Physiology & Behavior 104 (2011) 517–524

Contents lists available at ScienceDirect

Physiology & Behavior

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

The ovarian hormone estradiol plays a crucial role in the control of food intake in females

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ARTICLE INFO

Article history:
Received 28 January 2011
Received in revised form 13 April 2011
Accepted 13 April 2011

Keywords:
Estrous cycle
Sex differences
Estrogen receptor alpha
Meal size

ABSTRACT

Despite a strong male bias in both basic and clinical research, it is becoming increasingly accepted that the ovarian hormone estradiol plays an important role in the control of food intake in females. Estradiol's feeding inhibitory effect occurs in a variety of species, including women, but the underlying mechanism has been studied most extensively in rats and mice. Accordingly, much of the data reviewed here is derived from the rodent literature. Adult female rats display a robust decrease in food intake during estrus and ovariectomy promotes hyperphagia and weight gain, both of which can be prevented by a physiological regimen of estradiol treatment. Behavioral analyses have demonstrated that the feeding inhibitory effect of estradiol is mediated entirely by a decrease in meal size. In rats, estradiol appears to exert this action indirectly via interactions with peptide and neurotransmitter systems implicated in the direct control of meal size. Here, I summarize research examining the neurobiological mechanism underlying estradiol's anorexigenic effect. Central estrogen receptors (ERs) have been implicated and activation of one ER subtype in particular, ERα, appears both sufficient and necessary for the estrogenic control of food intake. Future studies are necessary to identify the critical brain areas and intracellular signaling pathways responsible for estradiol's anorexigenic effect. A clearer understanding of the estrogenic control of food intake is prerequisite to elucidating the biological factors that contribute to obesity and eating disorders, both of which are more prevalent in women, compared to men.

1. Introduction

Most would acknowledge that a strong male bias exists in both basic and applied animal research. Indeed, a recent, comprehensive survey of articles published in representative neuroscience journals revealed that the ratio of single-sex studies involving males versus females is almost 6 to 1 [1]. Similar surveys revealed failures to report the sex of subjects and, when both sexes were studied, failures to analyze and present data in a sex-specific manner [2]. Others have noted that the sex of tissues or cell lines is rarely reported [3]. This male bias and indifference towards sex-based research is difficult to justify in light of the many behavioral traits and physiological responses that are known to be sexually dimorphic.

An informal survey of the literature suggests that the male bias in neuroscience research extends to the study of ingestive behavior. The relative lack of female-based, feeding research is particularly troubling, given the higher rates of morbid obesity (characterized by a body mass index >40) and eating disorders in women than in men [4–7]. We and others have argued that an understanding of the normal control of food intake in females is prerequisite to identifying the biological factors contributing to the high prevalence of disordered eating in women. This review summarizes the evidence, derived primarily from rodent models, that the ovarian hormone estradiol plays a critical role in the physiological control of food intake in females. More recent studies designed to investigate the mechanism underlying estradiol's anorexigenic effect are also reviewed.

2. Estradiol is involved in the physiological control of food intake

In addition to its well characterized effects on reproductive behavior, it is now widely accepted that the ovarian hormone estradiol plays an important role in the normal control of food intake in a variety of species [8,9]. In women, fluctuations in daily food intake are correlated with changes in estradiol secretion across the menstrual cycle. The most robust change is a decline in average daily food intake during the peri-ovulatory period, which occurs after the initial (follicular phase) rise in plasma estradiol concentration [10,11]. Others have also reported that average daily food intake is lower during the follicular phase (when plasma estradiol levels are rising), relative to the luteal phase [10,12–14]. As might be expected, these cyclic changes in food intake are not apparent in women experiencing anovulatory menstrual cycles [15,16]. It remains less clear, however, whether food intake increases as a function of the

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doi:10.1016/j.physbeh.2011.04.014

declining estradiol levels in peri-menopausal women. For a more detailed discussion of the literature regarding the ovarian hormonal control of food intake in women, the reader is referred to the following review papers [9,17].

Estradiol's ability to influence food intake is best characterized in the female rat. As described in greater detail below, the pre-ovulatory increase in plasma estradiol concentration is associated with a transient decrease in food intake during estrus in cycling rats [18–22]. Moreover, bilateral ovariectomy produces a rapid (within 1 week) increase in food intake that promotes increases in adiposity and rapid weight gain [18,23–28]. These behavioral and physiological responses to ovariectomy can be normalized by a physiological regimen of estradiol treatment [29,30]. In comparison, a physiological regimen of progesterone treatment alone is not sufficient to attenuate ovariectomy-induced hyperphagia and it fails to alter estradiol's anorexigenic effect in OVX rats [24,31–33]. Thus, it is the decline in circulating estradiol, rather than progesterone, which promotes the rapid increases in food intake and weight gain in OVX rats. It should be noted, however, that OVX rats receiving a high dose of progesterone, in addition to estradiol, consume more food than OVX rats receiving estradiol alone [23,32–34]. Thus, large, pharmacological doses of progesterone can inhibit estradiol's anorexigenic effect.

The gonadal hormone testosterone also influences food intake and body weight. For example, orchiectomized rats display transient decreases in dark-phase meal number, but they are compensated for by increases in light-phase meal size such that daily food intake is not affected by the declining testosterone levels within the first two weeks following orchiectomy [35]. However, beginning about one month following orchiectomy, male rats display a decrease in daily food intake and concomitant weight loss [36,37], both of which can be attenuated by low, physiological doses of testosterone [35,36,38]. Thus, gonadectomy-induced changes in food intake and body weight develop more slowly in male rats, relative to female rats. Physiological doses of testosterone increase food intake in general and protein intake in particular. In comparison, pharmacological doses of testosterone can decrease carbohydrate intake, but this latter effect is likely mediated by aromatized metabolites of testosterone (e.g., estradiol) since carbohydrate intake is not influenced by the non-aromatizable androgen dihydrotestosterone [39,40].

