Chapter 9
The Effect of Maternal Overnutrition on Reward and Anxiety in Offspring

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Abstract Obesity has reached epidemic levels in developed countries. Maternal overnutrition has been linked to a number of poor health outcomes in offspring, including metabolic, cardiovascular and mental disorders, some of which do not become apparent until later in life. In particular, maternal overnutrition is linked to increased risk for hedonic and stress dysfunctions. Previous studies in animal models indicate that maternal overnutrition, typically using a diet high in fat, impacts the function of the mesolimbic pathway, leading to attenuated function of the reward system and decreased dopamine-related behaviour. Also maternal overnutrition affects the function of the hypothalamic–pituitary–adrenal axis, leading to activated stress system and increased anxiety-like behaviour. This chapter focuses on what is known about the effects of maternal intake of high-fat diet on the reward and stress systems in offspring brain and behaviour. We discuss the likely role of epigenetic regulation of these pathways in the long-term changes in brain function associated with the perinatal environment.

Keywords High-fat diet • Overnutrition • Maternal • Dopamine • Glucocorticoid • Stress • Diet-induced obesity • Anxiety • Reward • Epigenetics

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Abbreviations

D1R	Dopamine receptor D1
D2R	Dopamine receptor D2
DAT	Dopamine transporter
GR	Glucocorticoid receptor
HPA	Hypothalamic–pituitary–adrenal
MR	Mineralocorticoid receptor
NAC	Nucleus accumbens
PFC	Prefrontal cortex
TH	Tyrosine hydroxylase
VTA	Ventral tegmental area

9.1 Introduction

Disorders associated with lifestyle choices, such as the overconsumption of energy-rich foods, have reached epidemic levels in developed countries. Type 2 diabetes was once a disease primarily in adults. Increasingly, however, it is presenting in adolescents and even in children, as the incidence of obesity increases in these populations. In fact, childhood obesity has doubled in children and tripled in adolescents in the past 30 years [1], and, accordingly, one in every three American children born in 2000 is likely to be diagnosed with diabetes in their lifetime. In addition to being at higher risk for developing diabetes, obese youth are at greater risk for cardiovascular disease [2] and many other diseases, including psychiatric disorders later in life [3].

Globally, consumption of energy-dense foods high in fat has increased dramatically in the past 30 years, as has the average serving size. Compounding the problem, the higher caloric intake is tending to be accompanied by generally lower rather than higher levels of physical activity, corresponding to generally more sedentary lifestyles. In fact, the USA is ranked 1st in the world for percent of overweight individuals, with more than half of the American population being overweight. Worldwide, 2.3 billion people were overweight in 2010, and this number is predicted to increase.

Overnutrition is common among pregnant women [4], and it is clear that obesity propagates across generations. Thus, maternal obesity may have health consequences not only for the mother but also for her offspring. Postnatal lifestyle is the most immediate cause of obesity. However, in humans, evidence of the influence of maternal diet is found in the association between birth weight and adult obesity and metabolic disease. Likewise, animal studies have shown that maternal nutrition history predicts obesity in adult offspring, independent of postnatal diet [5].

It has been suggested that the transgenerational impact of maternal obesity occurs via metabolic programming [6]. During early critical periods in

development, the organism has the ability to adapt to the environment, and these adaptations are reflected in permanent changes in metabolic processes. The critical developmental time window for this programming is during gestation and lactation, a time when offspring are fed by their mothers and when offspring metabolism and risk for future obesity is particularly sensitive to maternal diet. Indeed, shifts in metabolic programming as a consequence of maternal diet during this period are considered to have at least contributed to the epidemic rise in obesity. Although it is likely that the long-term effects of changes in metabolic programming involve interactions with multiple neural systems (e.g. those related to the rewarding properties of food), the biological mechanisms mediating these long-term effects are largely unknown.

Eating behaviours are regulated by peripheral and central processes that directly or indirectly affect the brain's reward pathways. Palatable or high-fat diet activates dopaminergic pathways within the mesolimbic reward system, implicated in natural reward processes and drug addiction [7, 8]. As we discuss below, maternal high-fat diet alters dopaminergic gene regulation, dopaminergic transmission in the reward pathway and the locomotor-activating effects of amphetamine [9–11]. Moreover, activation of dopaminergic systems interferes with hormones such as leptin that regulate satiety, thereby promoting consumption of palatable food. Maternal overnutrition also affects anxiety behaviour and stress physiology in offspring [12, 13]. These effects of maternal diet are significant in that the motivational processes mediating responses to rewards and stressors are intimately related. For example, drug addiction is considered as a chronic cycle of reward-directed behaviour followed by withdrawal-induced negative affect [14]. It is possible that similar such cycle may operate in the context of natural reward-related behaviours, such as high consumption of palatable food [15].

