Chapter 10
The Implications of Maternal Obesity on Offspring Physiology and Behavior in the Nonhuman Primate

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Abstract Exposure to maternal obesity and high-fat diet (HFD) consumption during perinatal development impacts numerous aspects of offspring physiology and behavior. Epidemiologic studies indicate that maternal obesity is associated with increased risk for metabolic, mental health, and neurodevelopmental disorders. As factors such as a shared environment and genetics could contribute to this association, animal studies are critical. The use of nonhuman primates is particularly important as they have a similar developmental timeline, physiology, and behavior as humans. Evidence from animal models supports the findings from human studies and indicates that maternal obesity induced by HFD consumption impairs the development of many organ systems including the brain, pancreas, liver, and cardiovascular system. These studies suggest that offspring are predisposed to obesity due to hyperphagia, increased preference for fat and sugar, and reductions in energy expenditure. Rodent and nonhuman primate offspring exposed to maternal HFD consumption exhibit increased anxiety, impairments in social behavior, and decreased cognitive performance. These observed behavioral changes are though to be due to alterations in the development of neural circuitry critical in behavioral regulation such as the serotonin, dopamine, and melanocortin systems and increased activity of the hypothalamic–pituitary axis. Mechanisms for these developmental changes include alternations in maternal behavior due to HFD consumption and the increased levels of inflammatory factors, nutrients and hormones that are associated with maternal obesity. Given the high levels of maternal

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L.R. Green, R.L. Hester (eds.), *Parental Obesity: Intergenerational Programming and Consequences*, Physiology in Health and Disease,
DOI 10.1007/978-1-4939-6386-7_10

obesity and HFD consumption in developed nations, we postulate that future generations are at increased risk for obesity and metabolic, neurodevelopmental, and mental health disorders.

Keywords Maternal obesity • High-fat diet • Pregnancy • Energy balance • Energy expenditure • Food preference • Programming • Nonhuman primate • Anxiety • Autism • ADHD

10.1 Introduction to Maternal Obesity

Perinatal exposure to maternal obesity, impaired metabolic state, and high-fat diet (HFD) consumption is commonplace in developed nations. Currently, a third of women of childbearing age in the USA are obese and two-thirds are overweight [1]. Obesity during gestation is associated with adverse outcomes for both the mother and child such as gestational diabetes [2, 3], preeclampsia [4, 5], high blood pressure [6], placental dysfunction [7, 8], prematurity [9, 10], and infants born either large or small for gestational age [11]. Given the high prevalence of maternal obesity worldwide, it is critical to investigate the long-term effects of exposure to maternal obesity on the developing offspring. A HFD is commonly used to induce maternal obesity in animal models, and in humans a HFD typically accompanies maternal obesity. This chapter will discuss the effects of both maternal obesity and HFD consumption and will assume, except where noted, that maternal HFD consumption results in obesity. This chapter will also examine the impact of exposure to maternal obesity and HFD consumption during perinatal development on the physiology, behavior, neural development, and HPA axis of the offspring with a special focus on evidence from nonhuman primate (NHP) models.

10.2 Translational Potential of NHP Studies to Human Health

The development of research models of disease in animals has progressed our understanding of human diseases tremendously. From the basic biology of organ function, to the intricate communications between organ systems in endocrinology, to the study of the pathophysiology of debilitating diseases such as cancer, cardiovascular disease, and neurodegenerative diseases, animal models have helped us to devise methods and treatments to improve human health. In the field of developmental programming, rodent models fed a HFD have predominantly been used to study the effect of the maternal obesity on fetal development. These studies have been extensive and in depth, providing us with an understanding of how maternal diet can affect cardiovascular disease, glucose metabolism, and many other diseases. However, there are several limitations to solely using rodents when comparing the outcomes to human development.

The use of NHPs is particularly important in the examination of the impact of maternal obesity and HFD on offspring brain development, behavior, and physiology as these animals have a comparable developmental timeline, physiology, and behavior as humans. Nonhuman primates have a similar developmental ontogeny of the brain as humans with the majority of brain development occurring prenatally. This is an area of divergence between rodent and human development as much of the neural circuitry critical in regulating physiology and behavior occurs postnatally in rodents. For example, the melanocortinergic system, an important regulator of energy balance, develops rather late in development, occurring during the third week after birth in rodents [12, 13] and during the third trimester in humans and NHPs [14, 15]. The similar gestational and developmental timeline of NHPs and humans ensures that the developing offspring has similar exposure to the disrupted hormones, elevated circulating lipids, and nutrients associated with maternal obesity. Nonhuman primates also have similar placental structure and function allowing for the developing fetus to be similarly impacted by the excess nutrients and lipids transported through and the inflammatory factors secreted by the placenta. Another example of diverging physiology is the pathophysiology of obesity and the development of type 2 diabetes mellitus (T2DM). Rodents are often resistant to diet-induced obesity and generally do not develop diabetes [16], while NHPs develop the full spectrum of metabolic disease as observed in humans, including age or diet-induced obesity, hypertension, hyperlipidemia, insulin resistance, and central adiposity [17–20]. Nonhuman primates are also ideal for studies examining behavior as they have complex social and mental health-related behaviors allowing the behavior tests to be similar to those used in clinical assessment of human behavior. The NHP model of maternal obesity developed by our group also allows for the investigation of the relative impact of exposure to maternal metabolic phenotype (obesity and insulin resistance) versus HFD during pregnancy on the development of offspring physiology and behavior. In this NHP model, two-thirds of adult females become obese and insulin resistant when consuming the HFD, while one-third remain lean and insulin sensitive. This is important as human studies demonstrate a link between maternal obesity and the risk of offspring obesity [21] and mental health disorders [22–29]; however, these studies do not have the ability to separate diet effects from maternal metabolic phenotype effects. Considering the prevalence of obesity and wide consumption of a HFD worldwide, use of the NHP model to understand the impact of exposure to maternal obesity and HFD consumption is critical as it allows the direct translation of research findings to humans.

10.3 Adult Obese State

10.3.1 The Metabolic State during Maternal Obesity

Pregnancy requires metabolic, physiological, anatomical, and mental exertion from the mother. From early events like implantation to the increased requirements of nutrients necessary to feed the developing fetus, all these events are coordinated to prepare both mother and fetus for the labor, delivery, and feeding of the newborn child. This metabolically taxing state necessitates changes in maternal metabolism (glucose, insulin, leptin, lipids). For instance, pregnancy results in resistance to the action of the hormone insulin resulting in increased circulating glucose and lipids and therefore making higher levels available to the fetus [30–32]. Maternal hyperlipidemia is also present in pregnancy, manifesting as temporary rises in circulating triglycerides and cholesterol that provide a source of lipids for the developing fetus [33]. Obesity, a state already accompanied by increased levels of circulating triglycerides and insulin resistance, therefore exacerbates these rises in insulin [34] and lipids [35] during the pregnancy of an obese mother.

