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Research report

Effects of chronic testosterone administration on body weight and food intake differ among pre-pubertal, gonadal-intact, and ovariectomized female rats

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HIGHLIGHTS

- Androgen's actions on body weight (BW) in females have not been fully examined.
- T increased BW in pre-pubertal and intact female rats, but not in OVX rats.
- T decreased hypothalamic ERα in pre-pubertal and intact, but not OVX, rats.
- Action of T on BW was changed by gonadal steroid milieu.

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ABSTRACT

In females, estrogens play pivotal roles in preventing excessive body weight gain. On the other hand, the roles of androgen in female appetite and body weight regulation have not been fully studied. In this study, whether the roles of androgen in the regulation of body weight and appetite were different among ages and/or the estrogen milieu in females was evaluated. Body weight gain and food intake were increased by chronic testosterone administration in pre-pubertal and gonadal-intact female rats, but not in ovariectomized female rats. Testosterone administration also affected the serum leptin level and adipose leptin gene expression levels differently in each experimental condition. Hypothalamic mRNA levels of ERα, which plays pivotal roles in regulation of body weight and metabolism, were decreased by chronic testosterone administration in pre-pubertal and gonadal-intact female rats, but not in ovariectomized female rats. These results indicate that the effects of testosterone on body weight and appetite differed among ages and/or estrogen milieu in female rats, and that attenuation of estrogens' actions on the hypothalamus might be partly involved in the androgen-induced increases of body weight gain and food intake in females.

1. Introduction

Energy balance and reproductive functions are closely linked in most species. It has been reported that the sex hormones estrogen and androgen are involved in the regulation of appetite, energy metabolism, and body weight (BW) in mammals [1]. In females, estrogens play pivotal roles in preventing excessive BW gain. It has been shown that ovariectomy increased food intake (FI) and BW in female animals, and that these effects were prevented by estradiol (E2) replacement [1–5]. Similarly, E2 injection into the brain alters the pattern of feeding and BW in rats [6,7]. These estrogen effects on BW are primarily mediated by estrogen receptor-α (ERα) in the hypothalamic area, such as the arcuate nucleus (ARC) and paraventricular nucleus (PVN), and in the solitary tract in the brain stem [1–3,8]. Mutations of ERα genes induce obesity in humans and mice, and deletion of ERα blocks the effects of E2 on BW [9–11]. Unlike estrogens, the roles of androgen in female appetite and BW regulation have not been fully studied, although some studies indicated that androgen may be involved in dysregulation of appetite [1,12–14] and increase the risk of visceral adiposity in women and experimental animals [1,15–19]. Because androgen-administered animals tend to show disrupted

