hippocampal neurosteroidgenic enzymes in rat offspring, consistent with preclinical evidence that glucocorticoids contribute to hippocampal atrophy and associated neurobehavioral impairments (94–96).

These perinatal models of increased sugar exposure indicate the importance of further fetal programming research. Despite the limited studies and differences in sugar type, disturbances in a variety of mechanistic pathways disrupted cell signaling and neurogenesis. Further study is needed concerning potential differences between maternal sucrose and fructose consumption, as each results in unique patterns of maternal glucose and insulin response, affecting placental function (97). Additionally, it is unclear how glucose and fructose differentially affect the brain, or even whether fructose can cross the blood-brain-barrier. Recent clinical evidence suggests that peripheral levels of glucose determine central fructose concentrations (98) and that fructose could influence neural function by altering cerebral blood flow (99). Other aspects of carbohydrate intake, such as carbohydrate complexity and glycemic index, should be addressed in follow-up studies. Although current research is limited, preliminary evidence clearly suggests that maternal carbohydrate intake impacts offspring neurodevelopment.

FATTY ACIDS

The WSD is characterized by a high percentage of saturated fats, which are prevalent in most animal products, rather than unsaturated fats, which are common in plants and fish. Dietary fat is a triglyceride: a macronutrient composed of three fatty acid chains that cannot traverse the placental boundary unless it is broken down into component fatty acids (11). Maternal fatty acid consumption determines fetal availability, and animal research indicates that diets low in protein or high in sugar alter fetal fatty acid levels (59,97). These changes directly influence fatty acid profiles in the brains of offspring, which affects neurodevelopment; fatty acids are utilized in the brain for myelin synthesis, membrane components, cellular signaling, and energy (100,101). Altered fatty acid profiles are implicated in neuropsychiatric disorders (102), with specific polyunsaturated fatty acids (PUFAs) particularly significant to fetal neurodevelopment (103). Termed essential fatty acids because they must be derived from the diet, omega-3 (ω-3) and omega-6 (ω-6) PUFAs compete for access to the enzymatic pathway that produces long-chain products utilized throughout the

brain (Figure 3) (104). While long-chain ω-3 and ω-6 molecules are both crucial to neural function, the ω-3 end product has an enhanced role in neurodevelopment (104,105). The ratio of ω-6 to ω-3 is critical for brain development, and minor dietary changes in essential fatty acids can dramatically affect cerebral lipid profiles and neural function (106,107). In excess, maternal PUFAs are associated with neurobehavioral phenotypes similar to those found with WSD: mouse and rat offspring demonstrated impaired risk assessment and decreased hippocampal neurogenesis and synaptic transmission (108–110). Considering that current dietary practices reflect a ω-6–to–ω-3 ratio of 15:1 (significantly skewed in comparison with the 1:1 ratio maintained in a hunter-gatherer diet) (111), the influence of maternal fatty acids has important ramifications for offspring neurobehavioral development.

In an effort to simulate how essential fatty acids are altered in human diets, animal models swap fat sources with moderate levels of ω-3 PUFAs (such as canola or flaxseed oils) for low ω-3, high ω-6 fat sources (such as safflower or sunflower oils), producing experimental diets that are equally calorie and lipid dense (Table 3). Animal studies commonly examine a high ratio of ω-6 to ω-3 that results in a relative shortage of ω-3 PUFAs, reflecting the trend of ω-3–deficient foods in current dietary patterns. Adult mice with perinatal exposure to high maternal ratio of ω-6 to ω-3 consistently exhibited increased thigmotaxic, risk-aversion behaviors (112–114). Rat offspring also displayed elevated anxiety-like behaviors, and further showed that high maternal ratio of ω-6 to ω-3 exaggerated physiological stress response and increased behavioral despair (115). Although these studies demonstrated increased ratio of ω-6 to ω-3 in the brain during fetal and early postnatal development, the observed behavioral phenotypes in adulthood were not accompanied by long-term changes in brain essential fatty acid availability (113–115).

Despite normal brain lipid profiles, perinatal fatty acid exposure affects long-term neural function. Studies investigating the effect of essential fatty acid rehabilitation during different developmental stages found that altered maternal ratio of ω-6 to ω-3 through lactation impaired dopamine and serotonin release, reduced myelin yield, and delayed brain growth in adult mouse and rat offspring (116–119). Evidence from the perinatal period demonstrates that these neural processes, as well as hippocampal development and microglia activation, are already disrupted before weaning (120–125). Preweaning examinations additionally show that dietary PUFAs impact hippocampal neuroplasticity via impaired endocannabinoid signaling and glucocorticoid inhibition (126,127). This literature suggests that the timing of altered brain lipid availability during critical periods of development could contribute to neurobehavioral impairments later in life. However, a second interpretation is possible: the observed neural impairments in adulthood are due not to programmed changes in brain development but to the length of time between essential fatty acid rehabilitation and neurobehavioral assessment. Brain ω-3 PUFA levels take about 8 weeks to normalize after diet rehabilitation (128), and the lack of sustained neural impairment in early interventions is potentially due to the extended recuperation period (116,129). Although there is a wealth of potential mechanisms for fatty acid programming, few behavioral or neural outcomes have been examined >8 weeks after diet intervention, highlighting an important future direction for fatty acid and nutritional programming research.

