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Maternal high fat diet programs stress-induced behavioral disorder in adult offspring

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HIGHLIGHTS

- The effects of maternal HFD on offspring behavior did not persist into adulthood.
- Maternal HFD sensitizes offspring to the detrimental effects of stress on behavior.
- CUMS-treated offspring of HFD-fed dams have increased CGRP levels in hippocampus.
- Central infusion of CGRP antagonist produced antidepressant effect in HFD + CUMS rats.
- Maternal HFD attenuate the habituation of HPA profile responses to repeated stress.

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ABSTRACT

Early life exposure to specific environmental factors can contribute to development of behavioral disorders in adulthood. Although maternal high fat diet (HFD) consumption during the perinatal period has been reported to program offspring behavior, the underlying mechanisms remain to be elucidated. The present study was designed to evaluate the influence of maternal HFD on offspring behavior under nonstressed and stressful conditions, using male Sprague–Dawley offspring, which mothers were fed with HFD or normal diet (ND), receiving chronic unpredictable mild stress (CUMS) in the adulthood. We found that although the detrimental effects of maternal HFD consumption on offspring depressive behavior did not persist into adulthood, it markedly aggravated the behavioral disorder response to stressful challenge in adult offspring. Moreover, calcitonin gene-related peptide (CGRP) concentration in CSF and hippocampus were increased in the HFD + CUMS rats, compared to the ND + CUMS subjects. Another separate groups were fitted with intracerebroventricular (icv) cannulae. Central infusion of $\alpha CGRP_{8-37}$, a CGRP antagonist, produced antidepressant effects in HFD + CUMS rats, implying that the programming of maternal HFD on offspring behavior responses to stress may be mediated partially by endogenous central CGRP signaling. Moreover, we found that maternal HFD significantly exacerbated HPA profile response to acute restraint stress and attenuated the habituation of HPA responses to repeated restraint stress, suggesting that maternal HFD may program the changes of HPA-regulatory mechanisms. Overall, our findings suggest that maternal HFD influence adult depressive disorder response to stressful challenge, through the modulation of endogenous central CGRP signaling and HPA-regulatory components.

1. Introduction

The parental heredity and adult lifestyle are well-known to contribute to developmental and health problems, but epidemiological and animal studies suggest specific environmental factors that a developing offspring experiences during the perinatal period also play an important role in programming many aspects of physiology and behavior. Indeed, evidence suggests that epigenetic events initiated during the prenatal period can lead to persistent adaptations in structure, metabolism and physiology that predispose offspring towards disease and impaired physiology [1]. Moreover, maternal separation has been reported to increase susceptibility to obesity, insulin resistance, high blood pressure and cerebrovascular diseases in adult offspring [2–4], while neonatal bacterial challenge can also induce cardiovascular and cerebrovascular dysfunction in adult offspring [3–5]. Furthermore, specifically related to neurological or psychological function, maternal rejection or separation has been implicated in the development of depressive phenotypes in adult humans and animals [6,7].

Abbreviations: HFD, high fat diet; CUMS, chronic unpredictable mild stress; CGRP, calcitonin gene-related peptide; CSF, cerebrospinal fluid; HPA, hypothalamic-pituitary-adrenal.

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The environment that offspring experiences in the early life, including intrauterine and early postnatal environment, is highly influenced by maternal diet and metabolic status. Indeed, perinatal overnutrition or consumption of high fat diet (HFD) has been demonstrated to lead to health problems of adult offspring, such as metabolic syndrome, hypertension and cardiovascular dysfunction, in animal studies and epidemiological investigations [8–10]. In addition to the metabolic and endocrine systems, maternal HFD consumption also confers susceptibility to mental health and behavioral disorders in offspring, such as depression, anxiety, impairments in social behavior, cognitive deficit, reward-based behaviors, and attention deficit hyperactivity disorder in later life [11–14]. Based on above evidence, maternal HFD consumption plays an important role in offspring physiology and behavior, it should be pointed out, however, that other studies reported that adult offspring of HFD-fed dams can have normal glucose tolerance, body composition, as well as normal behavior and cognitive ability [11,15–17]. More importantly, in the light of the current stressful environment that many humans live in, it is important to address whether perinatal HFD may exacerbate the adverse effects of the stressful challenge on adult offspring physiology and behavior.

Calcitonin gene-related peptide (CGRP), a 37-amino-acid neuropeptide, best known for its potent vasodilatory properties [18,19], has been implicated in many aspects of the behavior. Functional studies suggest that CGRP may contribute to the modulation of many psychological and behavioral processes, such as stress responses, anorectic and fear-related behaviors [20–22]. Moreover, CGRP-immunoreactive (CGRP-ir) in the hippocampus is elevated in "genetically depressed" Flinders Sensitive Line rat, while maternal separation (a behavioral model of depression) could even exacerbate this elevation [23]. More specifically, a recent study shows that, through methylation of the CGRP gene, gestational environment programs adult depression-like behavior [24]. These results strongly indicate that genetic disposition and development stress may contribute to the susceptibility to depression, at least partially, by exerting CGRP-specific effects on adult neurobiology. Nevertheless, whether CGRP participates in the programming of maternal HFD on the adult behavior has not been investigated.

