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Ovarian hormones mediate running-induced changes in high fat diet choice patterns in female rats

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ABSTRACT

Physical inactivity and increased consumption of energy dense, high fat (HF) foods often leads to a state of positive energy balance. Regular exercise can facilitate the maintenance of a healthy body weight and mediate changes in dietary selection. Past studies using a two-diet choice (chow vs. HF) and voluntary wheel running paradigm found that when a novel HF diet and wheel running are simultaneously introduced, male rats show complete and persistent HF diet avoidance whereas the majority of females show HF diet avoidance for a few days, but then revert to HF diet preference. Ovariectomy (OVX) appears to decrease preference for the HF diet bringing it closer to that of males. Given that estradiol but not progesterone mediates changes in food intake and energy balance, we hypothesized that estradiol signaling is required for the reversal of HF diet avoidance in female rats. Accordingly, Experiment 1 compared the persistency of running-induced HF diet avoidance in males, sham-operated females, and OVX rats with replacement of oil vehicle, estradiol benzoate (E), progesterone (P), or both (E + P). The number of wheel running rats that either avoided or preferred the HF diet varied with hormone treatment. The reversal of HF diet avoidance in running females and OVX E + P rats occurred more rapidly and frequently than male running rats. E + P but not E or P replaced OVX wheel running rats significantly reversed HF diet avoidance. OVX oil rats avoided HF diet to the same extent as male rats for the first 11 days of diet choice and then rapidly increased HF diet intake and began preferring it. This incomplete elimination of sex differences suggests that developmental factors or androgens might play a role in sustaining running-induced HF diet avoidance. Subsequently, Experiment 2 aimed to determine the role of androgens in the persistency of running-associated HF diet avoidance with sham-operated and orchiectomized (GDX) male rats. Both intact and GDX male running rats persistently avoided the HF diet to the same extent. Taken together, these results suggest that activational effects of ovarian hormones play a role in female specific running-induced changes in diet choice patterns. Furthermore, the activational effects of androgens are not required for the expression of HF diet avoidance in males.

1. Introduction

Disordered eating behavior can result in two distinct phenotypes, obesity and anorexia, both of which involve a prolonged period of energy imbalance. Individuals with anorexia have low body weight, avoid high fat (HF) foods, and often engage in excessive physical activity (King et al., 1994; Mayer et al., 2012; Foerde et al., 2015; Steinglass et al., 2015). Conversely, a majority of obese individuals have increased preference and intake of energy dense, HF foods without sufficient physical activity or exercise (Drewnowski and Greenwood, 1983; Hill et al., 2012). Furthermore, there is a disparity in the prevalence of eating disorders between the sexes. Compared to men, women are at a higher risk for developing eating disorders including anorexia nervosa, bulimia, and binge eating (Hudson et al., 2007; Flegal et al., 2010). Similarly, rodent studies have found that female Sprague-Dawley rats are more prone to binge eating when given intermittent access to highly palatable food compared to males (Klump et al., 2013; Hildebrandt et al., 2014). Given these sex differences and the rapidly increasing prevalence of obesity [BMI $\geq$ 30 kg/m^2, (McCall and Raj, 2009)], it becomes important to characterize the neuroendocrine components underlying these sex differences.

Past studies found an inverse correlation between physical activity/energy expenditure and body fat in men but not women (Bjorntorp, 1989; Westerterp and Goran, 1997; Paul et al., 2004). This finding is not surprising because there are sex differences in the percentage of people who do not reduce body weight or body fat after regular,

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supervised exercise (e.g. non-responders). In females, roughly half of the study population show increased weight gain in response to exercise (Anderson et al., 2001; Donnelly and Smith, 2005). Paralleling the human literature, male but not female rats show suppressed weight gain and decreased adiposity after exercise (Rolls and Rowe, 1979; Pitts, 1984; Cortright et al., 1997; Schroeder et al., 2010; Carrera et al., 2011). That is, both human and rodent literature found a consistent effect of exercise on reducing body weight and adiposity in males but not females. Thus, the efficacy of body weight control through exercise appears to be sex specific and optimal obesity prevention and treatment approaches may differ for males and females.

The effects of exercise on food intake were investigated in humans and the effects were highly variable. The results of exercise effects range from increasing energy expenditure without a compensatory increase in food intake to having no effect on daily energy intake (Blundell and King, 1999; Scheurink et al., 1999; Melzer et al., 2005; King et al., 2009; Laskowski, 2012; Ebrahimi et al., 2013; Schubert et al., 2013; Donnelly et al., 2014). The factors influencing this variability are not well characterized. Moreover, some studies report no sex differences in the effect of exercise on appetite and food intake in humans (Pomerleau et al., 2004; Hagobian et al., 2009; Ebrahimi et al., 2013; Thackray et al., 2016). On the other hand, rodent models of voluntary exercise revealed sex differences in exercise-mediated changes in food intake. Upon running wheel access, male rats consistently exhibit anorexia after a bout of exercise is initiated (Tokuyama et al., 1982; Looy and Eikelboom, 1989; Kawaguchi et al., 2005; Carrera et al., 2011). Female rats, however, have been found to decrease (Tokuyama et al., 1982; Eckel and Moore, 2004) and increase (Carrera et al., 2011) food intake upon exercise. Again, the literature suggests that the effects of exercise are more variable and inconsistent in females compared to males.

