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Effects of high-fat diet on growth and depression-like behavior of prenatal stress offspring rats

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Abstract

To investigate effects of high-fat diet (HFD) on body length, weight and depression-like behavior of prenatal stress (PS) offspring rats. PS rat model was established by restraint stress. Sucrose preference and forced swimming tests were performed. Moreover, the effects of HFD on the growth and depression-like behavior in offspring rats were observed. Length of male and female HF group was significantly longer than that control, but length of male PS+HF group was significantly shorter than HF group. Body weight of male and female HF group was significantly higher than control, and body weight of male PS+HF group was significantly lower than HF group. No significant differences were observed in length between female PS +HF and HF groups. Compared with male PS+HF group, growth rate of male HF group was significantly higher. Moreover, HFD could reduce sucrose preference, and prolong immobility time of PS offspring rats. HFD can promote weight gain of male and female normal offspring rats. PS can partially inhibit effects of HFD on weight gain of PS male offspring rats, but exert no significant effects on PS female offspring rats. HFD can aggravate PS-induced depression-like behavior in offspring rats.

Keywords: high-fat diet; prenatal stress; growth; development; depression-like behavior.

Practical Application: this study demonstrates that high-fat diet during prenatal stress can significantly impact on the metabolism and depression-like behaviors of offspring rats, and emphasizes the significance of diet and emotional management of pregnant women during pregnancy.

1 Introduction

With the rapid development of economy, the people's diet constitution and habit have also changed, and the proportion of high-fat diet (HFD) has been gradually increased. HFD can increase the prevalence of obesity and heart diseases, as well as the mortality of cancer, which greatly affect the people's health (Last & Wilson, 2006; Kesse et al., 2006; Fung et al., 2001). The obesity may contribute to the occurrence and development of mood disorders (Rethorst et al., 2014). In addition, the risks of diseases, such as Alzheimer's Disease and other neurodegenerative disorders are also closely related to the diet with overdose of high saturated fat. Another study has also found that high-fat and -sucrose diet would impair the learning and memory function and decline the synaptic plasticity in rats, and the long-term HFD would result in depression and mood disorders (Yoon et al., 2012).

Psychological status of pregnant women affects the trajectory of fetal neurodevelopment, which is involved to the developing disease in adulthood (Beebe et al., 2008; Champagne, 2010). When pregnant women underwent significant stress, anxiety or depression, the risks of mental and mental illnesses would be potentially increased in their offspring (Talge et al., 2007). The systemic and non-specific stress responses in pregnant women, caused by the internal and external environmental changes, or the mental and psychological factors, have been referred as prenatal stress (PS). Previous studies have found that the neonatal birth, head circumference, and neurobehavioral scores would be reduced in the offspring from the mothers with PS (Su et al., 2015). In animal experiments, it has also been found that the neurological destruction would be observed in the hippocampus, and the incidence rate of depression-like behavior increased in the offspring from the mothers with PS (Guan et al., 2013; Jia et al., 2010).

Obesity, metabolic syndrome and type 2 diabetes (T2DM) can co-exist in the development of major depression (MDD) and anxiety (Fenton & Stover, 2006; Shinkov et al., 2018). In addition, the fat content is not only related to the energy intake, but also associated with the genetic and environmental factors (Nilsson & Skinner, 2015; Hanafi et al., 2016; Skinner, 2016). Accumulating evidence indicates that the intake of HFD during development would lead to poor health outcomes of growth and development after birth. The association between the HFD before and during pregnancy and the offspring metabolic diseases has been investigated in clinic, and the findings have shown that the decreased insulin sensitivity is closely related with the increased prevalence of diabetes (Guo & Jen, 1995; Painter et al., 2008). More and more studies have found that the HFD intake during pregnancy is closely linked with the changes in emotional behavior in their offspring (Bilbo & Tsang, 2010;

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Winther et al., 2018). Therefore, in this study, the effects of HFD of pregnant women undergoing PS on the growth and mentality of their offspring were investigated.

