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The effects of ovariectomy and lifelong high-fat diet consumption on body weight, appetite, and lifespan in female rats

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ABSTRACT

In females, ovarian hormones play pivotal roles in metabolic, appetite, and body weight regulation. In addition, it has been reported that ovarian hormones also affect longevity in some species. Recently, it was found that the consumption of a high-fat diet aggravates ovariectomy-associated metabolic dysregulation in female rodents. The aim of this study was to investigate the hypothesis that long-term high-fat diet consumption and ovariectomy interact to worsen body weight regulation and longevity in female rats.

At 21 days of age, female rats were weaned and randomly divided into two groups, one of which was given the high-fat diet, and the other was supplied with standard chow. At 23 weeks of age, each group was further divided into ovariectomized and sham-operated groups, and then their body weight changes, food intake, and longevity were measured until 34 months of age. The sham – high-fat diet rats exhibited greater body weight changes and higher feed efficiency than the sham – standard chow rats. On the other hand, the ovariectomized – high-fat diet and ovariectomized - standard chow rats displayed similar body weight changes and feed efficiency. The sham – high-fat diet and ovariectomized – standard chow rats demonstrated similar body weight changes and feed efficiency, indicating that the impact of ovariectomy on the regulation of body weight and energy metabolism might be similar to that of high-fat diet. Contrary to our expectations, ovariectomy and high-fat diet consumption both had small favorable effects on longevity. As the high-fat diet used in the present study not only had a high fat content, but also had a high caloric content and a low carbohydrate content compared with the standard chow, it is possible that the effects of the high-fat diet on body weight and longevity were partially induced by its caloric/carbohydrate contents. These findings indicate that the alterations in body weight and energy metabolism induced by ovariectomy and high-fat diet might not directly affect the lifespan of female rats.

1. Introduction

It has been well established that obesity and overweight are major risk factors for several diseases, such as diabetes, cancer, and cardiovascular disease (Manson et al., 2004; Mokdad et al., 2001). In females, ovarian hormones play a pivotal role in metabolic, appetite, and body weight (BW) regulation (Della Torre et al., 2014; Hirschberg, 2012; Hong et al., 2009; Kaaja, 2008; You et al., 2004). In humans, a deficiency of ovarian hormones in the postmenopausal period increases the risk of obesity and a range of metabolic disorders (Della Torre et al., 2014; Kaaja, 2008; You et al., 2004). Similarly, the short-term; i.e., for several weeks, abrogation of ovarian hormone production increases food intake (FI) and BW, and consequently induces obesity and associated comorbidities in experimental animals (Blaustein and Wade, 1976; Butera, 2010; Hirschberg, 2012; Hong et al., 2009; Iwasa et al., 2016). On the other hand, it remains unclear whether the long-term abrogation of ovarian hormone production also induces such unfavorable metabolic effects. Some studies have indicated that ovariectomy (OVX) induces increases in BW and fat deposition, even at 12 months after the surgery (Seidlova-Wuttke et al., 2012), whereas other studies have shown that it does not affect BW or fat mass at 8–10 months after surgery in female rodents (Gilbert and Ryan, 2014). Similarly, although the effects of long-term OVX on longevity have been examined, the results of these studies varied markedly. It has been reported that ovarian hormones might have a positive effect on longevity in humans and experimental animals (Asdell et al., 1967; Benedusi et al., 2014; Parker et al., 2009). Ovariectomy (OVX) is associated with a shortened lifespan in female rodents (Asdell et al., 1967; Benedusi et al., 2014), and women that undergo elective hysterectomy exhibit greater longevity than those who undergo hysterectomy combined with OVX (Parker et al., 2009). On the other hand, OVX increases longevity in stroke-prone spontaneously hypertensive female rats (Stier et al., 2003). Recently, Ludgero-Correia et al. reported that high-fat diet (HFD) consumption aggravates OVX-associated metabolic

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dysregulation in female mice (Ludgero-Correia et al., 2012). OVX mice that were fed a HFD for 18 weeks displayed greater fat weight and larger adipocytes than OVX mice fed standard chow (SC). As the high-fat diet used in this study also had a high caloric content and a low carbohydrate content, it is possible that the effects of the high-fat diet on body composition were induced by its caloric/carbohydrate contents. On the other hand, the long-term effects of OVX and HFD consumption on BW, FI, and lifespan have not been examined in females.

Thus, the aim of this study was to investigate the hypothesis that long-term HFD consumption and OVX interact to worsen BW regulation and longevity in female rats.

2. Materials and methods

2.1. Animals

All research involving vertebrates or cephalopods must have approval from the institutional animal care and use committee of the University of Tokushima and must be conducted according to the applicable national and international guidelines. Approval was received prior to the start of this research (No. 14060). Pregnant Sprague-Dawley rats (day 15 of pregnancy, BW: 350–380 g) were purchased (Charles River Japan, Inc., Tokyo, Japan) and housed individually under controlled lighting (12 h light, 12 h dark cycle) and temperature (24 °C) conditions. All animal experiments were conducted in accordance with the ethical standards of the institutional animal care and use committee of the University of Tokushima. The day the pups were born was considered to be day 1, and only female newborn pups were used for the experiment. To remove litter-based effects, the litters were combined, and 10–12 pups were randomly assigned to each dam.