In addition to the dysregulation of hormones such as insulin, maternal leptin resistance is also affected by maternal obesity. In normal physiology, pregnancy is associated with a state of leptin resistance [36, 37], where food intake increases even though circulating leptin levels are also increasing. The mechanisms for the increased levels of leptin and leptin resistance remain unclear, but it is very well known that leptin can have effects on brain development [38]. In addition, dysregulation of leptin has been implicated in the development of mental health disorders. Since maternal obesity already results in a state of hyperleptinemia, exposing the fetus in the early stages of development to these higher levels of circulating leptin could have significant effects for the offspring and obese mother. In addition to the dysregulation of insulin, triglyceride, and leptin levels, maternal obesity also predisposes the mother to many other complications, such as gestational diabetes, preeclampsia, and longer hospital stays [39].

10.3.2 Maternal Obesity in Humans is Associated with Inflammation

The obese state is associated with low-grade chronic inflammation. Adipocytes secrete inflammatory factors including c reactive protein, interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α [40, 41]. The levels of these circulating inflammatory factors are proportional to adipose tissue mass. Inflammatory cytokines are also elevated in many organs in obese individuals including the brain [40] and placenta [42, 43]. Elevated levels of these inflammatory factors increase the risk for many metabolic diseases including cardiovascular disease, heart disease, insulin resistance, type II diabetes mellitus, and hypertension [40]. The increased

inflammatory cytokines associated with obesity during gestation are believed to cause dysfunction in the endothelium [44] and placenta [45]. Maternal obesity during gestation exposes the developing fetus to an elevated level of inflammatory factors, which are postulated to impair the development of several organ systems including the brain.

10.3.3 Maternal Obesity Is Associated with Placental Dysfunction

Many of the pregnancy complications associated with maternal obesity [46] that impact the developing fetus are postulated to be associated with placental dysfunction. Evidence from animal models indicates that maternal obesity induced by consumption of a HFD causes placental inflammation decreasing functionality of the placenta. In sheep, maternal obesity impacts the placenta by increasing the activation of inflammatory cytokines and downstream signaling factors [47], reducing uterine blood flow, and causing a 33 % reduction in the mass [48]. A reduction in placental mass was also observed in rodents fed a HFD [49]. Similarly, in our NHP model, we report an increase in inflammatory cytokines in the placenta from adult female macaques consuming the HFD and an elevation in the levels of cytokines in the fetal compartment [50]. In macaques, maternal HFD consumption is also associated with a 35–50 % decrease in blood flow through the uterine artery to the placenta [50]. The obese state further exacerbates the placental dysfunction resulting in a higher rate of stillbirths, due to increased placental infarctions and reduced blood flow to the fetus [50]. Thus, evidence from animal models consistently indicates that maternal HFD consumption impairs placental function leading to pregnancy complications. Moreover, the elevated levels of inflammatory cytokines secreted by the placenta likely initiate the generation of cytokines by the fetus [51, 52], further increasing the inflammation that the fetus is exposed to during development. Increased levels of inflammatory cytokines modulate growth factors critical for fetal development [53] and impact the development of neural pathways critical in regulating behavior and physiology.

10.3.4 Maternal Metabolic State and Nutrition Impact Maternal Behavior

Mounting evidence supports an important and persistent role for parental care particularly during the early postnatal period on offspring behavior and physiology. A wide body of literature in rodents indicates that naturally occurring individual differences in maternal care during early development will program the behavior and response of offspring to stress [54, 55]. For example, rat offspring exposed to

decreased maternal attention and grooming exhibit increased anxiety-like behavior as adults [55, 56], and offspring from attentive mothers are less anxious and display improved regulation of stress [56, 57]. Offspring social behavior is also impacted by maternal behavior with male rats exposed to higher levels of maternal licking and grooming displaying less aggression toward their peers [55]. However, the impact of maternal diet on maternal behavior has been largely unstudied. Three studies indicate that maternal HFD increases nursing behavior [58–60]. The effects of increased nursing during the perinatal period on offspring behavior have not been directly assessed. However, overfeeding via experimental reduction of litter size results in offspring that are hyperphagic and heavier due to impairments in critical energy balance regulatory circuitry in the hypothalamus [61]. Two studies demonstrate an impact of maternal HFD consumption on maternal grooming [58, 59]. However, one study reports a decrease in grooming behaviors [58], while the other reports an increase in the grooming of pups [59].

Maternal behavior also plays an important role in programming offspring behavior in NHPs [62–65]. For example, infant rhesus macaques exposed to maternal rejection are at increased risk for later developing anxiety [62]. Interestingly, Japanese macaques exposed to early maternal rejection exhibit increased independence in social situations and decreased stress response as infants [64]. The offspring's behavioral outcome appears to be dependent on the developmental age when it is exposed to the maternal separation or rejection. Rhesus macaques that experienced maternal separation at 1 week of age demonstrated elevation in self-comfort behaviors such as thumb sucking, while maternal separation at 1 month of age resulted in offspring seeking increased social comfort [65]. The impact of maternal HFD on maternal behavior has not been previously examined in NHPs. For the past 5 years, we have characterized maternal infant interaction in control and HFD-consuming adult females. We observed an association between maternal HFD consumption and an increase in nursing behavior during the early postnatal period and a decrease in grooming behavior (Sullivan et al., in preparation), which is consistent with the findings in rodent models.

In humans, mental health disorder such as postpartum depression are well documented to influence maternal behavior towards her infant and increase the risk of offspring developing mental health disorders as adults [66]. Perinatal exposure to postpartum depression is associated with violent and internalizing behavior [66]. Daughters of mothers suffering from major depression are at increased risk of developing mental health disorders in adolescence [67]. As a HFD has been shown to increase the symptoms of postpartum depression, maternal diet may impact offspring behavior by modulating maternal mental health [68]. Preliminary evidence also indicates that mothers classified as obese interact differently with their infant offspring than mothers classified as normal weight. Obese mothers spent less time interacting and feeding their infants; however, these infants still had an increased overall caloric intake due to increased consumption of "complementary" foods (cereal, fruit pudding, apple sauce, etc.) [69]. Another study confirmed these findings by reporting that women who entered pregnancy in the obese state introduced complementary foods earlier than women whose pre-pregnancy weight was

classified as normal [70]. Together these studies provide evidence of the interdependence of maternal behavior with maternal diet and metabolic state, which may each impact offspring behavior. Future studies need to parse out the contributions of maternal behavioral differences versus maternal diet on offspring behavior. It is critical that future nutritional studies identify the optimal dietary composition to be consumed during gestation and lactation to benefit both maternal and infant behavior and decrease the infant's risk of developing neurodevelopmental and psychiatric disorders.

