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REVIEW

High-fat diet alters the dopamine and opioid systems: effects across development

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Consumption of a high-fat diet has been linked to obesity, dyslipidemia and cardiovascular disease. Less well appreciated are adverse effects on the brain and behavior. Recent research has shown that consumption of a high-fat diet can alter gene expression within the brain, and the dopamine and opioid neurotransmitter systems appear to be vulnerable to dysregulation. This review will focus on recent reports in both humans and animal models that describe adverse effects of high-fat diet consumption on the central reward circuitry. In addition, the importance of different development windows will be discussed, with effects observed in both the prenatal/perinatal time period and with chronic high-fat diet consumption in adulthood.

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INTRODUCTION

The risk for obesity is significantly increased when a person eats a calorically dense, high-fat diet. The negative health consequences of obesity are well described, and include increased risk for diabetes, cardiovascular disease, dyslipidemia, high blood pressure, and joint and sleep problems. More recently, adverse effects on the brain and behavior have been documented, which will be the focus of the present review, specifically how consumption of a high-fat diet during different developmental time periods can affect the function of the reward system in the central nervous system (CNS).

REWARD CIRCUITRY

The mesocorticolimbic reward circuitry refers to a series of interconnected brain regions that is activated by rewarding stimuli, including both natural rewards such as palatable foods or social interaction, as well as by drugs of abuse, such as cocaine or heroin. Typically, this circuitry refers to cells located within the midbrain structure of the ventral tegmental area, which project to forebrain structures, including the ventral striatum (nucleus accumbens) and the prefrontal cortex, with important contributions from the amygdala and certain hypothalamic structures as well (for example, orexin in the lateral hypothalamus). Dopamine (DA) is present in concentrated cell groups in the midbrain and to a lesser extent in the hypothalamus and olfactory bulbs. There are four primary DA pathways: the mesolimbic, mesocortical, nigrostriatal and tuberoinfundibular pathways. DA projections from the ventral tegmental area to prefrontal cortex (mesocortical) and nucleus accumbens and amygdala (mesolimbic) projections have been implicated in reward and incentive motivation by natural and pharmacological reinforcers,[1,2] novelty-seeking behavior[3] and locomotor activity.[4] Hypothalamic DA has an important role in neuroendocrine functions, particularly prolactin secretion,[5] and is known to regulate food intake.[6,7] The nigrostriatal pathway (damaged in Parkinson's disease) is critical for the generation of movement. There are currently five known DA receptors, all of which are G-protein-coupled receptors. The D1-like family includes D1 and D5, which are coupled to G_{as} and are considered stimulatory receptors. The D2-like family, D2, D3 and D4, is coupled to G_{ai}, with D2 acting both presynaptically as an autoreceptor and postsynaptically. The primary site of expression of D1 and D2 receptors is the striatum,[8] but both receptor subtypes have also been localized to the hypothalamus and prefrontal cortex.[9] DA uptake is facilitated by two transporters: vesicular monoamine transporter and, more specifically, the DA transporter (DAT), which clears DA from the synapse. Other important molecules related to dopaminergic function include DA- and cyclic AMP-regulated phosphoprotein (DARPP-32), a signaling molecule that acts downstream of both D1 and D2 receptors, and catechol-*O*-methyl transferase, an enzyme found in the synaptic cleft that degrades DA.

In addition to the DA system, opioids are also critical for encoding the rewarding properties of a stimulus.[10,11] The opioid system has three endogenous ligands, encoded by precursors such as preproenkephalin (PENK), prodynorphin and pro-opiomelanocortin. Similarly, there are three endogenous opioid receptors, delta, kappa and mu. With regard to consumption of a high-fat diet, PENK and μ-opioid receptor (MOR) have been implicated as critical factors. Direct stimulation of the MOR by an agonist, such as PENK, specifically stimulates the consumption of high-fat food.[12]

PRENATAL/PERINATAL VULNERABILITY

One developmental time period in which exposure to a high-fat diet is known to affect brain development is during prenatal development. Maternal consumption of a high-fat diet during pregnancy is associated with obesity. The incidence of obesity among pregnant women in the United States ranges from 20 to 38%.[13] The risk for a baby being born large-for-gestational age (LGA) increases nearly threefold with maternal obesity[14,15] and nearly fivefold in mothers with excessive gestational weight gain (GWG).[16] Further, the risk for obesity at 18 years of age is

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associated with excessive GWG of the mother during pregnancy, but only in women who were obese or overweight at the beginning of the pregnancy.[17] Maternal obesity also increases the risk for the development of gestational diabetes and excessive GWG. Pre-pregnancy obesity and gestational diabetes can interact to further increase the risk of LGA.[18,19] Diabetes in pregnancy also increases the risk for obesity in childhood[20] and in young adults,[21] although maternal obesity may be a stronger determinant than diabetes status, *per se*.[22,23] There is support in the literature for LGA increasing the risk for adverse neurobehavioral outcomes, such as autism spectrum disorders,[24,25] increased anxiety/depression,[26] difficulty with emotional regulation[27] and an increased risk for attention deficit hyperactivity disorder.[27–29] Attention deficits have also been observed in offspring born to mothers with diabetes before or during pregnancy.[30] Interestingly, reward system dysfunction can contribute to each of these disorders. To begin to understand the potential underlying mechanisms linking the maternal consumption of a high-fat diet with changes in the development of the reward system, it is important to develop relevant animal models.