In this chapter, we will discuss how maternal diet during and after gestation affects behaviour in offspring; furthermore, we will link behavioural outcome to neural mechanism and to the presentation of altered reward- and stress-related phenotype. To date, the hypothalamus, which regulates the homeostasis of energy intake, has provided the main focus for studies aimed at examining the influence of maternal overnutrition on brain function in offspring (see [16, 17]). More recently, however, this work has extended to include a consideration of the extrahypothalamic systems, including midbrain and cortical dopamine systems, and stress-related systems of the hypothalamus and limbic forebrain. It is these systems that will provide the focus in this chapter.

9.2 Studies of the Effects of Maternal Diet on Offspring: Caveats to Consider

Before proceeding with a discussion of the effects of maternal diet on behavioural and neural phenotype in offspring, caveats pertaining to work in the area more generally should be briefly addressed. First, it should be cautioned that studies of maternal overnutrition tend to be variable on a number of critical parameters. The majority of work in the area involves a maternal diet manipulation given during and/or after pregnancy, and most studies use diets that are high in fat. However, studies differ in the proportion and quality of fat (saturated, unsaturated or transfats) in the diet, the carbohydrate content, the use of 'cafeteria' diets in some cases and the timing of exposure to the diet manipulation (e.g., before, during and/or after pregnancy). Here, the focus will be on diets high in saturated fat, the most common fat used to drive overnutrition. Thus, we use the term 'overnutrition' interchangeably with 'high-fat diet', unless otherwise specified.

Second, it is worth noting that although the focus here is parental obesity and offspring behavioural phenotype, the majority of studies examining the behavioural effects of overnutrition are performed using diet-induced obesity models, where the diet is fed continuously in adulthood only. In these diet-induced obesity studies, therefore, it is not always clear whether the effects of the diet result from current diet, diet history or a combination. In the context of this chapter, the diet-induced obesity studies will serve to illustrate instances where the effects of high-fat diet in development diverge from those of chronic high-fat diet in adulthood, as well as where common brain mechanisms appear to be altered by high-fat diet exposure.

9.3 Effects of Maternal Overnutrition on the Offspring Dopamine System

Dopamine circuitry is associated with neural reward mechanisms that can serve to alter animals' preference for energy-dense palatable foods. The regulation of food intake by the central nervous system involves homeostatic mechanisms in the hypothalamus and interactions with the mesolimbic dopamine pathway mediating reward and motivation [18]. Both natural reinforcers (e.g. palatable food such as high-fat diet) and drug reinforcers act on the mesolimbic pathway, which originates in the ventral tegmental area (VTA) and provides dense dopamine innervation of the nucleus accumbens (NAC) and prefrontal cortex (PFC). Activation of this pathway by both natural rewards and drugs of abuse results in increased dopaminergic transmission within the NAC.

In rodents, the development of dopaminergic neurons is not fully established until the second and third weeks of postnatal life, a time period that overlaps with maternal lactation [19]. Thus, it has been considered that the maternal nutritional

environment may alter the function of the mesolimbic pathway to alter behavioural and neural responses in offspring, including overconsumption of a high-fat diet.

9.3.1 Reward-Directed Feeding Behaviour and Psychostimulant-Induced Locomotor Activity

In rodent models, maternal overnutrition increases the preference for palatable foods in offspring. For example, maternal consumption of a palatable high-fat diet 3 months prior to conception, and during gestation and lactation, increases preference for fat and sugar intake in the offspring [9]. Human studies are in support of these findings, indicating that maternal dietary content predicts adiposity in childhood [20] and that child fat intake is associated with prenatal rather than postnatal maternal fat intake [21].

Appetite regulation is largely mediated by hypothalamic regions involved in appetite control and by peripheral factors such as leptin, insulin and ghrelin that regulate energy balance [22]. Offspring exposed to maternal high-fat diet appear to have an increased hunger for fat-rich food that overrides satiety signals that usually maintain the balance between energy intake and expenditure in the body. Clearly, however, feeding is about more than the regulation of energy intake and expenditure; it produces a pleasure state that involves the activation of reward pathways in the brain.