10.4 The Impact of Maternal Obesity on Offspring Physiology

10.4.1 Energy Balance Regulation

Human studies consistently demonstrate that maternal obesity is associated with increased risk of the child developing obesity and metabolic disorders [21]. The impact of maternal obesity on offspring risk of obesity appears to be independent of co-occurring metabolic disorders such as diabetes mellitus, as women with obesity and normal blood glucose regulation still have children who are heavier and have increased adipose tissue mass [71]. Even though evidence from human studies implicates exposure to maternal obesity and HFD in programming offspring obesity, numerous environmental and genetic factors could also contribute to the association. It is very challenging to accurately measure the diet of pregnant women and is potentially unethical to manipulate the diet until we gain a further understanding of the optimal diet during gestation. It is also very difficult to accurately measure energy expenditure and energy intake in children. Thus, animal models of maternal obesity and HFD consumption are critically important to directly examine mechanism, identify critical periods of development, and develop potential therapeutic interventions.

Using an NHP model of HFD-induced maternal obesity, our group documented an increase in body weight, adiposity, and leptin levels in juvenile offspring exposed to maternal obesity and HFD consumption [72]. In this model, we note that both maternal HFD and obesity play a role in programming an offspring's body weight as juvenile offspring from control mothers that spontaneously develop obesity were heavier than offspring from lean control mothers [73]. Rat pups exposed to maternal HFD consumption during gestation and lactation are heavier and have increased adiposity and hyperglycemia as compared to pups exposed to a control diet [74]. Mouse offspring of diet-induced maternal obesity exhibit increased food intake and decreased locomotor activity resulting in increased adipose tissue mass [75]. Together these studies provide consistent evidence that in animal models, exposure to maternal HFD consumption programs offspring to be at an increased risk of obesity.

Rodent studies consistently find that exposure to maternal HFD consumption during perinatal development programs hyperphagia [75–77]. Exposure to maternal HFD consumption has been well documented to impact the development of neural circuitry in the hypothalamus critical in food intake regulation [78, 79] including the melanocortinergic system (discussed in detail in Sect. 10.6.1). Rat offspring exposed to maternal HFD consumption during early development exhibit an increase in the expression of the orexigenic peptides galanin, encephalin, and dynorphin in the paraventricular nucleus of the hypothalamus (PVH) and melanin-concentrating hormone and orexin in the lateral hypothalamus [76]. Gestational exposure to maternal HFD also triggers the growth of neuronal and neuroepithelial cells of the third ventricle and stimulates their migration to the hypothalamus producing a greater percentage of neurons expressing orexigenic peptides [76]. Lastly, HFD exposure reduces offspring's sensitivity to leptin's anorectic action [77]. Rodent studies provide evidence that maternal HFD consumption during fetal development disrupts the development of critical neural circuitry in the hypothalamus resulting in hyperphagia.

In contrast to the numerous studies that have investigated the effect of maternal HFD and obesity on offspring food intake, very few studies have examined the impact on energy expenditure. In the NHP model, we note that HFD consumption results in a compensatory increase in physical activity; however, this increase appears to be independent of maternal diet [80]. In rodent models, physical activity has been assessed in a few studies. However, the findings to date are inconsistent potentially due to the use of different measurement techniques and experimental designs. Dark cycle locomotor activity measured via telemetry was found to be reduced in mouse offspring exposed to maternal HFD consumption during gestation and lactation [75]. In another murine model, male offspring exposed to maternal HFD consumption during gestation were hyperactive during the open field test [81]. However, this increase in activity is likely to indicate anxiety as it was observed in a novel environment. A rat study examined locomotor activity during the day by placing rats in a box that detected activity via animal's movement across electromagnetic fields and found that offspring exposed to a diet high in saturated fat (coconut oil) during gestation and lactation did not exhibit a difference in activity as compared to animals exposed to the control diet [82]. However, in the same study rat offspring exposed to a diet high in unsaturated fat (sunflower oil) during perinatal development exhibited an increase in locomotor activity [82]. Thus, the type of fat in the diet impacts the directionality of the change in physical activity due to perinatal dietary programming. The primary component of energy expenditure is metabolic rate. However, the effects of maternal HFD consumption and obesity on metabolic rate have only been examined in one study. The examination of perinatal programming by maternal HFD and obesity on offspring metabolic rate is an important future direction of the field. In addition, future studies should examine the impact of perinatal HFD exposure on metabolic

adaptation to different states of energy balance such as dieting, fasting, and chronic consumption of a HFD.

10.4.2 Food Preference

Mounting evidence indicates that perinatal nutrition and maternal metabolic state impact children's food preference and feeding behavior. An increased preference for high-fat food in children aged 3–5 years was related to increased body fat of the child, as measured by skinfold thickness, and increased parental weight [83]. In addition, children with parents of normal weight consumed a reduced percentage of calories from fat than children with parents who were overweight [84]. However, environmental factors such as familiarity with high-fat foods and genetic factors can also contribute to difference in food preference; thus, the impact of programming by maternal obesity and HFD consumption remains uncertain. Animal studies are critical in elucidating the role of programming by HFD and obesity versus shared environmental factors on offspring food preference.

In NHPs, exposure to maternal obesity and HFD consumption during perinatal development programmed an increased preference for fat and sugar in offspring [73]. This finding was confirmed by rodent studies that also document an increased preference for fat and sugar in offspring exposed to maternal HFD consumption. For instance, exposure to a junk food diet during gestation or lactation programmed an increased preference for fat, sugar, and salt in adult rat offspring [77, 85, 86]. Interestingly, the type of fat that the offspring is exposed to during the perinatal period impacts the offspring's preference for fat, with offspring exposed to diet high in saturated fat displaying a preference for fat, whereas offspring exposed to a diet high in polyunsaturated fatty acids do not [86]. As discussed in Sect. 10.6.3, evidence from rodent [82] and NHP [73] studies indicates that exposure to maternal HFD consumption impacts the development of the dopamine system which likely contributes to the observed differences in food preference. Evidence from human, NHP, and rodent studies consistently report an increased preference for fat and sugary food in offspring exposed to maternal obesity and HFD consumption. It will be important for future studies to determine the role that the type of fat plays in programming food preference, as this will guide nutritional studies focused on determining the optimal perinatal diet.