2. Materials and methods

2.1 Study animals

All rats in this experiment were housed in an animal room at 24 °C, with the humidity of 60% and a 12-h (8:00 am to 20:00 pm) light-dark cycle, with free access to drinking water and diet. All procedures in the experiment were performed in approval from the Local Ethics Committee. Female rats (weighing 230-250 g) and male rats (weighing 280-350 g) made to copulate in cages at 20:30 pm, at a ratio of 3:1. The vaginal examination was performed for the female rats before 8:30 am the next morning. The positive results indicated the pregnancy Day 0, and the pregnant rats would be raised in a single cage.

2.2 Procedure of PS

The PS model was established according to previously described studies (Sun et al., 2013; Koehl et al., 1999). Briefly, the pregnant rats were placed in a plastic cylindrical device with transparent openings at both ends, with the inner diameter of 6 cm. The vent was fixed at one end, and the other end was appropriately adjusted according to the length of the pregnant rat. The restraint stress was carried out 3 times a day (45 min each time), that was, at 8:00-11:00, 12:00-15:00, and 16:00-19:00, from 14 to 20 days during pregnancy. In order to prevent the habitation, the time interval between each stress stimulus would be no less than 2 h. Meanwhile, some pregnant rats were randomly selected and given with high-fat diet (RD12451; Ready Bite, Shenzheng, Guangdong, China). After the weaning of the rats at Day 21, 1-2 offspring rats were randomly selected from each litter for subsequent experiments. Each of these offspring rats was housed in a single cage, at 24°C, with the humidity of 60% and a 12-h (8:00 am-20:00 pm) light-dark cycle. According to the stress condition of pregnant rats and different diets, their male and female offspring were divided into the following four groups: the CON (n=5; offspring from normal pregnant rats), PS (n=5; offspring from PS pregnant rats), HFD (n=5; offspring from HFD pregnant rats), and PS+HF (n=5; offspring from HFD/PS pregnant rats) groups. At 30 and 37 days after birth, the body length (cm) and body weight (g) were measured. The changes in body length and body weight were observed.

2.3 Sucrose preference test

Deletion is the central symptom to depression-like behavior. The sucrose preference test was performed herein to assess and reflect the depression-like behavior in rats. All rats were given 2% (w/v) sucrose solution and drinking water at the same time for 24 h. On the next day, the water was banned for 3 h before the behavioral experiment, and then two identical drinking bottles were weighted (trying to make the volume of drinking water similar to the sucrose solution). To prevent rats from becoming habitual for the location of the drinking bottles, the bottles of the sucrose solution and drinking water were alternately placed every day. The consumption of sucrose solution and drinking water within 1 h was recorded for the rats in each group. Experiments were performed in triplicates. The sucrose preference was used as a measure for the depression-like behavior, based on the following formulation: Sucrose preference = Sucrose solution consumption / (Drinking water consumption + Sucrose solution consumption) × 100%.

2.4 Forced swimming test

For the forced swimming test, the rats were placed in a cylindrical glass cylinder, with a height of 50 cm and an inner diameter of 30 cm. The glass cylinder was filled with water of 30 cm in depth, and the water temperature was 25±1°C. During the forced swimming test, the swimming state of the rats within 10 min was recorded with the SMART3.0 camera system (Panlab; Barcelona, Spain), and the cumulative immobility time was also recorded. The animal behavior could be divided into the following four categories: (1) Swimming (freely swimming in the water); (2) Climbing (the front paws swiping the water or touching the cylinder wall); (3) Diving (the whole body diving underwater); and (4) No moving (floating on the surface, or without obvious activities in the limbs). At the beginning of the test, the rats often tried hard to swim, attempting to escape, but after a period, they often floated in an inactivity, showing a state of desperation. The longer the rats stayed, the stronger the depression degree would be. When the rat no longer struggled, instead floating in the water and remained motionless, or only showing some slight movements (keeping the head floating on the water surface), the time for this state was considered as the immobility time. Immobility time was used as a measure for the depression-like behavior.

2.5 Statistic analysis

Data were expressed as mean ± SEM and the SPSS 18.0 software was used for statistical analysis. Offspring data analyses were performed by the one-way ANOVA. $P < 0.05$ was considered as statistically significantly.

