Physiology & Behavior 95 (2008) 501–507

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Ovarian hormones inhibit fat intake under binge-type conditions in ovariectomized rats

Zhiping Yu [a], Nori Geary [b,c], Rebecca L. Corwin [a,*]

[a] Department of Nutritional Sciences, The Pennsylvania State University, University Park, Pennsylvania, 16802, USA
[b] Physiology and Behaviour Group, Institute for Animal Science, ETH Zurich, 8603 Schwerzenbach, Switzerland
[c] Department of Psychiatry, Weill Medical College of Cornell University, New York, NY 10021, USA

ARTICLE INFO

Article history:
Received 19 February 2008
Received in revised form 15 July 2008
Accepted 16 July 2008

Keywords:
Binge eating
Bulimia
Estradiol
Progesterone
Fat intake
Female

ABSTRACT

Binge eating is more common in females than in males. This study investigated the effects of ovarian hormones on binge-eating behavior in a diet-related rat model. Six groups of ovariectomized Sprague–Dawley rats were used (n=13/group). All rats had continuous access to chow and water throughout the study. One half of the rats were injected every fourth day with estradiol benzoate (2 μg/100 μl sesame oil) and progesterone (500 μg/100 μl sesame oil); the other half received only the sesame oil vehicle. Three feeding protocols were tested in each hormone injection condition: (1) chow only: no additional dietary fat access; (2) low-restriction: 1-h fat access every day; (3) high-restriction: 1-h fat access on Monday, Wednesday, and Friday. As previously reported in intact male and female rats, the high-restriction groups exhibited binge-like increases in 1-h energy intake during fat access. The major new finding of this study is that 1-h energy intake was tonically, but not cyclically, reduced in the hormone-treated high-restriction (binge) rats. Specifically, both low- and high-restriction hormone-treated rats consumed significantly less energy than did the oil-treated rats during the 1-h fat period (p<0.0001) and overall (p<0.0001), indicating a tonic inhibition of eating. However, food intake during the 1-h fat access period was also cyclically reduced in the hormone-treated low-restriction rats, but not in the hormone-treated high-restriction rats. These results indicate that the normal cyclic inhibitory influence of ovarian hormones on eating, but not their normal tonic inhibitory influence, is disrupted by conditions leading to binge-type eating.

1. Introduction

Bingeing-related eating disorders including binge eating disorder (BED) and bulimia nervosa (BN) have become important health issues in western countries [1–4]. Like other eating disorders, BED and BN are more common in females than in males. American women are 1.5 times more likely than men to develop BED and 3 times more likely to develop BN [4–6]. In Norway, the female–male ratio is 1.7:1 for lifetime prevalence of BED and 3:1 for lifetime prevalence of BN in adolescents [7]. Furthermore, people who do not meet the criteria for bingeing-related eating disorders (bulimia nervosa, binge eating disorder, binge/purge subtype of anorexia nervosa) also binge eat. For instance, one study reported a binge eating prevalence of 24% in a randomly sampled population of women, whereas the prevalence of bulimia nervosa was only 1.5% [8].

Although biological sex differences ultimately arise from the different genotypes of males (XY) and females (XX), after early development most sex differences are mediated through hypothalamic–pituitary–gonadal (HPG) axis function, especially the actions of gonadal steroid hormones — androgens, estrogens and progesterones [9,10]. Several effects of gonadal steroid hormones on food intake have been well documented in both humans and animals [11–13]. Food intake in women varies with the phase of the menstrual cycle, with a decrease in the peri-ovulatory phase, when plasma estradiol concentration peaks; conversely, food intake generally increases in the luteal phase, when plasma progesterone levels are high [14–16]. Adult female rats and mice also eat different amounts of food across the estrous cycle, which is usually 4 days in length. Rats and mice eat least near the time of ovulation, during what is called the estrus phase, which occurs just after estradiol peaks, and eat most during diestrus, when estradiol levels are lower [11,12]. This cyclic food intake pattern is thought to be due to inhibitory effects of estradiol on eating [17]. In rats, pharmacological progesterone treatment can reduce the intake-reducing effects of estradiol, but so far no physiological action of progesterone on eating has been shown [11–13]. The decrease in eating during the peri-ovulatory phase of the ovarian cycle is referred to as the cyclic inhibitory effect of estradiol on eating [18]. In addition, ovariectomy (OVX) dramatically increases food intake and body weight in rats and mice, and administration of estradiol brings food intake and body weight back to a normal physiological level [11–13].