10.4.3 Pancreas

The relationship between glucose homeostasis and maternal diet was originally discovered in a cohort of men born in Hertfordshire, UK, in whom it was observed that there was a relationship between birth weight and glucose intolerance at a later age [87]. This relationship was underscored by findings from studies of people who

were in gestation during the Dutch Hunger Winter [88, 89], where a severe famine restricted nutrients during a very sensitive time of development, which ultimately resulted in the metabolic changes later in life. For instance, by performing glucose tolerance testing in men and women from the Dutch Famine Birth Cohort, de Rooij et al. demonstrated that people exposed mid-gestation to severe nutrient restriction had a dysfunction in insulin secretion [88]. Contrary to famine, the global epidemic of obesity has been paralleled by a global increase in diabetes. In the USA, the number of people diagnosed with diabetes has quadrupled in the last 30 years, and currently almost 10 % of the population has this disease [90]. Of people with diabetes, 90–95 % of the cases are T2DM. The pathophysiology of T2DM is a complex interplay between genetics, epigenetics, and environment. Recent research in several models, including human, are focusing on the role of maternal obesity in the development of diabetes and the central role the pancreas plays in this.

There are several important differences in the rodent versus the primate in regard to the pancreas. For instance, the timing of development occurs during different windows of gestational age [91], the intra-islet cytostructure is different, as well as the innervation of the islets [92–94]. To obtain a better understanding of the effect of maternal obesity on glucose homeostasis, research will need to investigate the changes in the pancreas of NHPs. Using a NHP model of maternal obesity, our group has demonstrated that maternal HFD leads to dysfunctional development of the fetus [50, 72, 95, 96]. Indeed, as was observed in the other tissues such as liver and placenta, maternal obesity resulted in dysregulation of the islet composition, demonstrating that a HFD fed during the gestational period results in a decrease in α-cells, thus increasing the β- to α-cell ratio [97] in 1-year-old animals. This work postulates that the decrease in the number α-cells is a compensatory response to the increased production of glucose by the liver in these animals. Although this question has not been directly addressed, there is a possibility that the paracrine action of α-cells could affect insulin secretion. Future work should focus on determining which components of the diet are driving the changes in α-cell development. Subsequent work in this model investigated the vascularization and innervation of the islet. Pound et al. demonstrated that offspring from obese NHP mothers have decreased innervation and vascularization in the third trimester of development and that this reduction in vascularization persists at least 1 year postnatally [98].

10.4.4 Cardiovascular System

Cardiovascular disease is particularly affected by the increasing rates of obesity, hypertension, and diabetes [99, 100]. The original work by Dr. David Barker in humans clearly demonstrated that birth weight is correlated with subsequent cardiovascular disease, highlighting the fact that the heart and other players in the cardiovascular system are affected by the fetal environment [101–103]. The importance of maternal diet in cardiovascular programming was underscored by rodent

studies that showed that a maternal low protein diet induced hypertension in offspring [104]. Further studies in both rodent and human models confirmed and expanded upon these studies, showing that other maternal insults can have dramatic effects on the cardiovascular system, including maternal obesity [105–108]. The breadth of research studying the effects of maternal obesity has used the rodent as an experimental model because of the short life span, lower cost, and availability of genetic models. To date, only a handful of studies have utilized the NHP model to study the impact of maternal obesity and all have focused on the early indicators of vascular dysfunction.

Recent work using a baboon model demonstrated that feeding newborn baboons a HFD for the first 16 weeks of life resulted in long-lasting changes in adipose development independent of body weight, although these preweaning diets did not necessarily increase atherosclerosis at 5 years of age [109, 110]. New work is now demonstrating that it is the combination of maternal diet and postweaning diet that is detrimental to the development of cardiovascular disease. Early changes in gene expression and the expression of microRNA have been described in a model of maternal obesity in the baboon [111] where the mothers were fed a high fat/high fructose diet. In these fetuses, investigated during the third trimester, there was already evidence of myocardial fibrosis. On the molecular level, there was differential expression of several of the cardiac microRNAs, perhaps a sign of maternal programming. Our work using the earlier described model of maternal obesity in the Japanese macaque demonstrated that both a maternal and postnatal HFD exacerbate the development of vascular and endothelial function [96], resulting in increased intimal thickness in the abdominal aorta and a decrease in the vasodilation capacity in offspring of obese mothers. Interestingly, some of the negative effects of maternal HFD on offspring cardiovascular function were partially ameliorated when offspring were weaned onto a healthy diet. This suggests that an early dietary intervention may be effective in mitigating cardiovascular dysfunction programmed by maternal obesity and HFD consumption.

10.4.5 Liver

Maternal obesity and/or gestational diabetes is a major contributor to the increase in nonalcoholic fatty liver disease (NAFLD) in obese children [112, 113] and neonatal infants [114, 115]. Research in rodent and other animal models are now demonstrating that this excessive hepatic lipid storage is occurring during fetal development [116, 117]. Maternal obesity results in elevated glucose, insulin, and fatty acid levels during development of the fetus, and this presents an issue early on in development when the fetus has not developed subcutaneous fat storage. Although the liver requires lipids for normal functioning during development, excess lipids can be cytotoxic. Excess levels of intracellular lipids can cause a variety of cellular damage, including the production of reactive oxygen species. This finding has been demonstrated in many different animal models, including the NHP. McCurdy

et al. demonstrated that during fetal development, offspring from obese monkeys consuming a HFD had threefold higher levels of triglyceride in the liver. This resulted in early signs of liver toxicity as evident by increased levels of oxidative stress at the cellular level [72]. Similar results have been observed with studies in mouse models [118, 119], demonstrating that early exposure of the fetus to maternal HFD consumption can lay the foundation for future NAFLD. Subsequent studies in the NHP showed that fetal exposure to a HFD resulted in persistent changes, even if the postnatal diet was switched to low fat [120]. This phenotype could be the result of extensive epigenetic programming in the liver. Studies in rodents, humans, and NHPs have identified several epigenetic changes in response to exposure to a HFD either during adulthood [121] or fetal development [122, 123], the contribution of these changes to programming of NAFLD is a topic of future research. In addition, research by Grant et al. showed that hepatic innervation and hepatocyte apoptosis is different as well, providing evidence that many pathways in the NHP liver are affected by maternal diet [95, 124]. An interesting observation from the study by McCurdy et al. was the inclusion of animals that remained lean on the HFD. When studying offspring from these non-obese mothers, it appeared that similar dysfunction was noted in the liver, suggesting that the majority of the liver damage can be contributed to maternal diet, independent of maternal obesity. More importantly, a reversal of the HFD to regular chow during the pregnancy of obese mothers partially reversed the liver damage [72]. Although additional work needs to be done, these findings could support clinical dietary interventions during pregnancy as a first step in combating early NAFLD.