3 Results

3.1 Effect of HFD on length of PS offspring rats

To investigate the effects of HFD on the length of PS offspring rats, the length of the offspring of each group on Days 30 and 37 after birth were recorded and investigated, and the 7-d growth rate of the body length was calculated. Our results showed that, on Day 30 after birth, for the male offspring, the body length of the HF group was significantly higher than the control group (17.4 ± 0.42 cm vs 14.6 ± 0.12 cm; $P < 0.01$), while the length of the PS+HF group was also significantly lower than the HF group (16.5 ± 0.5 cm vs 17.4 ± 0.42 cm; $P < 0.01$; Figure 1A). Similar results were obtained on Day 37 after birth (Figure 1A). To further understand the development of male offspring, the growth rate of the body length within 7 d was investigated. Our results showed that there no significant difference in the growth rate between these four groups (16.45 ± 3.1%, 16.13 ± 3.61%, 13.48 ± 2.15%, and 16.19 ± 3.22%, respectively;

$P = 0.648$; Figure 1B). Taken together, these results suggest that, HF can increase the length of normal male offspring, while PS can inhibit the effect of HF on body length, with however no significant effect on the growth rate. To investigate whether there was a gender difference for the effect of HFD on the length of PS offspring rats, the effects of HFD on the length of female PS offspring rats were recorded and analyzed. Our results showed that, on Day 30 after birth, for the female offspring, the length of the HF group was also significantly longer in the HF group than the control group (15.83 ± 0.76 cm vs 13.4 ± 0.42 cm; $P < 0.01$; Figure 1C), which showed no significant difference in the body length when compared with the PS + HF group (15.5 ± 0.87 cm vs 15.83 ± 0.76 cm; $P = 0.512$; Figure 1C). Moreover, on Day 37 after birth, these female offspring showed comparable length as the male, and similar results were observed for the body weight on Day 30 after birth (Figure 1C). Moreover, there was no significant difference in the growth rate between these four female groups (8.23 ± 4.89%, 4.88 ± 1.41%, 6.49 ± 5.9%, and 4.3 ± 3.88%, respectively; $P = 0.583$; Figure 1D). Taken together, these results suggest that the effect of HF on the length of female offspring is slightly different from that for males. Although HF can promote the length of normal female offspring, PS does not influence the effect of HF on the growth of female offspring.

3.2 Effect of HFD on body weight of PS offspring rats

To understand the effects of HFD on the growth and development of PS offspring rats, the body weights of the offspring on Days 30 and 37 after birth were also investigated, and the 7-d body growth rate was calculated accordingly. Our results showed that, on Day 30, for the male offspring, the body weight of the HF group was significantly higher than the control group (138.57 ± 10.58 g vs 73.54 ± 11.18 g; $P < 0.01$; Figure 2A), while the weight of the PS+HF group was significantly lower than the HF group (103.11 ± 10.63 g vs 138.57 ± 10.58 g; $P < 0.01$; Figure 2A). Similar results were observed for the comparison of the body weights on Day 37 after birth (Figure 2A). On the other hand, the 7-d growth rate was investigated. Our results