ANIMAL MODELS

In animals, maternal consumption of a high-fat diet has been linked to a range of negative CNS outcomes, including increased anxiety-like behaviors,[31,32] decreased hippocampal dendritic arborization,[33] increased hypothalamic neurogenesis of orexigenic neurons (which can drive overeating and increase the obesity risk)[34] and alterations in the expression of serotonergic genes, dopaminergic genes, inflammation-related genes and neuropeptides related to food intake/metabolism.[31,32,34,35] Not all areas of the brain appear to be similarly sensitive to the effects of maternal consumption of a high-fat diet, as arcuate to paraventricular projections are not affected by maternal diet,[36] yet these projections are affected by maternal insulin status,[37] highlighting the complexity of the interactions between maternal environment (diet, obesity, diabetes) and the offspring outcome.

Maternal consumption of a high-fat diet during pregnancy and lactation can change gene expression in the offspring brain, leading to behaviors that increase the risk for obesity. Changes in the systems that are involved in the homeostatic regulation of feeding have been documented. For instance, maternal consumption of a high-fat diet from embryonic day 6 to postnatal day 15 in rats resulted in an increased expression of orexigenic peptides in the lateral hypothalamus,[34] which was attributed to increased neurogenesis of these neuronal populations. Importantly, these authors also included a group of offspring from high-fat-fed dams cross-fostered to control-fed dams at birth, which resulted in similar findings, emphasizing the importance of the prenatal environment in driving the observed phenotype. Maternal high-fat diet can also alter the function of neurons from the ventromedial hypothalamic nucleus, which demonstrate differential responses to glucose and long-chain fatty acids in offspring from dams fed a high-fat diet.[38] Changes in gene expression of neuropeptides that control homeostatic food intake (for example, melanocortins and neuropeptide Y) in the arcuate nucleus have also been documented in the offspring of dams fed a high-fat diet.[35,39,40]

Importantly, a number of laboratories have identified changes in the reward circuitry in offspring from dams fed a high-fat diet, leading to an increased preference for high-fat or high-sugar foods in offspring from the affected pregnancies; in other words hedonically driven feeding. It has been shown that when pregnant rat dams are fed a 'junk-food diet' (for example, biscuits, pancakes, chocolate and cheese (high fat/high sugar)), the offspring have a significantly increased preference for fatty, sugary and salty foods.[41,42] In addition, rat offspring from dams fed a high-fat diet in the last half of pregnancy and through lactation increased their operant responding for high-fat pellets, in essence working harder than control animals for the fat pellet.[43] Similarly, early-life exposure to a high-fat diet (in the 3rd postnatal week) also programmed a greater preference for fat as an adult.[44]

Altered reward system function can also be seen in the behavioral response to drugs that engage the DA system. In one study, rat dams were exposed to highly palatable diet during pregnancy and lactation, and pups were then weaned to either control or palatable diets. Offspring that had both prenatal and postnatal exposure to high-fat diet demonstrated a sensitized locomotor response to amphetamine.[45] In a different study, the high-fat diet was given in the last week of gestation and during lactation, and contrary to the previous study, these affected offspring demonstrated a blunted response to amphetamine.[46] These two studies highlight one of the key variables known to factor into the relationship between maternal diet and offspring reward-related behavior—the precise developmental window of exposure to the high-fat diet.

In terms of the mechanism mediating changes in the activity of the reward circuitry, both DA and opioid systems have been shown to be affected by maternal consumption of a high-fat diet. Maternal junk-food diet consumption in rats altered the expression of both MOR and DAT, and the direction of these changes varied by the age of the offspring.[42] Perinatal exposure to the high-fat diet in rats was also shown to have profound effects on DA system gene expression and function.[43,46] Finally, lactational exposure to a cafeteria-style diet led to altered levels of both DA and serotonin.[47] This effect extends to early life as well, as mice fed the high-fat diet during the 3rd postnatal week also showed evidence of altered DA-related gene expression in the nucleus accumbens.[44]

The data from the research team in my lab were obtained using a model of LGA in which pregnant female mice are fed a high-fat diet through pregnancy and lactation. The pups are born LGA, maintain a higher body weight through weaning, at which point all offspring are weaned to the control diet, and within approximately 1–2 weeks, the weight difference normalizes. When these offspring are tested as adults, they have a significantly greater preference for both sucrose and fat.[48] Gene expression analyses revealed that expression levels of both DA-related genes (*DAT*, *D1* and *D2*) and the opioid-related genes (*MOR* and *PENK*) were significantly altered in the reward circuitry of LGA animals.