Evidence in support of PUFA programming is provided by models of fatty acid supplementation to nutritionally complete chow. Perinatal exposure to fish oil supplement decreased behavioral despair in adult rat offspring (130,131), reflecting clinical interest in associations between depression and ω-3 PUFAs (132). Nonessential fatty acids also present strong evidence of lasting neurobehavioral impairment. Maternal supplement with hydrogenated vegetable fats, such as those found in margarine, induced stress sensitivity and behavioral inflexibility, decreased hippocampal plasticity factors, and increased neuroinflammation at the detriment of cellular function in adult rat offspring (133,134). Strikingly, rats exposed to hydrogenated fat during gestation or lactation exhibited decreased hippocampal ω-3 PUFA 9 weeks after diet intervention (133). The long-term depletion of ω-3 PUFA with maternal hydrogenated fat exposure could be due to interference caused by the presence of trans fats in offspring neural lipid profile. Trans fats are essentially nonexistent in natural food sources, and it is possible that developing brains have an

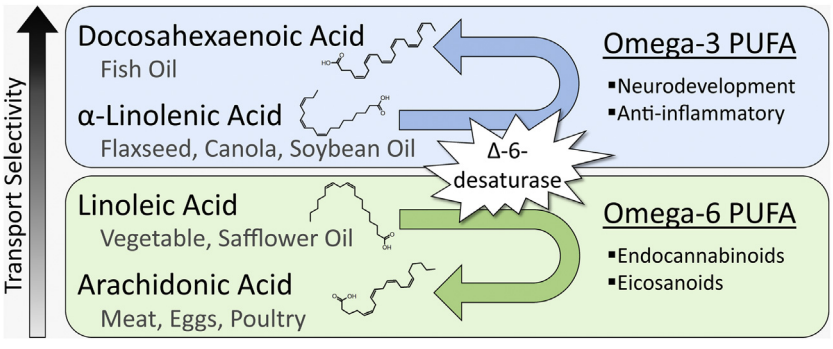

Figure 3. Essential fatty acid balance. Essential fatty acids are polyunsaturated fatty acids (PUFAs) that can be obtained only from dietary sources. These PUFAs have one of the double bonds in their hydrocarbon chain located on the third or sixth carbon from the end: omega-3 (ω-3) or omega-6 (ω-6) PUFA, respectively. The most basic essential fatty acids are linoleic acid (18:2 [18-carbon chain, two double bonds]; ω-6) and α-linolenic acid (18:3; ω-3). Once consumed, commonly via plant-based oils, these molecules can be endogenously modified by a stepwise pathway of desaturase enzymes that convert them into long-chain molecules: arachidonic acid (20:4; ω-6) and docosahexaenoic acid (22:6; ω-3). Linoleic and α-linolenic acids compete for access to these enzymes, meaning that excess of either contributes to a relative deficiency of the opposing long-chain product. Arachidonic and docosahexaenoic acids have unique neurodevelopmental functions and can also be obtained directly from diet. PUFAs can cross both the placenta and the blood-brain barrier via gradient-dependent diffusion and active transport. The relative abundance of these nutrients in fetal blood and in cerebrospinal fluid suggests that essential fatty acids can be preferentially transported in a selective order: docosahexaenoic acid > α-linolenic acid > linoleic acid > arachidonic acid. The exact controls and implications of this transport selectivity are uncertain; however, it is clear that dietary maternal fatty acid imbalance has important ramifications for fetal essential fatty acid availability and neural function.