10.5 Maternal HFD Consumption Programs Offspring Behavior

10.5.1 Exposure to Maternal Obesity Increases the Risk of Mental Health Disorders

Evidence from epidemiologic studies indicates that exposure to an unhealthy diet and maternal obesity during early development increase the risk of the child developing mental health and neurodevelopmental disorders including attention deficit hyperactivity disorder (ADHD) [25, 125] and autism spectrum disorder (ASD) [23]. Children from mothers who were obese during pregnancy were more likely to have difficulties in emotional regulation [26] and increased risk of depression and withdrawal [126]. Importantly the high prevalence of obesity in women of childbearing years in recent decades is postulated to contribute to the concurrent increase in the rates of ASD [27] and ADHD [127–129] in the USA. Exposure to maternal obesity during gestation was reported to double the risk of a child developing ADHD symptoms [125]. Also, children with ADHD are twice as likely

to have a mother who was obese [25]. Risk of ASD and developmental delays in children aged two to five were also shown to be increased by perinatal exposure to maternal obesity [23].

Metabolic disorders associated with obesity may also be associated with increased risk of offspring developing neurodevelopmental and mental health disorders. The number of studies examining the impact of maternal metabolic disorders on offspring's risk of neurodevelopmental and mental disorders is limited, focusing primarily on diabetes. Children exposed to diabetes during gestation display greater rates of ADHD symptoms [130]. Gestational diabetes is also associated with increasing the offspring's risk for anxiety, depression, and social problems [131]. Exposure to maternal diabetes is associated with greater risk of ASD and developmental delays in young children [23]. Hypertension and pre-eclampsia during gestation were also associated with increased ASD risk [132–134]. Together this evidence suggests an important link between exposure to maternal obesity and associated metabolic disorders and offspring mental health and risk for behavioral disorders. However, the relative contribution of the prenatal versus shared postnatal environment remains unclear, as does the contribution of each metabolic disorder. Also, common genetic factors could underlie both obesity and mental health disorders. To more fully examine these questions, well-controlled animal experiments are needed. Substantial evidence from animal models demonstrates that maternal consumption of a HFD during the perinatal period impacts various aspects of offspring behavior.

10.5.2 Maternal HFD Impacts Offspring Anxiety

Exposure to maternal HFD during gestation is associated with heightened anxiety in both NHP [135] and rodent offspring [136]. Male rodent offspring whose mothers consumed a diet with a high content of saturated or trans fat during the perinatal period displayed increased anxiety in adulthood. Interestingly, a difference in anxiety behavior was not evident in female offspring indicating gender differences in maternal diet programming of offspring behavior [136]. However, female offspring from both diet groups had a higher level of anxiety than male offspring; thus, it is possible that a ceiling effect prevented the increase anxiety in HFD female offspring to be detected. In this model, the investigators postulate that maternal intake of a HFD increases offspring exposure to inflammatory factors that directly impact brain development [136]. In an NHP model of HFD-induced maternal obesity, our group has demonstrated an increase in anxiety in female, but not male Japanese macaque offspring [135, 137]. The increase in anxiety in female offspring was associated with a suppression of central serotonin synthesis in offspring from HFD mothers [135, 137]. Importantly, this increase in anxiety in female macaque's offspring is consistent with the evidence in humans that reports a marked gender dimorphism in anxiety prevalence. In humans, females reported to have an increase in anxiety susceptibility and a more profound link between anxiety

and obesity [138]. There is evidence in rodent models that the developmental time period in which offspring are exposed to the HFD impacts the outcome on offspring's behavior. With offspring exposed to a HFD during gestation exhibiting increased anxiety [136], while those exposed to the diet solely during lactation do not. In the NHP model of maternal HFD consumption, the developmental timing of HFD exposure has not yet been examined as mothers consume the HFD during both gestation and lactation.

Human studies support the findings from animal studies and contribute to the evidence that maternal obesity increases the risk of offspring anxiety. Children from mothers who were obese during pregnancy were more likely to have difficulties regulating emotions such as sadness and fear [26] and were reported to have an increased risk for internalizing problems including depression and withdrawal [126]. Maternal obesity is associated with pregnancy complications such as infants being born small or large for gestational age [11, 139, 140], which increases the likelihood of offspring developing anxiety and depression as adolescents [141]. Also, as noted above offspring exposed to maternal obesity are at a much greater risk of becoming obese themselves as children and adults. Childhood obesity is associated with higher rates of internalizing behaviors such as anxiety and depression and social problems [131]. Measures of obesity during infancy (high birth weight and top 10 % ponderal index) were found to be positively associated with adult depression [142]. Moreover, obesity in adulthood is well documented to be associated with anxiety and depression [143].

10.5.3 Maternal HFD Programming of Social Behaviors

Social interaction and the development and maintenance of social networks are critical for the survival of most species as they allow for procreation, procurement of food and resources, and protection from predators. Recent evidence indicates that maternal diet and metabolic state during the perinatal period may impact offspring social behavior. The first evidence that maternal diet impacted offspring social behavior came from a study by Raygada et al. in which investigators found that maternal consumption of diet high in polyunsaturated fatty acids led to increased aggression in female offspring in three different strains of mice [144]. This increase in aggression was postulated to be due to an upregulation of protein kinase C (PKC) activity in the hypothalamus. To date, very few studies have examined the impact of maternal HFD on offspring social behavior. Kang et al. found that female offspring from HFD mothers exhibited social impairments using a social interaction test [81]. Interestingly, the deficits in social behavior were not found in male offspring and a dietary intervention during the lactation period was found to reduce the social deficits in HFD female offspring. In this study, increased inflammatory cytokines and microglial activity were also observed in female HFD offspring and were postulated to underlie the deficits in social behavior. These findings from rodent studies are consistent with the results in our NHP

model in which we observe a decrease in social interactions in HFD offspring when exposed to a novel peer and in their normal social housing (Sullivan et al. in preparation). These findings from animal models support evidence in human studies that indicate that disorders such as ASD, which are characterized by impairments in social behavior, occur at higher rates in offspring from obese mothers [23].