POSTNATAL EFFECTS OF A HIGH-FAT DIET

The prenatal and early postnatal weeks are a period of significant brain growth and development, and thus it is not surprising that exposure to a nonoptimal diet (high fat) during this critical phase of development could result in adverse consequences for CNS function. But what about exposure outside of this critical window? To answer this question, data from the research team in my lab and others were obtained by investigating the effects of chronic consumption of a high-fat diet by adult animals. Increasing evidence from both animal models and humans supports the idea of an association between obesity and a general decrease in gene expression and function within the central reward system. A number of excellent recent reviews have addressed this question directly,[49–52] and thus this review will highlight only a subset of the data from both obese human patients and animal models showing decreased reward system function in obesity.

In humans, functional imaging technology has been used to document differential patterns of brain activation in obese patients. One study examined activational patterns in the brains of lean and obese men and women, in response to evaluating immediate rewards versus long-term negative consequences. Obese women showed greater response to immediate reward (even in the face of delayed negative consequences) as opposed to lean women, and this differential response was not observed in

obese men.[53] Another important imaging study demonstrated that youth who are at risk for obesity (defined as having both parents overweight/obese) showed an increased activation of the reward circuitry in response to food or monetary rewards,[54] suggesting that parental obesity can contribute to the child's risk for obesity. This same research group has also shown that reduced responding of the striatum to palatable food consumption can develop with weight gain, as opposed to existing prior to weight gain.[55] Therefore, collectively, these two studies suggest a situation in which a predisposition to find highly palatable foods more rewarding may lead to an overconsumption of these foods and the subsequent diminished reward responding that develops with weight gain/obesity.

In rodents, there is increasing evidence across a number of different animal models demonstrating a link between obesity/high-fat diet consumption and a decrease in reward system function. By using brain reward threshold as a measure of reward system activity, chronic high-fat diet consumption was shown to decrease brain reward threshold, and this effect was mediated by downregulation of the D2 receptor. Importantly, the effect persisted for 2 weeks after termination of the diet.[56] In a similar study, 28-day consumption of high-fat diet was found to impair insulin-activated signaling kinase AKT activity, which led to DAT downregulation.[57] The DAT expression was rescued and the behavioral responses normalized after AKT overexpression. Downregulation of D1 and D2 in NAc of rats was observed after exposure to a high-fat/high-sucrose diet. This effect persisted after removal of the high-fat/high-sucrose diet and was linked to the diet consumption *per se* rather than associated weight gain.[58] In addition, consumption of a high-fat diet was shown to attenuate amphetamine-conditioned place preference and operant responding for sucrose and to decrease DA turnover.[59] Finally, consumption of a high-fat cafeteria diet was shown to lower both basal levels of DA and DA release in response to food or amphetamine.[60]

In addition to DA, opioids and the MOR in particular are important in reward of palatable foods.[61,62] Through the work in our laboratory, we were the first to show that consumption of a high-fat diet could downregulate the expression of the MOR within reward circuitry structures. In mice that chronically consume a high-fat diet (from 3 to 20 weeks of age), the MOR expression is decreased within the reward circuitry and unchanged in the hypothalamus. In addition, the research team in my laboratory identified altered DNA methylation and recruitment of the transcriptional repressor MeCP2 as an important mechanistic step in the process of MOR downregulation.[63] In fact, changes in DNA methylation are also important for driving dopaminergic gene expression changes in response to high-fat diet consumption/obesity.[64]

CONCLUSION

It is clear that consumption of a high-fat diet can affect the brain reward system. During early development, a high-fat diet can change DA and opioid gene expression within reward circuits. One outcome of this altered gene expression is an increased preference for palatable foods, which are typically calorie dense. This can establish a feed-forward perpetuation of the obesity risk, with maternal consumption of a high-fat diet during pregnancy increasing the risk for obesity in offspring by increasing fat preference.

However, it is not only in early development when the brain is thought to be relatively more plastic that consumption of a high-fat diet can affect CNS reward system function. Both DA and opioid systems can be downregulated in response to chronic exposure to a high-fat diet (and the resultant obesity) in adulthood. This decreased reward system activity can lead to continued consumption of a high-fat diet, as an individual needs to consume more high-fat diet to reach their reward 'set point'.[65] This behavioral response pattern is similar to that seen during chronic drug use, where chronic intake of the rewarding stimulus leads to brain changes that increase the likelihood of persistent intake.[49]

It is clear that consumption of a high-fat diet can affect the function of the CNS reward system, partly by changing the expression of DA- and opioid-related genes. Research within the field has now begun to address critical mechanistic questions including the following: (1) defining critical periods of high-fat diet exposure, (2) defining the precise stimulus (for example, high-fat diet versus the resultant obesity) and (3) investigating the reversibility of some of these changes. A full understanding of how high-fat diet affects the function of the brain reward system may lead to more informed prenatal advice, as well as more targeted therapeutics to aid obese patients with initiating and maintaining weight loss.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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