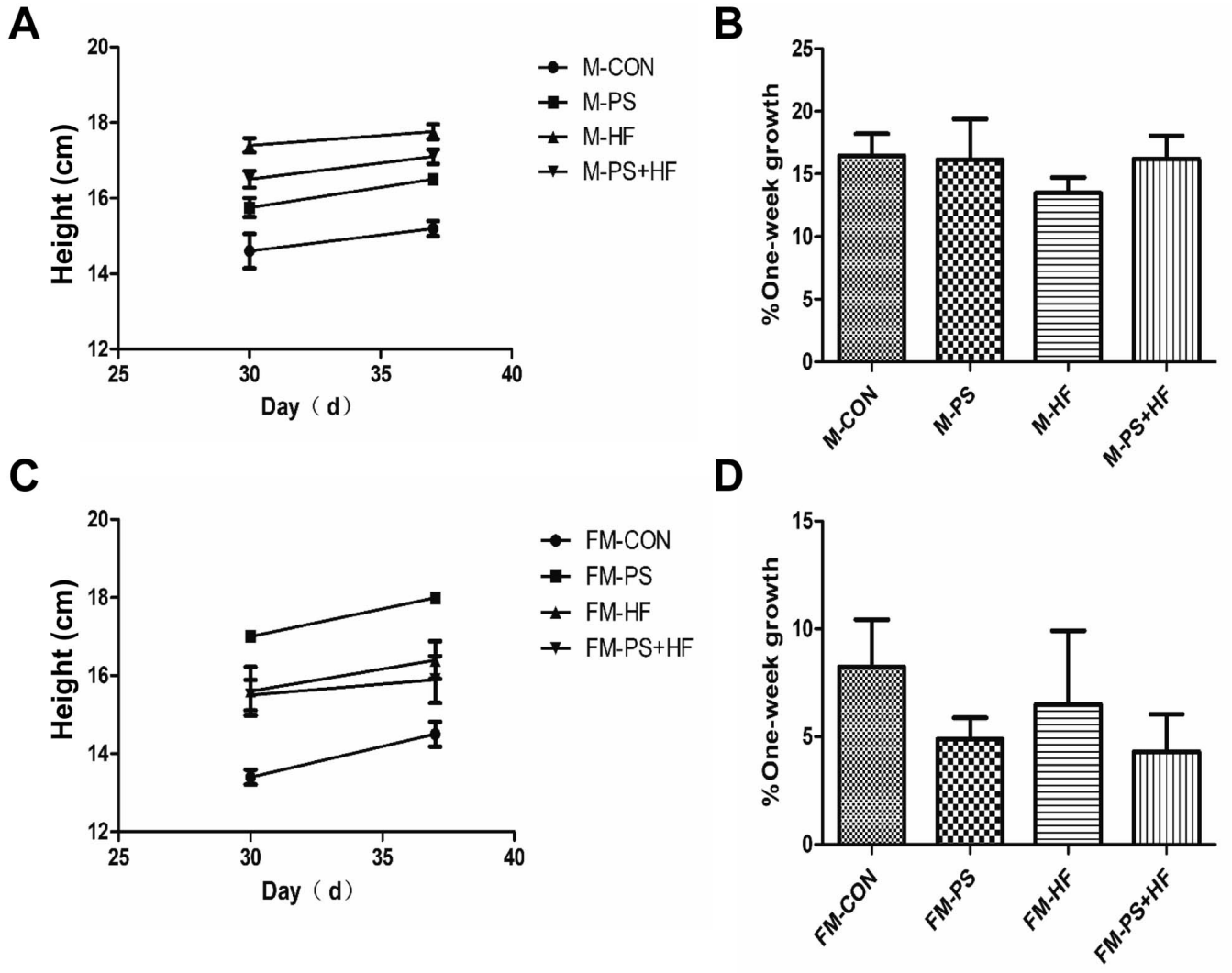

Figure 1. Effects of HFD on length of PS offspring rats. (A) The effects of HFD on the length of PS male offspring rats; (B) The effects of HFD on the growth rate of PS male offspring rats; (C) The effects of HFD on the length of PS female offspring rats; (D) The effects of HFD on the growth rate of PS female offspring rats.

showed that, the growth rate of the HF group was significantly higher than the control group (40 ± 3.36% vs 35 ± 6.16%; $P < 0.05$; Figure 2B), and the growth rates were significantly higher when compared with the PS+HF group (40 ± 3.36% vs 29.2 ± 4.86%; $P < 0.05$; Figure 2B). These results suggest that HF can significantly increase the body weight of normal male offspring, and the growth rate is significantly accelerated, but PS can significantly inhibit the effect of HF on the weight gain. Similarly, the effects of HFD on the body weight of female PS offspring rats were also investigated. Our results showed that, on Day 30 after birth, for the female offspring, the body weight of the HF group was comparable with that of the males, which was also significantly higher than the control group (129.58 ± 5.82 g vs 64.4 ± 9.09 g; $P < 0.01$; Figure 2C), and significant differences were observed when compared with the PS+HF group (129.58 ± 5.82 g vs 97.38 ± 20.57 g; $P < 0.01$; Figure 2C). Similar results with the male offspring were observed for the offspring on Day 37. Our results showed that, the body weight of the HF group was significantly higher than the CON and PS+HF groups (Figure 2D). There was no significant difference in the body weight growth rate (%) between the four female groups (32.25 ± 5.21 g, 25.43 ± 2.23 g, 27.65 ± 1.97 g, and 27.64 ± 4.7 g, respectively; $P = 0.087$; Figure 2D), showing dramatic difference compared with the male offspring.