10.5.4 The Impact of Maternal HFD Consumption on Learning and Memory

Epidemiologic studies have recently linked obesity and consumption of a HFD in adulthood with cognitive impairment [145], Alzheimer's disease [146], and dementia [146]. A high intake of saturated fat during midlife was associated with decreased cognitive function and memory and an increased risk of cognitive impairments [145], while a high intake of polyunsaturated fats and fish was associated with improved memory and cognitive function [145]. Rodent studies support these findings by providing consistent evidence that consumption of a HFD accompanied by obesity impairs spatial learning and memory [147–155]. To date, the impact of consumption of a HFD and obesity during adulthood on cognition have not been examined in NHPs. It will be important for future studies to pursue this as NHPs provide an important link between the mechanistic studies possible in rodents and epidemiologic evidence from human populations.

A limited number of studies have examined the effects of exposure to maternal HFD and obesity during perinatal development on offspring cognition. However, the existing data come primarily from rodent studies and indicate that exposure to maternal HFD consumption and obesity is associated with cognitive impairments. A deficit in spatial memory measured using a Morris water maze was recently documented in adult male rats that were exposed to a diet high in saturated or trans fats during perinatal development [136]. This memory deficit was associated with inflammation in brain regions critical for cognitive function such as the hippocampus as evidenced by increased peripheral and hippocampal cytokine expression in response to a bacterial challenge and hippocampal microglial activation [136]. A second study confirmed these findings as impairments in spatial learning and memory were observed in adult rats [156]. The cognitive impairments observed in this model were associated with impairments in hippocampal development including decreased brain-derived neurotrophic factor (BDNF) and activity-regulated cytoskeletal-associated protein levels. A mouse study also observed that exposure to a diet with high lard content during perinatal development reduced both spatial memory and cognition in adult offspring [157]. A second mouse study found that diet-induced obese females had offspring with decreased BDNF synthesis in the hippocampus, which was associated with impaired dendritic arborization of hippocampal neurons [158]. These offspring were also identified to have delays in spatial learning when they were young. However, in this study cognitive

impairments were not evident in adult animals [158]. Male rat offspring exposed to maternal HFD consumption during gestation and lactation that continued consuming the HFD exhibited a decline in memory retention, but not acquisition in the Morris Water maze [159]. Maternal HFD consumption has also been associated with increased markers of oxidative stress and inflammation in the brain [159]. Overall, preliminary evidence from rodent studies indicates that exposure to maternal obesity and HFD consumption during early development may decrease offspring cognition. It is important that the impact of maternal diet and obesity is examined in larger animal models, such as NHPs, which share a similar trajectory of brain development and in which higher levels cognitive function can be assessed. Moreover, it will be important for future studies to parse out the contribution of pre- versus postnatal HFD to programming cognition. Lastly, though preliminary mechanistic targets have been identified such as reduced BDNF, increased oxidative stress, and inflammation, it is critical that mechanistic studies are expanded to enable the development of therapeutic interventions.

10.6 Maternal HFD Consumption Programs Brain Development

10.6.1 Melanocortinergic System

The hypothalamic melanocortinergic system is collection of neural circuits that are critical regulators of energy homeostasis [160], blood pressure regulation [161, 162], and sexual behavior [163]. The melanocortin system is comprised of a set of transmembrane receptors (MC1R–MC5R) [164] that are responsive to cleavage products of the precursor proopiomelanocortin. For our purposes, we will focus on alpha-melanocyte-stimulating hormones (alpha-MSH), which inhibit food intake, and agouti-related peptide (AGRP), which promotes hunger. These two peptides regulate food intake by acting on melanocortin receptor subtype 3 (MC3R) and melanocortin receptor subtype 4 (MC4R). As the melanocortin system is one of the primary regulators of energy balance, a number of studies have examined the impact of maternal obesity and HFD consumption on this system as a potential mechanism to explain the increased risk of obesity in offspring from obese mothers. In NHPs, we observe a reduction in the expression of AgRP mRNA and protein and an increased expression of POMC and MC4R in the arcuate nucleus of the hypothalamus (ARC) of fetal offspring [165]. Recent data from the model indicate that in juvenile NHP offspring, both maternal and postweaning HFD consumption suppress the density of AgRP staining in the paraventricular nucleus of the hypothalamus (PVH) and postweaning HFD consumption suppressed AgRP density in the ARC [80]. Many rodent studies also observe a programming effect of maternal HFD consumption during early development. However, these studies are inconsistent and report either an increase or a decrease in AgRP expression. In a rat model,

maternal HFD consumption-induced obesity was found to increase the mRNA expression of AgRP, POMC, and MC4R in the whole hypothalamus of fetal offspring [166]. However, another rat model examined the impact of exposure to maternal HFD consumption during the last 2 weeks of pregnancy and noted a decrease in the expression of AgRP and NPY in offspring at weaning [76]. A third rat study also noted that maternal HFD consumption decreased NPY and AgRP mRNA expression [167]. These differences between studies are likely due to differences in the composition of the experimental and reference diets and the length of exposure to the diets and thus the degree of maternal obesity and metabolic dysfunction. It is important to note that the melanocortinergic system develops rather late in development, occurring during the third week after birth in rodents [12, 13], and during the third trimester in humans and NHPs [14, 15]. These species difference in brain ontogeny makes the NHP model particularly important in the translation of findings to humans. The central melanocortin system appears to be impacted by inflammatory factors. Exposure of rodent hypothalamic explants to the inflammatory cytokine IL-1B results in a suppression of AgRP release and an increase in POMC release [168, 169]. Thus, we postulate that maternal obesity-induced inflammation impairs the development of the central melanocortin system impacting offspring physiology and behavior.

10.6.2 Maternal HFD Consumption Suppresses the Development of the Serotonin System

The serotoninergic system plays an essential role regulating numerous aspects of behavior and physiology including energy balance regulation and digestion. Serotonin (5-HT) is involved in neural development impacting neuronal growth, synapse formation, and migration of neurons [170, 171]. Decreased central serotonin levels are associated with mental health disorders including anxiety [172] and depression [173]. Reductions in brain serotonin are also reported in neurodevelopmental disorders such as ADHD [174] and ASD [42, 175]. Moreover, selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed to treat these mental health and neurodevelopmental disorders. During pregnancy, the serotonin system also plays a key role in regulating the maternal immune system to prevent allogeneic rejection of the fetus [176] and placental blood flow. Thus, changes in the development of the serotonin system due to exposure to maternal obesity and HFD consumption may underlie behavioral disorders.