Recent studies have suggested that pre- and postnatal (perinatal) exposure to a diet high in fat increases the preference for high-fat diet and the drive to consume palatable foods in adulthood. Likewise, maternal consumption of a palatable diet increases the preference and consumption of food that is high in fat and sugar, when compared to a micronutrient-balanced control diet [9, 23] or food rich in proteins [10, 24]. Importantly, the increased preference for palatable food by maternal overnutrition appears not to be due to increased appetite per se. When animals are given a control diet instead, they do not show increased appetite (i.e. increased consumption) for the control food [12, 24, 25]. These studies suggest that maternal effects on offspring dietary preferences involve changes in the salience of particular food-related stimuli (i.e. palatable diet), rather than merely an increase in energy intake. As was mentioned above, studies in humans likewise show that specific dietary preferences for fats are associated with maternal food intake during pregnancy [20, 21].

9.3.2 Dopamine-Related Neural Gene Expression

Although little work has been done to explore the neurobiological basis of the effects of maternal diet on food preferences in offspring, there are data consistent

with the idea that dopamine is involved. Indeed, maternal overnutrition has been shown to alter the expression of multiple dopamine-related genes in the mesolimbic pathway of adult offspring, including tyrosine hydroxylase (TH), dopamine receptors D1 and D2 (D1R, D2R) and dopamine transporter (DAT) [10, 11, 26]. However, the direction of expression of these changes and the specific dopaminergic genes exhibiting changes is variable between studies, possibly owing to differences related to the specific diet administered. Of note, increased DAT expression in the NAC is associated with DNA hypomethylation, suggesting that the change in gene expression is transmitted via an epigenetic modification [9].

As discussed, both natural and drug reinforcers alter the function of the dopaminergic system. Thus, an interesting question is whether maternal overnutrition alters the sensitivity of offspring to the locomotor-activating effects of psychostimulants. Indeed, the activational effects of drugs such as amphetamine, cocaine and morphine are mediated via dopamine transmission in the NAC [27]. In one study that addressed this question, it was found that maternal overnutrition was associated with attenuated amphetamine-induced locomotion and attenuated expression of amphetamine-induced sensitization [11]. Moreover, the attenuated effect of amphetamine on locomotor activity corresponded to blunted dopamine transmission in the NAC [26].

9.3.3 Models of Diet-Induced Obesity

As mentioned, models of diet-induced obesity involve exposing rodents to a high-fat diet for a long period of time in adulthood. Overall, the results of these studies are in agreement with observations relating to the effect of maternal overnutrition in offspring. Thus, rodents consuming a high-fat diet exhibit increased motivation to work for sucrose pellets [28], attenuated amphetamine-induced locomotor sensitization [29] and decreased dopamine turnover in the mesolimbic system (NAC) [30]. Also similar to the effects of maternal overnutrition, diet-induced obesity leads to changes in dopamine-related gene expression in the mesolimbic pathway, including reduced expression of TH, D1R and DAT in the NAC [29, 31]. Altogether, these studies consistently point to associations between consumption of high-fat diet and blunted reward function at both behavioural and neural levels.

One neurochemical of relevance to this discussion is leptin. Leptin is an adipose-derived hormone that acts on hypothalamic leptin receptors to regulate energy balance. Specifically, leptin regulates appetite by signalling when an individual has had enough to eat [32]. However, whereas increased leptin levels generally suppress feeding behaviour, a failure to do so is commonly found in cases of obesity, including obesity in pregnancy [33]. This so-called leptin resistance is also reflected in the results of studies utilizing maternal high-fat diet and diet-induced models of obesity [34–36].

Of note, leptin is known to regulate dopaminergic state, via actions at leptin receptors in the VTA. For example, infusion of leptin into the VTA reduces the

firing rate of dopamine neurons, while blocking the leptin receptors reverses this effect [37]. Additionally, conditional leptin receptor knockdown by siRNA in the VTA leads to an overall increase in feeding, as well as a preference for high-fat diet, as measured by the amount of food consumed after switching from standard to high-fat diet [37].