3.3 Effects of HFD on sucrose preference in PS offspring rats

To understand the role of HFD in the depression-like behavior in PS offspring rats, the effects of HFD on total drinking water and sucrose preference were first investigated. Our results showed that, the sucrose preference of the male offspring rats in the HF group was significantly lower than that control group (40.72 ± 3.72% vs 69.67 ± 8.73%; $P < 0.01$; Figure 3). Moreover, HFD caused a decrease in sucrose preference in PS offspring rats (25.95 ± 5.45%

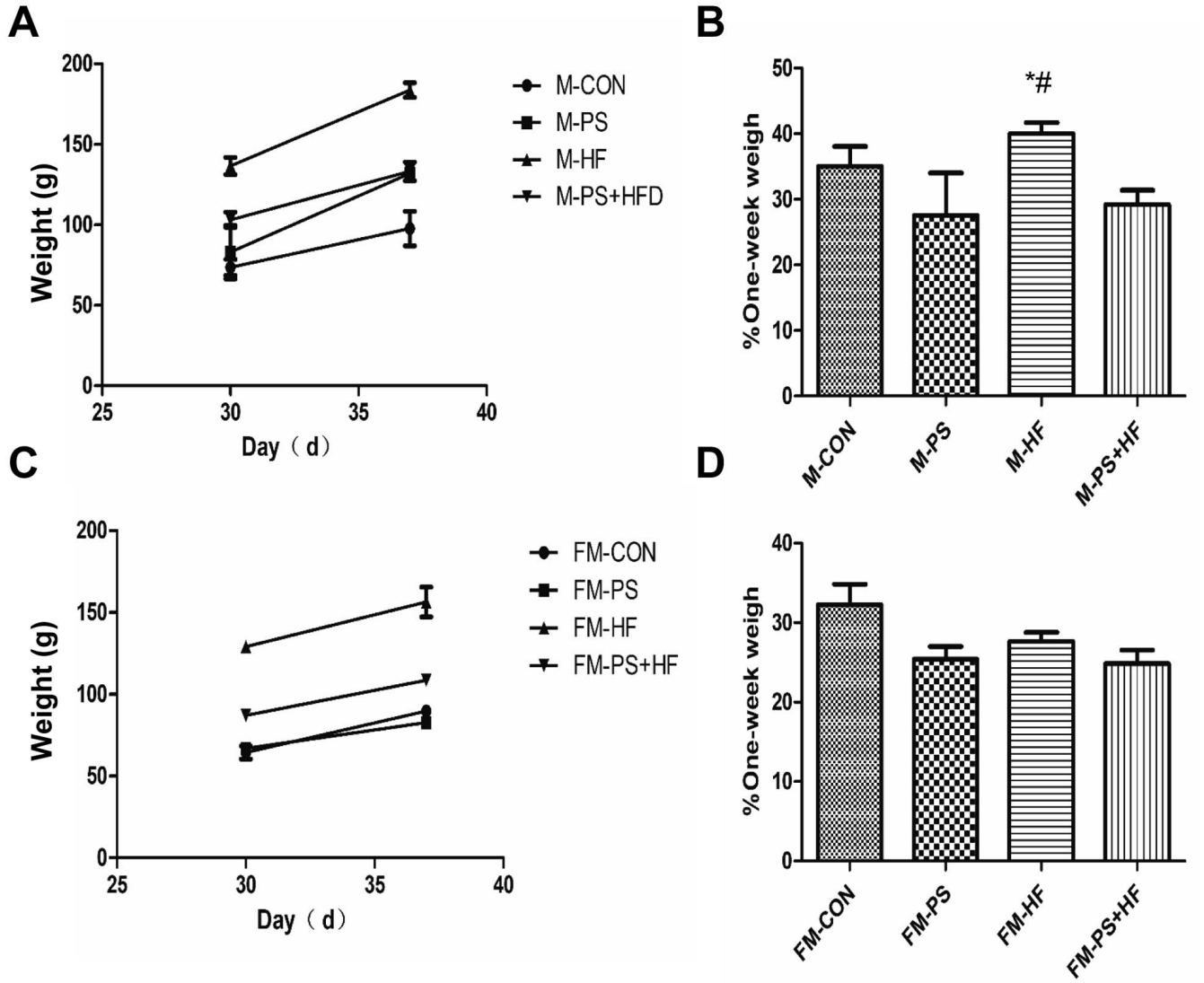

Figure 2. Effects of HFD on body weight of PS offspring rats. (A) The effects of HFD on the body weight of PS male offspring rats; (B) The effects of HFD on the body weight gain rate of PS male offspring rats; (C) The effects of HFD on the body weight of PS female offspring rats; (D) The effects of HFD on the body weight gain rate of PS female offspring rats. Compared with the control (CON) group, $^{*}P < 0.01$; compared with the PS+HF group, $^{\#}P < 0.01$.

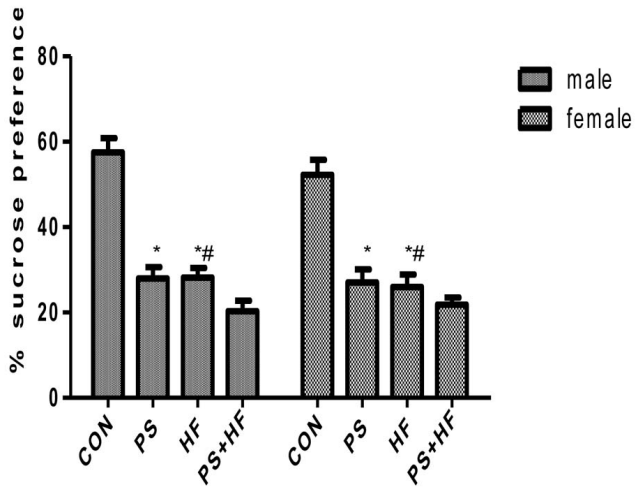

Figure 3. Effects of HFD on sucrose preference in PS offspring rats. The sucrose preference test was used to study the depression-like behavior of the offspring rats. Compared with the control (CON) group, $^{*}P < 0.01$; compared with the PS+HF group, $^{\#}P < 0.01$.