* Corresponding author. 110 Chandlee Laboratory, The Pennsylvania State University, University Park, PA 16802, USA. Tel.: +1 814 865 6519; fax: +1 814 863 6103.
E-mail address: rxc13@psu.edu (R.L. Corwin).

0031-9384/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.physbeh.2008.07.021

There is some evidence for a similar effect in women [14]. Thus, in addition to its cyclic effects, estradiol also has tonic inhibitory effects on eating [11,12,18].

The frequency of binge-type eating has been reported to change during the menstrual cycle. In women with BN, binge frequency increased during the luteal phase and menses [19–21]. In one study of women with BN, a significant negative association between estradiol and binge frequency as well as a significant positive association between progesterone and binge frequency were reported [22]. In a community sample of women, changes in a modified Emotional Eating subscale of the Dutch Eating Behavior Questionnaire (DEBQ) also were associated with cyclic hormone fluctuations. Specifically, higher scores (consistent with binge eating) were obtained when estradiol was low and progesterone was high [23]. In none of these studies, however, have alterations in binge size with the menstrual cycle been reported. Finally, bingeing may disrupt menstrual cyclicity and ovarian hormone function [24–26]; in three studies, 37–64% of women with BN experienced oligomenorrhea [27–29]. How binge behavior and HPG function might interact has not been established, and the necessary mechanistic studies are difficult in human subjects. Animal models, therefore, are needed.

Several animal models have been developed to study binge eating [30]. In the present study a limited-access binge-eating model is used. In this model, rats are given access to a source of dietary fat for one or two hours per day three times a week, with nutritionally complete rat chow and water always freely available. Fat intakes during the fat-access period are much higher under this 3-day limited-access condition than when rats are offered fat for similar periods every day [31–35]. The model has face validity in that it reproduces a key criterion for human binge eating: the consumption of more food during a brief period than is normally consumed under similar circumstances. In addition, body weight typically does not differ between binge rats and chow controls. This is also similar to the maintenance of normal body weight by most patients with bulimia nervosa [1] as well as recent data showing that most people who binge are not obese [4]. Therefore, rats with 3-day limited access are referred to as bingeing rats, and the three weekly fat access days are called binge days. Although the rats consume large amounts of energy on binge days relative to controls, they eat less chow on the non-binge days. Due to this “overeat/undereat” or “sawtooth” intake pattern, body weight typically does not differ between binge rats and chow controls. Thus, factors involved in binge behavior can be studied without obesity-related confounds that might influence food intake.

Although both intact female and intact male rats exhibit binge behavior with this protocol, the energy consumed during the limited-access period by females is much smaller than that consumed by males [32,33,35]. In addition, the day-to-day intake patterns are different; that is, the overeat/undereat pattern is not as regular in females [33]. A possible reason for the smaller binge size in intact females compared to males may be the tonic inhibitory effect of estradiol on eating. The irregular day-to-day intake pattern, on the other hand, may be due to estradiol's cyclic inhibitory effect during the estrus phase, which falls randomly on binge and non-binge days.

The rationale for the present study rests on reports, first, that higher levels of estradiol have been associated with decreased binge frequency in women with BN [22] and, second, that estradiol can elicit both tonic and cyclic inhibitory effects on eating under non-binge conditions in women and in female animals [17,36]. Tonic and cyclic effects of ovarian hormones on binge behavior, however, have not been investigated. Therefore, we sought to investigate the tonic and cyclic effects of ovarian hormones on binge eating behavior in the limited fat access animal model. Specifically, we hypothesized that in this model: 1) binge size and daily food intake would be reduced in hormone-treated binge OVX rats compared to vehicle-treated binge OVX rats due to tonic inhibitory effects of estradiol on eating, 2) binge size and daily food intake would be reduced on the day of the hormone treatment cycle modeling estrus (day 4) due to cyclic inhibitory effects of estradiol, and 3) day-to-day intake patterns of daily food intake would be different in hormone-treated and vehicle-treated binge rats due to the cyclic influence of ovarian hormones.