In accordance with its effects on dopaminergic transmission in VTA, leptin modulates the induction of locomotor sensitization to amphetamine. In one study, the sensitizing effect of amphetamine on locomotor activity was prevented in ob/ob mice lacking the genes coding for leptin [38]. Conversely, systemic treatment with leptin for 2 weeks resulted in the induction of amphetamine sensitization in the knockouts and an enhancement of this effect in wild-type mice [38].

Although maternal overnutrition is known to result in the expression of chronically high levels of leptin in offspring, these offspring exhibit reduced sensitization to the locomotor-activating effects of amphetamine [11]. This result would seem at odds with what might be expected based on the outcome of the work with ob/ob mice. It is possible, however, that differences in the developmental context of leptin exposure in these two models may induce changes in leptin levels within specific neural circuitries. Also, in the context of developmental exposure to high-fat diet, the mechanism for high leptin levels in offspring appears partly due to the increased number of new neurons expressing a number of orexigenic peptides, galanin, encephalin and dynorphin, in the hypothalamus that are known to interact with anorexigenic peptides such as leptin [23]. These data suggest changes in brain structure with exposure of offspring to maternal high-fat diet that are not observed with genetic deletion of leptin.

9.4 Effects of Maternal Overnutrition on the Offspring Stress Response System

In humans, exposure to maternal overnutrition and high-fat diet during development increases the risk in offspring of developing anxiety disorders and depression [39]. A number of lines of evidence suggest that the increased in risk may be driven, at least in part, by disruption in the development of neural pathways regulating responses to stress [40, 41].

9.4.1 Anxiety Behaviour and Stress Physiology

Animal studies have shown that exposure to maternal overnutrition impacts the expression of anxiety-like behaviour across the lifespan. For example, in a rat model, maternal overnutrition increased anxiety-like behaviour in adult offspring, as measured in the Open Field and Elevated Plus Maze tasks [12, 42, 43]. These

results are similar to primate studies showing that developmental exposure to maternal overnutrition increases novelty-induced anxiety in adult offspring [40, 44]. Finally, in human studies, results generally point to a positive association between the co-occurrence of childhood obesity and anxiety disorders [45].

The expression of anxiety-like behaviours is known to be sensitive to changes in the function of the hypothalamic–pituitary–adrenal (HPA) axis, which mediates the endocrine response to stress in part through negative feedback inhibition of corticosterone release. Likewise, maternal overnutrition influences the function of the HPA axis of offspring in a long-term manner. For example, maternal overnutrition is associated with lower levels of circulating corticosterone in male and female rats [12] and mice [46], and female rats exposed to maternal overnutrition exhibit prolonged elevation in corticosterone after physical restraint stress [12]. Likewise, neonatal rats exposed to maternal overnutrition exhibit an elevated corticosterone response to ether stress, suggesting that the programming of the HPA axis by maternal high-fat diet occurs in early postnatal life [47].

9.4.2 Stress-Related Neural Gene Expression

HPA function can be altered by changes in the expression of mineralocorticoid (MR) and glucocorticoid receptors (GR) within limbic brain areas, including the amygdala and hippocampus; these receptor populations differentially regulate basal and stress-activated levels of corticosterone in circulation [48, 49]. Of note, we recently reported that MR and GR transcripts are elevated in the amygdala of offspring whose mothers were fed a high-fat diet during pregnancy and lactation [12]. These data are in agreement with other studies of maternal stress manipulations, showing that increased GR in the amygdala enhances the corticosterone-mediated response to stress [50]. They are also in agreement with a study showing that the offspring of nonhuman primates fed with high-fat diet exhibit increased hypothalamic expression of proopiomelanocortin transcript, a gene that affects HPA function by altering levels of adrenocorticotropin-releasing hormone and, in turn, cortisol release [51].

9.4.3 Stress-Related Responses in Models of Diet-Induced Obesity

The behavioural effects of chronic exposure to high-fat diet in adult rats are similar to those of the offspring of mothers fed a high-fat diet. For example, after 10–12 weeks of consuming a high-fat diet, adult rats exhibited a relative increase in behavioural anxiety on the elevated plus maze, open field and light dark task [52, 53]. Moreover, these elevated anxiety-like behaviours are associated with an

altered HPA axis response, consisting of elevated corticosterone levels after restraint stress. These results agree with several other studies showing that chronic consumption of a high-fat diet in adulthood generally leads to elevated circulating levels of glucocorticoids and an enhanced corticosterone response to stress [54–56], but see [57]. Finally, chronic consumption of a high-fat diet exacerbates the effects of stress by impairing the negative feedback inhibition of the corticosterone response to psychosocial stress [53, 58].