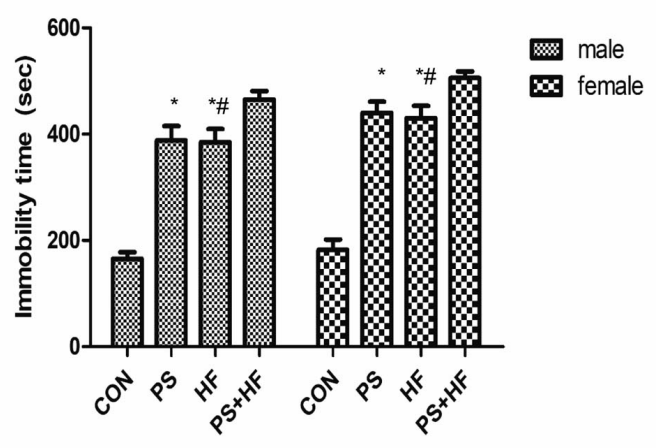

Figure 4. Effects of HFD on immobility time in PS offspring rats. The forced swim test was used to study the depression-like behavior of the offspring rats. Compared with the control (CON) group, $^{*}P < 0.01$; compared with the PS+HF group, $^{\#}P < 0.01$.

vs 40.72 ± 3.72%; $P < 0.01$; Figure 3). Our results suggest that, HFD could significantly reduce the sucrose preference of PS offspring rats. In addition, similar results were observed for the female offspring (Figure 3).

3.4 Effects of HFD on immobility time in forced swimming test of PS offspring rats

In order to clarify whether the HFD would aggravate the depression-like behavior of PS offspring rats, the immobility time of the offspring rats in the forced swimming test was determined. Our results showed that the immobility time of the HFD offspring rats was significantly higher than the control group (266.01 ± 23.59 s vs 172.5 ± 13.57 s; $P < 0.01$; Figure 4). Moreover, HFD increased the immobility time of PS offspring rats (332.62 ± 23.37 s vs 290.75 ± 18.73 s; $P < 0.01$; Figure 4). These results suggest that, the immobility time of the offspring rats would be increased, and it has been further verified that the HFD can aggravate the depression-like behavior caused by PS.