Evidence from animal models of HFD-induced maternal obesity supports human evidence that impairments in the development of serotonin neural pathways are a potential mechanism for the changes in offspring behavior. In NHPs, we observe impairments in the development of the serotonin system in fetal offspring and increased anxiety in infant female offspring [135]. Recent data indicate that the female offspring exhibit an increase in anxiety behaviors into the juvenile time

period and that this is associated with a persistent suppression of serotonin synthesis in the dorsal raphe [137]. These findings are supported by similar findings in a rodent model. Murine offspring exposed to maternal HFD consumption were documented to have an increase in 5-HT1AR, the inhibitory autoreceptor, in the ventral hippocampus and increased anxiety behaviors [177]. Increased exposure to inflammation is documented in pregnancies complicated by obesity and HFD consumption [44, 178, 179], and the development of serotoninergic neural pathways is sensitive to inflammation [180]. Thus, we postulate that the increased inflammation induced by maternal obesity/HFD consumption impairs the development of the serotonin system leading to behavioral abnormalities in offspring. In our NHP model, we document that maternal HFD consumption increases inflammation in the placenta [50] and in the hypothalamus of the fetal offspring [165]. Given the similarities in the timing of brain developmental and physiology between NHPs and humans, a similar mechanism may contribute to the increased risk of psychiatric and neurodevelopmental disorders in offspring exposed to maternal obesity during perinatal development.

10.6.3 Programming of the Dopaminergic System by Maternal HFD

The dopaminergic system is another neural system that is critical in the regulation of behavior and physiology and appears to be impacted by exposure to maternal obesity and HFD consumption. Alterations in the dopamine (DA) system are postulated to underlie a number of neurodevelopmental (ASD [181–183], ADHD [184–186]) and mental health (schizophrenia [187–189], anxiety [190, 191], and depression [192, 193]) disorders. In NHPs, exposure to maternal HFD consumption was recently found to suppress offspring dopamine signaling in the prefrontal cortex as evidenced by a decrease in DA fiber projections and levels of the dopamine receptors 1 and 2 protein [73]. Evidence from rodent studies provides additional evidence that exposure to maternal HFD during gestation and lactation impairs the development of the DA system. In a rat model, perinatal exposure to maternal HFD consumption resulted in increased DA in the nucleus accumbens and reduced sensitivity to DA, as evidenced by reduced locomotor response to a psychostimulant [82]. Rat offspring from HFD mothers were also found to display an elevated DA response to acute stress and did not display the normal desensitization to repeated exposure to the stressor [194]. In a mouse model, maternal HFD consumption altered methylation and expression of DA genes [195]. Similar to the 5-HT system, the DA system is sensitive to exposure to maternal inflammation [196]. Thus, elevated perinatal exposure to inflammation associated with maternal obesity is thought to impact development of the DA system and increase offspring risk of developing psychopathology.

10.7 Maternal HFD Consumption Programming of the HPA Axis

Cortisol release from the hypothalamic–pituitary adrenal (HPA) axis plays a critical role in regulating psychological and physiologic stress. Stress triggers the hypothalamic paraventricular nucleus to release corticotropin-releasing hormone (CRH) and antidiuretic hormone (ADH) into the hypothamo-hypohyseal portal system triggering the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary into systemic circulation. Circulating ACTH stimulates the release of glucocorticoids (primarily cortisol in humans and NHP and corticosterone in rodents). In addition to being stimulated by CRH, ACTH levels are also regulated by the hypothalamic suprachiasmatic nucleus (SCN) resulting in a circadian rhythm of ACTH and cortisol release, with levels of both hormones being lowest at night [197]. Interestingly, a number of studies find that the response of the HPA axis to stress also exhibits diurnal variation [197]. CRH is also expressed in areas of the brain important in behavioral regulation such as the amygdala and lateral bed of the nucleus stria terminalis [198] where it is postulated to regulate anxiety and fear. Given, the important role of the HPA axis in the regulation of behavior and physiology, it is important to examine the impact of maternal obesity and diet on the function of the HPA axis.

Human studies note an association between heightened activity of the HPA axis and mental health disorders including anxiety and depression [199]; thus, programming of the HPA axis by maternal HFD and obesity is a potential mechanism for the increase in anxiety observed in offspring exposed to maternal obesity and HFD. In NHPs, we note that maternal HFD consumption and obesity result in an increase in both acute stress response (plasma cortisol) and chronic stress response (hair cortisol) in infant and juvenile offspring [137]. This evidence is supported by rodent studies that also indicate an increase in corticosterone in offspring exposed to maternal HFD consumption. Male rat offspring exposed to a HFD during the last week of gestation and lactation exhibited elevated basal levels of corticosterone on postnatal day 10 [200]. Another study which examined the impact of HFD exposure during gestation and lactation noted that adult rat offspring had reduced basal corticosterone but an elevated and longer lasting corticosterone response to stress which was accompanied by an increase in anxiety behaviors [201]. This study also noted an elevated number of receptors for glucocorticoids in the amygdala [201]. As glucocorticoid action in the amygdala regulates CRH expression and anxiety-like behavior [198], this could be a mechanism by which exposure to maternal HFD increases anxiety in offspring. Glucocorticoid levels in the amygdala have not yet been examined in NHP exposed to maternal HFD. It will be important for future studies in NHPs to fully characterize the HPA axis and extrahypothalamic CRH expression and glucocorticoid receptors.

10.8 Mechanisms by Which Maternal HFD Consumption and Obesity Influence Offspring Physiology and Behavior

10.8.1 Inflammation-Induced Programming

As discussed above maternal obesity is associated with elevated levels of inflammatory factors such as c reactive protein, IL-6, IL-1β, and TNF-α [40]. Recent evidence indicates that many of these inflammatory factors can cross the blood placental barrier, triggering the release of additional inflammatory cytokines from the placenta that subsequently impact the developing fetus. Evidence from animal models extend these studies by documenting that maternal HFD consumption increases inflammatory markers, microglial activation, and changes the behavior of offspring. In NHPs, exposure to maternal HFD consumption causes elevated levels of circulating inflammatory markers in the fetus and increased microglial activation in the brain, which likely contribute to observed impairments in the development of the dopaminergic [73], melanocortinergic [165], and serotonergic systems [135] and a long-term impact on behavior and physiology [135, 165]. These findings are supported by evidence from a rat model that found that maternal HFD consumption results in increased microglial activation in the hippocampus and increased anxiety and impairments in spatial learning in adult male offspring [136]. A mouse study which examined both male and female offspring noted increased proinflammatory cytokines and microglial activation associated with increased anxiety behavior and impaired social behavior in female offspring exposed to HFD during gestation [81]. In this murine model, male offspring exposed to maternal HFD during gestation were noted to display hyperactivity. Placement of the dams onto a control diet during the lactation period was found to reduce the neural inflammation, social impairments, and anxiety observed in female offspring, but did not affect the hyperactivity observed in the male offspring [81], highlighting that the timing of the dietary exposure dramatically impacts the behavioral outcome and that various behaviors have different sensitive periods to maternal HFD developmental programming. In humans, exposure to elevated proinflammatory cytokines during perinatal development has been shown to impact brain development and increase risk for behavioral and metabolic disorders. Exposure of the developing fetus to an inflammatory environment is associated with prematurity, low birth weight [202], and increased risk of ADHD [203], ASD [204], and schizophrenia [205]. Also, exposure to increased levels of inflammatory markers during the neonatal period has been shown to increase risk for several serious metabolic diseases including heart disease, cardiovascular disease, type II diabetes mellitus, and hypertension [40]. Data from both human and animal studies demonstrate that exposure to elevated inflammatory factors during the perinatal period impairs the development of several neurotransmitter systems that regulate physiology and behavior such as the serotonin, dopamine, and melanocortin systems [40, 180, 206]. Exposure to inflammation is nonspecific