Chronic exposure to high-fat diet in adulthood also leads to alterations in stress-related gene expression within stress-related neural circuitry that is similar, but not identical, to those of offspring exposed to maternal overnutrition. For example, animals consuming high-fat diet show reduced transcript in the hippocampus of both MR and GR, when compared to animals consuming standard house chow [52]. The offspring of animals exposed to maternal overnutrition, on the other hand, exhibit increased expression of the GR transcript within the amygdala. Given the opposing roles of the hippocampus and amygdala in the regulation of the HPA axis, however, both findings are consistent with the idea that the stress system is heightened in response to both dietary manipulations and that both manipulations lead to enhanced behavioural anxiety.

9.5 Relationship Between Food and Drug Addiction

Based on the relationship between maternal overnutrition and responses to psychostimulants in offspring, it is of interest that drug addiction, like disorders involving food consumption, has been linked to dysregulation within the primary brain pathways regulating reward and stress. Characterized by compulsion to seek drugs, drug addiction consists of a chronic cycle of drug intoxication followed by withdrawal and relapse [14]. This cycle corresponds to powerful positive reinforcement (drug intoxication) and, over time, the emergence of a negative emotional state (anxiety) after withdrawal. It has been argued that this negative emotional state may, at least in the short term, perpetuate drug seeking [14]. It has also been argued that drug addiction is characterized by a shift in the motivational processes mediating ongoing consumption from positive reinforcement induced by the drug to negative reinforcement resulting from the relief of negative affect upon resuming drug taking [14]. And it has recently been proposed that a similar transition may occur in the case of disordered eating leading to obesity [15]. Although the motivational and corresponding neural mechanisms involved in drug addiction are perhaps better understood than those involved in obesity, it has been suggested that compulsive drug and food consumption may be regulated by common neural and molecular mechanisms, including those related to dysregulated dopaminergic and stress-related function [59].

9.6 Conclusion and Prospective: The Potential Role of Epigenetic Mechanisms

In this chapter, we have highlighted research concerning reward- and stress-related effects that may help explain the rapid rise in metabolic dysfunction in offspring as a result of maternal diet. This question is particularly relevant since up to 30 % of human pregnancies in developed countries are now complicated by factors owing to maternal obesity [60]. Identifying the mechanisms through which maternal overnutrition results in altered reward and stress pathways later in life will enable the understanding of risk factors for disorders characterized by dysregulated hedonic and negative emotional states.

Epigenetic mechanisms, which modify gene function in the absence of a change in gene sequence, have been proposed to program gene expression as a function of early-life experience [12]. Long-term changes in gene regulation can occur via epigenetic modifications of DNA and chromatin structure. In contrast to chromatin modifications, which may be transient and are tightly coupled to gene expression, DNA methylation is a relatively stable modification that, in regulatory elements, typically leads to persistent repression of gene expression [61]. For example, levels of maternal behaviour received within the first week of life are associated with offspring HPA function and levels of DNA methylation in stress-related genes [62, 63]. Recently, a number of studies of candidate genes have indicated that maternal overnutrition alters levels of DNA methylation in gene promoters in offspring [9, 64–68].

With the support of technological advances in high-throughput DNA sequencing, it is now possible to extend this work from a consideration of candidate genes to candidate pathways. Many of the ways in which environmental exposures alter epigenetic mechanisms in offspring remain unknown. Improved methods for genome-wide detection of epigenetic alterations, however, have greatly advanced complex disease research by providing the means to identify mechanisms leading to stable changes in cellular function [69]. How these changes might distribute across dopaminergic and HPA-related gene networks is one related topic of active research.

In future research, it will be of interest to identify how epigenetic marks indicating enhanced or repressed transcriptional potential may relate to dysfunction in reward and stress pathways across a variety of conditions. Because epigenetic marks are potentially reversible, identifying the manner in which they are altered in the dopaminergic and HPA-related pathways of offspring whose mothers who were fed a high-fat diet will offer insight into mechanisms leading to stable disease states; this work may also inform novel routes to pharmacological intervention. Altogether, such studies will illuminate our understanding of risk factors for disorders characterized by dysregulated emotional processing.

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