The present study was designed to evaluate the effects of maternal HFD on offspring behavioral phenotype at different developmental stages, with additional emphasis on the contributions of maternal diet to the psychological and neurological consequences of stress. Moreover, the involvement of CGRP in the programming of maternal HFD was investigated by examining the levels of CGRP in the central nervous system in the models. Furthermore, we investigated whether intracerebroventricular (icv) administration of CGRP antagonist $CGRP_{8-37}$ would attenuate depressive-like behaviors in adult stressed HFD offspring. In addition, the neural pathways that regulate stress responses are also involved in the modulation of behavior, and the available literature strongly suggests interactions between the two systems. Thus, we further examined the involvement of hypothalamic-pituitary-adrenal (HPA) axis activity in the processes, by investigating the HPA profile responses to acute psychological stress (restraint stress) and the repeated stress-induced habituation of HPA activity in HFD offspring.

2. Materials and methods

2.1. Animals

Female Sprague–Dawley (120–140 days) rats, obtained from Wenzhou Medical University, were housed under controlled conditions (12 h:12 h light–dark, with lights on at 0700 h; temperature at 22 ± 2 °C) and provided with food and water ad libitum. The rats were fed with either a standard normal chow diet (ND; n = 8; 21% kcal fat, 17% kcal protein, 63% kcal carbohydrate; Medicience Ltd., Jiangsu, China) or high fat diet (HFD; n = 12; 45% kcal fat, 20% kcal protein, 35% kcal carbohydrate; Medicience Ltd.), for 10 days before mating and throughout pregnancy and lactation. The day of parturition was set as day 0, and litters, including females and males, were evenly culled to 8 per mother on day 1. Pups were kept with their mothers until weaning on day 21. Thereafter, weaned male rats were housed 3 per cage and fed a normal chow diet. All male offspring from one dam were used in the same experiment and distributed randomly in the groups. Animal weight and food intake were recorded weekly in offspring post-weaning.

In order to assess the impacts of high-fat feeding during pregnancy and lactation on offspring depressive behavior under nonstressed or stressful conditions, the male ND and HFD offspring were subjected to 14-day CUMS or normal circumstance in experiment 1: (1) ND rats with normal circumstance (n = 9); (2) ND rats treated with CUMS (n = 9); (3) HFD rats with normal circumstance (n = 9); (4) HFD offspring treated with CUMS (n = 9). Another sets of HFD + CUMS rats were used in experiment 2 involving the drug administration: (1) HFD + CUMS rats treated with vehicle (n = 8); (2) HFD + CUMS animals treated with CGRP antagonist (n = 9). Moreover, another groups of rats were used in experiment 3 to investigate the changes of HPA profile responses to acute and repeated restraint stress in offspring: (1) ND rats (n = 9); (2) ND rats treated with restraint (n = 9); (3) HFD rats (n = 9); (4) HFD animals treated with restraint (n = 9). All animal procedures were performed in accordance with the Guidelines of the Chinese Council on Animal Care and approved beforehand by the Institutional Animal Care and Use Committee of Wenzhou Medical University. All surgical procedures were carried out under ketamine anesthesia (100 mg/kg i.p.; Pharmacia and Upjohn, Crawley, UK) and xylazine (10 mg/kg i.p.; Bayer, Leverkusen, Germany).

2.2. CUMS procedures

At the age of 120-day, the CUMS procedure was performed on animals as described previously [25], with minor modifications. The procedure contained 9 different stressors randomly arranged day and night across 14 consecutive days: 18 h water deprivation, 20 h food and water deprivation, 12 h of 45°cage tilt, 21 h wet cage, overnight illumination, 2 min swimming in water at 4 °C, 2 min swimming in water at 45 °C, 1 min tail pinch and 2 h immobilization.

2.3. Behavioral assessments

Sucrose preference test (SPT), open-field test (OFT) and forced swimming test (FST) were employed five times to assess the depressive-like behaviors. The behavioral assessments were conducted at the age of 56, 120, 127, 134 and 141 days to observe the effects of maternal HFD on behaviors at the different stages. SPT and OFT were used to investigate the effects of drugs on depressive-like behavior in rats.

2.3.1. Sucrose preference test

The SPF was used to operationally determine anhedonia. In the SPT which was conducted between 0900 h and 1000 h, the animals were allowed to consume water and 1% sucrose solution for 1 h after 20 h food and water deprivation. The sucrose preference index was calculated according to the following ratio: sucrose preference = sucrose intake (g)/sucrose intake (g) + water intake (g). The sucrose preference was monitored with nonstressed (young and adult) and stressful conditions.

2.3.2. Open-field test

The OFT was performed to evaluate general locomotor and rearing activity of rats. The apparatus consisted of a dark varnished wooden box (100 cm square chamber, 40 cm high walls) with the floor divided into 25 equal squares. Locomotor activity was defined as at least three paws in a quadrant and rearing behavior defined as the animal standing upright on its hind legs were tallied over a 3-min period. The OFT was