2. Materials and methods

2.1. Subjects

Seventy-eight female Sprague–Dawley rats (Harlan, Indianapolis, IN; 60 days of age and initially weighing 184–218 g) were individually housed in stainless-steel cages (Length:Width:Height=48.5 cm:30 cm:20.5 cm) with continuous access to water and pelleted chow (Laboratory Rodent Diet 5001, PMI Feeds, Richmond, IN; macronutrient content (g/kg diet, kcal/kg diet, percent of calories): protein (234, 936, 28%), fat (45, 405, 12%), carbohydrate (490, 1960, 60%); total, 3.3 kcal/g). The vivarium was maintained at 22±2 °C with a 12/12 h light–dark cycle (lights off at 1900 h). All procedures were approved by the Pennsylvania State University Institutional Animal Care and Use Committee.

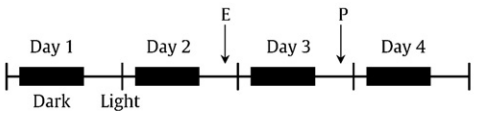
2.2. OVX and cyclic hormone treatment

After a one-week period of adaptation to the vivarium, rats were given overnight access to a bowl of solid fat [Crisco® All-Vegetable Shortening (partially hydrogenated vegetable oil), J.M. Smucker Co., Orrville, OH; 9.17 kcal/g] clipped to the front of cage, in addition to their continuously available chow and water. This was done to prevent neophobia during the rest of the study. Three days later, the rats were anaesthetized (1 ml/kg body weight, intraperitoneally: IP) with a mixture of 70 mg/kg Ketamine (Phoenix Science Inc., St. Joseph, MO) and 2 mg/kg Xylazine (Phoenix Science Inc., St. Joseph, MO), with 0.2 ml/kg supplements given as needed, and a bilateral OVX was performed using a dorsal approach.

After 4–5 days of postoperative recovery, when body weights had returned to their pre-surgical levels, rats were matched for body weight and overnight fat intake and divided into two groups. One group (OVX+EP, n=39) was subcutaneously (SC) injected with 17-β-estradiol-benzoate (Sigma, 2 μg/100 μl sesame oil) in the middle of the light phase every fourth day and with progesterone (Sigma, 500 μg/100 μl sesame oil) 1 day later; the other group (OVX+OIL, n=39) was injected with the sesame oil vehicle on the same days. Injection days were followed by 2 non-injection days. The hormone treatment regimen is shown in Table 1. These hormone injection regimens produce near-physiological levels of estradiol [17] and progesterone [37], and maintain normal body weight, food intake, spontaneous meal patterns, and sexual receptivity (lordosis) in OVX rats [17]. Note that the day of estradiol injection is labeled Day 2 of the treatment cycle and the progesterone injection day is labeled Day 3.

Table 1
Cyclic ovarian hormone treatment regimen

	Day of treatment cycle			
Group	Day 1	Day 2	Day 3	Day 4
EP	–	E	P	–
OIL	–	Oil	Oil	–



Cyclic ovarian hormone treatment regimen used throughout the study. All rats were ovariectomized. The 24-h test days begin and end at the tick marks, i.e. at 1600 h, 3 h prior to lights off. Hormones were injected at 1300 h (the middle of the light phase) on Day 2 and Day 3 of the cycle, so that Day 4 of the treatment cycle models the estrus phase of the ovarian cycle in intact rats. E=2 μg β-estradiol 3-benzoate/100 μl sesame oil/rat; P=500 μg progesterone/100 μl sesame oil/rat.