Table 3. Fatty Acid Studies

Source	Model	Strain/ Species	Subject Sex	Diet Manipulation[a]	Diet Exposure Period	Behavioral Assays	Testing Age	Significant Outcomes
Models With High Ratio of ω-6 to ω-3 PUFAs								
Jones *et al.*, 2013 (112)	Mouse	C57BL/6J	Male and female	Safflower oil, 51.3:1 (control: soybean oil, 6.9:1)	Preconception and perinatal	EPM, OFT[b]	8–9 weeks	Increased risk aversion (EPM)
Sakayori *et al.*, 2016a (113)	Mouse	C57BL/6N	Male and female	Safflower oil, 74.4:0.3 (control: canola oil, 2.2:1)	Preconception and perinatal	OFT, EPM	13–15 weeks	Increased thigmotaxis and risk aversion (OFT, EPM)
Sakayori *et al.*, 2016b (114)	Mouse	C57BL/6N	Male and female	Safflower oil, 74.4:0.3 (control: canola oil, 2.2:1)	Preconception and perinatal	OFT, EPM, FST	13–15 weeks	Increased thigmotaxis (OFT, EPM) Further increased risk aversion in male mouse offspring (OFT) Increased activity in female mouse offspring (EPM)
Chen *et al.*, 2013 (115)	Rat	Sprague Dawley	Male	Sunflower oil, 61:0 (control: sunflower plus fish oil, 2.6:1)	Perinatal	EPM, FST	10 weeks	Increased thigmotaxis (EPM) and behavioral despair (FST)
Supplement Models								
Roversi *et al.*, 2016 (134)	Rat	Wistar	Male and female	3 g/kg daily gavage: hydrogenated vegetable fat (control: water)	Preconception and perinatal	EPM	6–7 weeks	Decreased open arm time and head dipping (EPM)
Pase *et al.*, 2017 (133)	Rat	Wistar	Male	3 g/kg daily gavage: hydrogenated vegetable fat (control: soybean/ fish oil mix)	Gestation and lactation	Novel object recognition, Y maze	12 weeks	Any HVF reduced novelty preference, with lactation period HVF showed long-term novelty aversion (NOR) Any HVF decreased spontaneous alternations (Y maze)
Ferraz *et al.*, 2008 (130)	Rat	Wistar	Male	3 g/kg daily gavage: coconut fat, fish oil (control: no supplement)	Preconception and perinatal	OFT, EPM, FST	15 weeks	Fish oil decreased immobility time (FST)

ω-3, omega-3; ω-6, omega-6; EPM, elevated plus maze; FST, forced swim test; HVF, hydrogenated vegetable fat; NOR, novel object recognition; OFT, open field test; PUFA, polyunsaturated fatty acid.

[a]Diet manipulations indicate the source of fat used to generate the listed experimental ratios of ω-6 to ω-3. Models with high ratios of ω-6 to ω-3 elevate ω-6 at the expense of ω-3, producing a relative ω-3 deficiency. Investigators used different oils to modify the ratio, except for Chen *et al.* (115), who supplemented the deficient diet with fish oil to alter the essential fatty acid ratio. Supplement models provided animals with nutritionally complete chow and thus did not examine ω-3 deficiency.

[b]Open field tests that did not consider zone differences were used to assess activity only, not threat response.

impaired ability to accommodate this unusual lipid form. By extension, it follows that the influence of fatty acid availability on offspring behavioral programming is moderated by the capacity of the developing brain to efficiently optimize neural lipid content. The observed effects of maternal ω-3 deficiency on offspring negative-valence behaviors could be compounded when altered fatty acid availability is accompanied by protein deficiency, calorie density, and increased sugar.

CONCLUSIONS

Current animal literature supports the programming effect of maternal nutrition on negative-valence behaviors of offspring. Maternal protein deficiency and fatty acid manipulation exaggerated fear response, with exposure to sustained threat inducing behavioral despair in a potentially sex-dependent manner. Alternatively, WSD exposure during the lactation period impaired risk assessment and response. Furthermore, a model of elevated maternal sugar consumption during pregnancy impaired offspring attention and impulse control. These behavioral alterations are supported by long-term disruptions in neural processes associated with neuropsychiatric disorders. Perinatal nutritional programming resulted in persistent impairments in synaptic plasticity and neurotransmitter systems as well as neurogenic, apoptotic, and brain growth anomalies. Reported outcomes were observed after macronutrient supply was normalized, suggesting that nutrition during critical periods of perinatal development contributes to programming of offspring neurobehavioral impairment.

The strong foundation of literature supports continued investigation of nutritional programming mechanisms. To date, the manner by which maternal macronutrients trigger neurobehavioral abnormalities is understudied, though evidence from each macronutrient model implicates altered placental function. Importantly, the placenta is regulated by many

factors modified by diet, including nutrient availability, maternal stress response, inflammation, and offspring growth factors. The ability to initiate diet manipulation immediately prior to conception or to cross-foster offspring is a strength of animal models and is a useful approach for limiting potentially confounding metabolic effects. Current limitations of animal models, including the inconsistency of diet formulations and use of physiologically irrelevant nutritional values, can be improved to enhance translatability. To date, a significant portion of animal studies have exclusively investigated the hippocampus. Examining other brain regions will help generate a more holistic understanding of observed neurobehavioral impairments and increase relevance to human psychopathology. These translational efforts can be further enhanced by increased use of animal models with more complex behavioral phenotypes and similar developmental ontogeny and neuroanatomy to humans. While the presented literature included a near-balanced mix of male and female offspring, sex was often not considered in statistical analysis; future studies should investigate the extensive contributions of sex to neurobehavioral outcomes. Altogether, the presented literature has paved the way for focused, future research to identify the contribution of maternal nutrition to offspring neuropsychiatric risk.

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