4 Discussion

Previous studies have shown that changes in the intrauterine environment during pregnancy would affect the fetus development, probably inducing several health problems such as the fetal skull deformity and myocardial structure damage, which might also have long-term effects on the fetal physiological system (Babenko et al., 2015; Barker, 2001). Carmichael & Shaw (2000) have reported that the prenatal psychosocial stress factors can enhance the incidence of congenital malformations, such as that the probability of suffering from neural tube defects would be increased by nearly 2 folds. Epidemiological researches have also shown that PS can significantly affect the head circumference and body weight at birth, especially for the reduced head circumference, indicating that PS can have specific impacts on the fetal brain development (Lou et al., 1994). In this study, we found that PS significantly reduced the body weight of the offspring, with similar results for the males and females, and there was no significant difference in the weight growth rate, suggesting relatively stable effects. In addition, we also detected that PS caused a significant decrease in the length compared with the control group, further confirming that PS can significantly affect the growth and development of the offspring rats. Interestingly, our results showed that, under the action of HFD, the weights of male and female offspring rats were significantly increased, and the weight gain of PS offspring rats was reduced. We speculate that those results may be due to the fact that PS would weaken the effects of HFD on the weight gain. However, differential results were observed for the animal length, which showed significant gender difference. Although HFD could promote the length of normal offspring, in the PS male offspring, the promoting effects of HFD on animal growth was partially inhibited. For PS female offspring, however, no significant effect was found. This difference may be caused by the abnormal hormone expression in males and females due to gender differences.

Our previous studies have confirmed that the stress on mothers during pregnancy not only affects the neurodevelopment of the offspring, but also causes abnormal behaviors, as well as cognitive and neuropsychiatric diseases, such as depression and anxiety (Jia et al., 2010; Lin et al., 2018; Lu et al., 2017). Recently, studies have also found that HFD can cause depression-like behavior in mice by affecting hippocampal synaptic plasticity, certain inflammatory factors, and neuropeptide Y expression levels (Wu et al., 2018; Hassan et al., 2018). Moreover, HFD in pregnant mothers would also lead to depression-like behavior in offspring rats (Gawlinska et al., 2019). Interestingly, in the offspring rat models isolated from the mother, the HFD in pregnant mothers would prevent the depressive-like behavior in the offspring (Rincel et al., 2016). Therefore, in addition to affecting the growth and development of PS offspring, HFD will affect the animals' emotional changes, which might be focused on in our further studies in the future. The sucrose preference test and forced swimming test were performed herein to assess

the as a method to study depression-like behavior. The sucrose preference test is one of the most commonly used methods for detecting the depression-like behavior, and the reduced sucrose preference reflects lacking of pleasure. Lacking pleasure means a decrease in sensitivity to rewards and other reactions, or a decline in the ability to express experience, which is a basic feature for depression in clinic. The forced swimming test is another most widely used method to detect depression-like behavior. In this study, our results from the sucrose preference test showed that PS caused the decline of sucrose preference in the offspring rats, showing obvious depression-like behavior, while the HFD resulted in a decrease in the sucrose preference of PS offspring. Therefore, these results suggest that HFD significantly aggravates the depression-like behavior of rats. Similar results were found in the forced swimming test. PS lead to prolonged immobility time of offspring rats, while HFD prolonged the immobility time. The above behavioral results indicate that HFD can significantly enhance the occurrence of depression-like behavior in offspring rats.

In conclusion, our results showed that HFD promoted the weight gain of male and female normal offspring rats, and elongated the length of normal male offspring. However, PS partially inhibited the effect of HFD on weight gain in PS male offspring rats. PS female offspring rats showed no significant effect on body weight gain and length. Moreover, HFD can aggravate the depression-like behavior of PS in male and female offspring rats. It have been preliminarily confirmed that HFD may be one of the key factors causing depression-like behavior, and the specific mechanism of action needs to be further studied in the future.

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