and is thus likely to impact many neural pathways. It is important that future research fully characterizes the impact of inflammation induced by maternal obesity and HFD consumption on the developing brain. Also, given the dramatic impact that exposure to inflammation has on offspring risk of metabolic and behavior disorders, it is critical that therapeutic interventions using anti-inflammatory agents are examined. A recent rodent study has examined one such possible therapeutic intervention, ursolic acid, which was observed to ameliorate the impairments in cognitive function observed with HFD consumption [157].

10.8.2 Programming by Excess Hormones and Nutrients

Maternal obesity or maternal overnutrition disrupts the normal development of many different organ systems in almost all mammalian species, as has been described in previous sections. Although obesity is an incredibly complex and multifactorial disease, there are several obvious changes in nutrients and hormones that have been demonstrated to direct or at least play a significant part in the maternal programming of the fetus. Often, these altered levels of hormones and nutrients act in concert to prepare the fetus for postnatal life. However, questions remain about the contribution of individual nutrients or hormones to maternal programming.

In maternal obesity, hyperglycemia is a hallmark of metabolic syndrome. To investigate whether high glucose intake during pregnancy in the absence of obesity can lead to programming changes, D'Alessandro et al. fed rats a high sucrose diet during pregnancy and lactation [207]. Despite not seeing any changes in body weights in the offspring, animals that were exposed to a high sucrose diet anytime during development demonstrated increases in blood glucose levels, as well as dyslipidemia with high circulating levels of very-low-density lipoproteins and triglycerides. This suggests that high sucrose exposure can program both glucose metabolism and hepatic lipid metabolism [207, 208]. Other studies in rodents have demonstrated that a similar model of sucrose consumption during pregnancy can program changes in the cardiovascular system [209]. There are currently no human situations where the contribution of just hyperglycemia during development can be studied to determine the effect on the developing fetus. Epidemiological studies in humans looking at the contribution of hyperglycemia in cases of nonobese gestational diabetes argue that just having hyperglycemia can alter the physiology of the offspring [210–212]. A large population study that underscored this finding was the HAPO study (Hyperglycemia and Adverse Pregnancy Outcome) in which the consortium confirmed that neonatal adiposity was correlated with maternal glucose levels [213], although this programming in neonates did not translate into an association with childhood obesity when the offspring reached the age of 5–7 years [214].

In the NHP, no current studies have investigated the direct role of glucose or fructose on the development of the offspring in the absence of a HFD. One study did

attempt to develop a model of type 1 diabetes in NHPs and determine the effect of hyperglycemia on offspring. The authors determined that the hyperglycemia, as a result of β-cell destruction with streptozotocin, results in large for gestational age offspring as well as hyperglycemia and hyperinsulinemia in the fetuses [215].

The experimental models for studying maternal obesity almost always utilize a diet that is high in saturated fat with simple sugars as the source of carbohydrate. Although some studies have addressed the contribution of simple sugars in developmental programming (see section above), there is little known on the direct and isolated effect of dyslipidemia on programming in the NHP. Research in our NHP model of gestational obesity has demonstrated that exposure to a diet high in saturated fats and sucrose resulted in significant elevated levels of triglycerides in the liver of the fetus [72]. This in utero exposure to high levels of lipids resulted not only in oxidative stress in the liver but also increases acetylation of histone H3, a hallmark of epigenetic programming [123]. Further, this study highlighted some of the molecular mechanisms involved in epigenetic programming by maternal obesity in NHPs. The importance of decreases in NAD-dependent protein deacetylase sirtuin 1 (SIRT1), an important player in epigenetic modifications, was underscored by the changes in known targets of SIRT1 like peroxisome proliferator-activated receptors gamma and alpha. Taken together, this study very elegantly showed that a maternal HFD, resulting in liver triglyceride levels threefold of normal, can result in epigenetic alterations that can have a deleterious effect on the future development of liver disease. It is also important to note that these changes were driven by the consumption of a HFD and were unrelated to maternal obesity.

Interestingly, when animals from a subsequent study were studied at 1 year of age, only offspring from mothers that demonstrated sensitivity to the maternal diet (insulin resistance) retained the increased levels of triglycerides in the liver [120]. It will be interesting to determine whether the epigenetic changes that were observed in the fetus persist in the animals after 1 year of age. Regardless, it is apparent that although consumption of a maternal HFD can result in epigenetic programming of the fetus, it requires insulin resistance in the mother to have dysfunctional lipid handling at 1 years of age. This observation clearly suggests that programming is a combinatorial process, which includes many different aspects of maternal obesity including nutrient excess, insulin resistance, and inflammatory processes.

10.9 Conclusions

Evidence from epidemiological studies and animal models indicates that perinatal exposure to maternal obesity and HFD consumption has a considerable impact on the physiology and behavior of the developing offspring. A number of mechanisms have been identified to contribute to maternal obesity and HFD consumption programming of offspring development including placental dysfunction and exposure to elevated levels of inflammatory factors, nutrients (glucose, triglycerides), and metabolic hormones (leptin, insulin) that impact the developing brain, liver,

pancreas, and cardiovascular system. Changes in these organ systems result in sustained alternations in the offspring physiology leading to susceptibility to obesity. Furthermore, impairments in the development of neurotransmitters systems important in behavioral regulation such as the serotoninergic, dopaminergic, and melanocortinergic systems lead to persistent changes in behavior including increased anxiety, impaired social behavior, and decreased cognitive function. The alarmingly high rate of maternal obesity and HFD consumption in Western nations places future generations not only at increased risk for obesity and metabolic disorders but also at heightened risk of developing neurodevelopmental disorders such as ASD and ADHD and mental health disorders such as anxiety. Given the substantial healthcare costs associated with each of these disorders, it is critical that future studies identify interventions that are efficacious in preventing and reducing the impact of maternal obesity and HFD consumption on offspring development.

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