2.2. Experimental protocol

At 21 days of age (3 weeks (wk) of age), female rats were weaned and randomly divided into two groups, one of which was given the HFD (HFD-60; Oriental Yeast Co. Ltd., Tokyo, Japan; 506.2 kcal/100 g, 62.2% of the provided calories were derived from lard-based fat, 18.2% were from protein, and 19.6% were from carbohydrates) (n = 14), and the other was supplied with SC (type MF; Oriental Yeast Co. Ltd., Tokyo, Japan; 359 kcal/100 g, 12.8% of the provided calories were derived from fat, 25.6% were from protein, and 61.6% were from carbohydrates) (n = 15). These foods also contain adequate amounts of vitamins and minerals. At 23 wk of age, each group was further divided into OVX or sham-operated (sham) groups; i.e., the rats were divided into OVX-HFD (n = 7), OVX-SC (n = 7), sham-HFD (n = 7), and sham-SC (n = 8) groups. All surgical procedures were carried out under anesthesia with sodium pentobarbital. In the sham groups, the ovaries were just touched with forceps. Water containing ibuprofen (0.1 mg/ml) was provided during the three days after surgery to reduce the rats' postoperative pain. BW and food intake (FI) were weighed weekly throughout the experimental period (until 138 wk of age). Generally, two rats were housed in each cage, and they were differentiated by their ear hole markings. The food consumption of the rats in each cage was measured once a week. When two rats were housed in one cage, the mean consumption value was used as the value for each rat. Housing the rats in pairs was considered to be appropriate for this study because it helped to avoid 1) the isolation stress that would have been induced by housing the rats individually and 2) discrepancies between calculated and real food consumption values due to group housing (Nilsson et al., 2001). The health statuses of the rats were checked daily; i.e., we checked whether they were suffering from ill health or had died unexpectedly. The rats were euthanized via the intraperitoneal injection of sodium pentobarbital for humane reasons if their conditions worsened and it was considered that they were unlikely to survive for more than a week. Namely, when rats could hardly move and could not take any food and water by themselves, they were euthanized.

2.3. Statistical analysis

Statistical analyses were performed via mixed model ANOVA or two-way factorial ANOVA followed by the Tukey-Kramer post-hoc test or the Student's *t*-test. All results are expressed as mean plus standard error of the mean (SEM) values. Cohen's d (small effect = 0.2, medium effect = 0.5, large effect = 0.8) and Eta squared (η2) (small effect = 0.2, medium effect = 0.5, large effect = 0.8) are reported when analyses were undertaken by Student's *t*-test and ANOVA, respectively.

3. Results

The mean BW of the pups at 3 wk of age was 56.6 ± 0.27 g. As noted above, the rats were randomly divided into the HFD and SC groups. The mean BW of the HFD group was 56.7 ± 0.41 g, and that of the SC group was 56.5 ± 0.37 g. Mixed model ANOVA showed that the main effect of diet on BW was not significant during the period from 3 to 23 wk of age, whereas the interaction between diet and time had a significant effect on BW (diet: F (1,27) = 0.471, P = 0.498, η2 = 0.013; time: F (20,540) = 990.1, P < 0.01, η2 = 10.15; interaction: F (20,540) = 2.51, P < 0.01, η2 = 0.026). It also demonstrated that the main effect of diet on the change in BW was not significant, whereas the interaction between diet and time had a significant effect on the BW change (mixed model ANOVA; diet: F (1,27) = 0.424, P = 0.521, η2 = 0.012; time: F (20,540) = 993.4, P < 0.01, η2 = 10.8; interaction: F (20,540) = 2.52, P < 0.01, η2 = 0.028) (Fig. 1A and B). However, at 23 wk of age the BW and BW changes of the HFD group did not differ from those of the SC group (BW: Student's *t*-test, P = 0.13, Cohen's d = 0.58; BW change: Student's *t*-test, P = 0.13, Cohen's d = 0.59) (Table 1). Mixed model ANOVA showed that the main effect of diet on FI was significant during the period from 3 to 23 wk of age, as was the effect of the interaction between diet and time on FI (diet: F (1,27) = 304.2, P < 0.01,

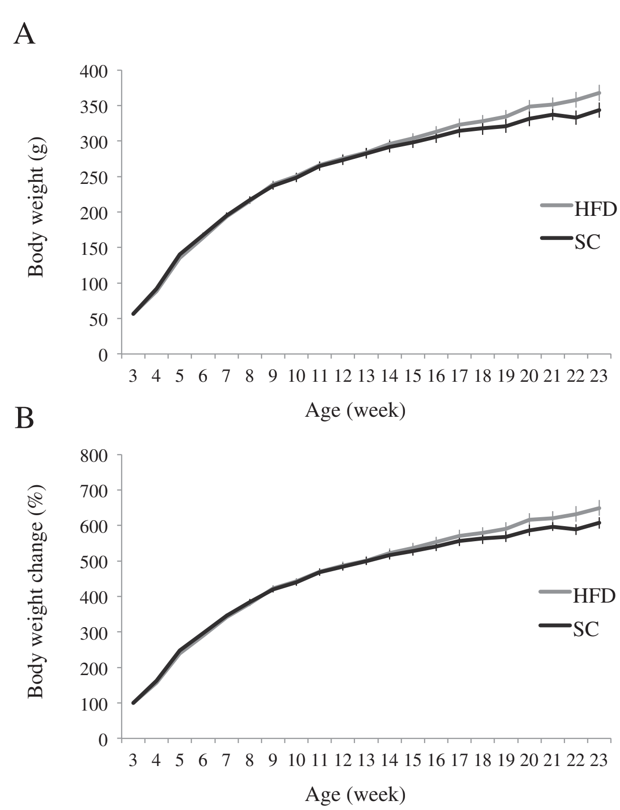

Fig. 1. Body weight (BW) (A) and BW changes (B) seen in high-fat diet (HFD)- or standard chow (SC)-fed rats between 3 and 23 wk of age. BW changes are expressed as percentages of BW at 3 wk of age. Data are expressed as mean and SEM values.