Given that both the human and rodent literature report that exercise can affect food intake and body weight, more recent research has focused on whether or not exercise can induce changes in diet choice, specifically preference for palatable, HF foods. Studies using self-report data found that individuals who successfully maintained weight-loss ≥13.6 kg for at least 1 year exercise regularly and consume low-energy, low-fat diets (Klem et al., 1997; Shick et al., 1998). Studies using data from the National Weight Control Registry found that exercise alters dietary selection of macronutrients (Klem et al., 1997; Shick et al., 1998; Wing and Hill, 2001; Catenacci et al., 2014). Nevertheless, whether exercise alone is sufficient to drive changes in diet choice remains unclear. Thus, our laboratory utilized a rodent model of voluntary exercise to address this issue. In our model, rats are given simultaneous access to two diets (chow vs. HF) and running wheels. Upon wheel running access, male rats decrease intake and preference for a previously preferred HF diet (Scarpace et al., 2010; Shapiro et al., 2011; Scarpace et al., 2012; Liang et al., 2015). When wheel running and HF diet are introduced simultaneously, male rats show complete and persistent HF diet avoidance (Moody et al., 2015). In contrast, the majority of female rats initially avoid the HF diet but after a few days, they reverse their HF diet avoidance. Ovariectomy (OVX) appears to increase the persistence of HF diet avoidance to a similar degree to that observed in male rats (Moody et al., 2015).

To our knowledge, no study has examined the influence of sex hormones on running-induced changes in diet choice. Previous studies have repeatedly shown that sex hormones play a major role in the control food intake (Asarian and Geary, 2013; Begg and Woods, 2013). After OVX, rats increase food intake and body weight for approximately 1 month and then maintain food intake and body weight at 20–25% above sham-operated controls (Wade and Gray, 1979). Estradiol, given centrally or peripherally, results in decreased food intake, adiposity, and body weight (Wade and Gray, 1979; Asarian and Geary, 2002; Santollo et al., 2010; Eckel, 2011). Conversely, progesterone treatment alone has no effect on food intake, adiposity, or body weight (Wade and Gray, 1979; Gray and Wade, 1981; Asarian and Geary, 2006; Yu et al., 2011). When both estradiol benzoate and progesterone are replaced, OVX rats transiently increase body weight and food intake (Wade and Gray, 1979; Varma et al., 1999). Castrated males treated with low dose testosterone increase food intake and body weight (Gentry and Wade, 1976a; Nunez et al., 1980; Chai et al., 1999). By contrast, high dose testosterone replacement results in decreased food intake, adiposity, and body weight (Gray et al., 1979) most likely through the aromatization of testosterone to estrogenic metabolites (Nunez et al., 1980; Siegel et al., 1981). Given the well-established effects of estradiol on food intake (Eckel, 2011) and the finding that diet choice patterns did not differ among wheel running gonadally-intact male and OVX rats (Moody et al., 2015), Experiment 1 was designed to determine whether ovarian hormones are necessary for the pattern of HF diet preference that is characteristic of the gonadally-intact female Based on past findings that estradiol alone can reduce food intake and body weight (Wade and Gray, 1979; Geary and Asarian, 1999; Asarian and Geary, 2002; Butera, 2010), we hypothesized that estradiol signaling in OVX rats is required for the expression of female specific diet choice patterns. The result that OVX only partially eliminated sex differences prompted us to question whether androgens play a role in mediating the persistency of HF diet avoidance in males. Thus, in Experiment 2, male rats were sham-operated or orchiectomized (GDX) to determine whether the lack of androgens would disrupt the maintenance of running-induced HF diet avoidance in GDX rats.

2. Methods

2.1. Experiment 1

2.1.1. Subjects

20 male (250-275 g) and 100 female (150-175 g) Sprague-Dawley rats (SD, Envigo, Indianapolis, IN) at the age of ~7–8 weeks upon arrival were the subjects of this experiment. The rats were individually housed in polyethylene tubs on a 12:12 light-dark cycle (lights on at 0200 h) with ad lib access to a standard chow diet (3.1 kcal/g, 58% carbohydrate, 24% protein, and 18% fat; Teklad global 2018, Teklad Diets, Madison, WI) and tap water during habituation. All experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Illinois, Urbana-Champaign and are in accordance with the Guide for the Care and Use of Experimental Animals (National Research Council, 2011).

2.1.2. Procedures

2.1.2.1. Bilateral ovariectomy and sham surgery. After habituation, female rats underwent either sham or bilateral ovariectomy (OVX) surgery (Idris, 2012). No surgery was performed on the male rats. Anesthesia was induced and maintained using 4% and 2% Isoflurane (Midwest Veterinary Supply, INC, Lakeville, MN), respectively. The Isoflurane was delivered in conjunction with oxygen through a nose cone. Rats were shaved dorsolaterally and the surgical area was disinfected using sequential iodine and ethanol wipes. Prior to making an incision, rats received a 5 mg/kg subcutaneous (s.c.) injection of Carprofen as an analgesic. A skin incision was made down the dorsal midline of the rat. After dissecting through the underlying fascia, a cut was made in the muscle lateral to the midline to expose the abdominal cavity. The ovary was pulled out through its surrounding adipose tissue and the uterine horn was ligated below the ovary. Then, the ovary was cut and the remaining tissue returned to the abdominal cavity. The muscle incision was sutured and the procedure was repeated on the contralateral side. Finally, the skin incision was sutured and antibiotic ointment was applied. Identical incisions were made for sham surgeries but the ovaries were left intact. Following surgery, rats were returned to their home cage and sutures were removed approximately 6 days post-surgery.

2.1.2.2. Vaginal cytology. Successful OVX surgery and hormone