2.1. Estradiol exerts both phasic and tonic decreases in food intake

The mid-1920s marked the first reports of phasic decreases in food intake during the estrous stage of the female rat's reproductive cycle [41,42]. Interestingly, some have argued that the exclusion of female rats from behavioral experiments may be linked to this and other early reports (e.g., [43]) that locomotor activity fluctuates across the ovarian reproductive cycle (reviewed in [1]). More contemporary studies have shown that this phasic decrease in food intake is correlated with fluctuations in plasma estradiol concentration. In female rats, plasma estradiol concentration begins to rise during diestrus, peaks during the afternoon of proestrus, and then falls rapidly to basal levels at the onset of estrus [44–47]. The feeding rhythm across the ovarian reproductive cycle is just as predictable. Daily food intake typically peaks during diestrus and reaches a nadir during estrus (e.g., [21,22]). Thus, the phasic decrease in food intake during estrus is believed to be mediated by the pre-ovulatory increase in plasma estradiol concentration. An important detail that is often overlooked or misrepresented in published studies is that the decrease in food intake during estrus is temporally associated with low, rather than high, circulating levels of estradiol.

Drewett [22] was the first to recognize that estradiol also exerts a tonic inhibitory effect on food intake. This action of estradiol is revealed in OVX rats, which display increases in daily food intake that exceed that consumed by cycling rats [18,23–28]. This sustained increase in food intake appears sufficient to account for the ovariectomy-induced weight gain (reviewed in [17]), which results primarily from the deposition of adipose tissue [25,48,49]. Interestingly, this tonic inhibitory effect of estradiol on food intake may not be expressed in mice. A recent study by Overton et al. [50], demonstrated that ovariectomy-induced increases in the weight gain of C57BL/6 mice was due entirely to a decrease in energy expenditure, manifested as a decrease in both metabolic rate and locomotor activity, with no significant increase in food intake [50]. In this same study, ovariectomy-induced weight gain in Long-Evans rats was due to an increase in food intake and a decrease in locomotor activity, with no change in metabolic rate [50]. Although it remains to be determined whether the phenotype of OVX C57BL/6 mice extends to other strains of mice, the data derived from rat studies indicate that estradiol exerts both tonic and phasic inhibitory effects on food intake that appear critical for the regulation of body weight. That sex differences in food intake are minimized in aged (i.e., reproductively senescent) rats [51], suggests that the phasic and tonic anorexigenic effects of estradiol are critical to the increased daily caloric intake that is often observed in male and female rats of reproductive age.

As would be expected, bilateral ovariectomy abolishes estradiol's phasic inhibitory effect on food intake. Geary and colleagues have, however, developed an acute, physiological regimen of estradiol replacement (a single, subcutaneous, injection of 1–2 μg of estradiol every fourth day) that models the 4-day, cyclic pattern of plasma estradiol concentration and food intake observed in cycling rats. Specifically, this estradiol replacement protocol produces changes in plasma estradiol levels in OVX rats that are similar in both the magnitude and duration to that observed in cycling rats. In addition, food intake is reduced every fourth day, beginning ~30 h after injection of estradiol [30]. Rather than relying upon chronic estradiol replacement via silastic implants containing crystalline estradiol, the adoption of this acute (physiologically-relevant) estradiol replacement protocol in OVX rats has greatly influenced our understanding of the mechanism underlying estradiol's phasic inhibitory effect on food intake (e.g., [31,52–57]).

2.2. Estradiol selectively affects the control of meal size

Analysis of the spontaneous feeding patterns of cycling rats reveals that the decrease in food intake during estrus is mediated by a selective decrease in meal size with either no change or, more commonly, a non-compensatory increase in meal frequency [18,19,21]. It appears unlikely that rats eat less during estrus as a result of being diverted from feeding by other competing behaviors, such as the increases in locomotor and sexual activity that occur during estrus. First, increasing the opportunity to exercise fails to alter the magnitude of the estrous-related decrease in meal size in rats with and without access to running wheels [21]. Second, providing opportunities to engage in sexual or other social behaviors do not prevent estrous-related decreases in food intake in a variety of species including cats, cows, and baboons [58–60]. Thus, the decrease in food intake during estrus appears to involve a selective change in the neurobiological controls of meal size. Likewise, it has been shown that the hyperphagia following ovariectomy is also mediated by an increase in meal size [18,30] that can be normalized by acute estradiol treatment [29,30].

According to the theory developed and tested by Smith [61–63], the controls of meal size are either direct or indirect. The direct controls of meal size arise from the sensory stimulation of pre-absorptive receptors in the oral cavity and upper digestive tract that are sensitive to the chemical, mechanical, and colligative properties of ingested food. The resulting positive and negative feedback signals, activated by preabsorptive food stimuli, are integrated in the brainstem to provide the direct controls of meal size. The indirect controls of meal size operate independently of these preabsorptive receptors and function to modify the direct controls of meal size. As described in an earlier review [64], estradiol does not fit the definition of a direct control of meal size but rather appears to function as a rhythmic, inhibitory, indirect control of meal size. This theoretical