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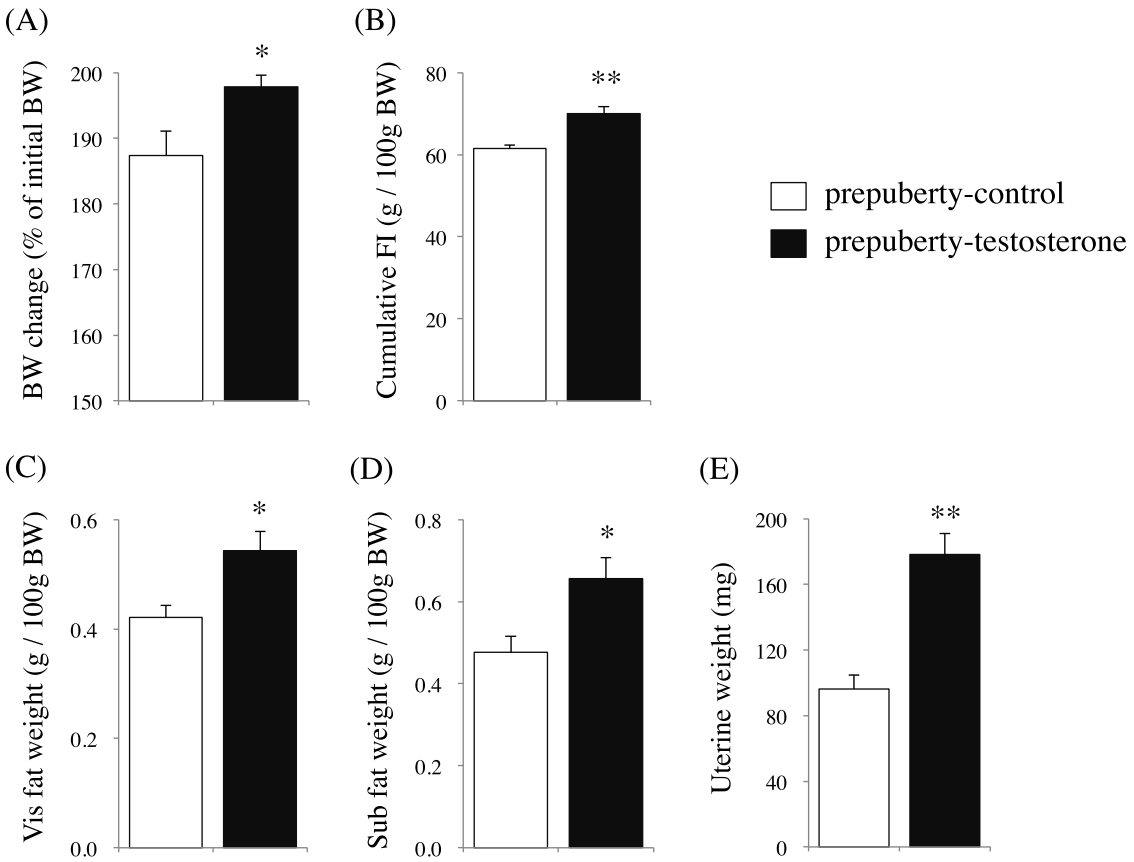

Fig. 1. (A) Body weight (BW) change (% of initial BW), (B) cumulative food intake (FI) (g/100 g BW), (C) visceral fat weight (g/100 g BW), (D) subcutaneous fat weight (g/100 g BW) and (E) uterine weight in control (□) and testosterone-administered (■) pre-pubertal female rats. The mRNA expression levels of control rats are expressed as 1.0. Data are expressed as means ± SEM. * $P < 0.05$, ** $P < 0.01$ vs. control.

ovulation, as well as changes in BW and fat mass, these animal models have been used to study the pathology and origins of polycystic ovary syndrome (PCOS), which is one of the common causes of anovulation and metabolic abnormalities in women of reproductive age [20]. Because almost of all these studies focused on the effects of androgen in humans and experimental animals of reproductive ages, there are only limited data on the role of androgen in the regulation of appetite, energy metabolism, and BW in pre-pubertal and postmenopausal ages. Although some data suggest that androgen also negatively affects BW and metabolism in these ages [21,22], to the best of our knowledge, no studies have examined the physiological mechanisms of such androgen actions using experimental animals. In addition, it has been reported that the effects of androgen on BW and energy metabolism in males do not correspond to those in females of reproductive age. As mentioned above, hyperandrogenism may promote the dysregulation of appetite, BW, and body composition in females [1], whereas, testosterone deficiency increases the amount of visceral adipose tissue and insulin resistance in males, and these changes are associated with an increased risk of diabetes and metabolic syndrome [23]. Therefore, the difference in the estrogen milieu may be related to the difference in androgen effects between sexes, and that the roles of androgen on the regulation of BW and appetite may also differ among ages and/or the estrogen milieu in females. In the present study, the effects of chronic administration of testosterone, one of the most important androgens, on BW, FI, and body composition were examined in pre-pubertal, ovarian-intact (reproductive age), and ovariectomized (reproductive age) female rats. Ovariectomized rats were used for the post-menopausal model. In addition to peripheral and hypothalamic orexigenic and anorexigenic factors, hypothalamic estrogen and androgen receptors and aromatase were measured, because these steroidal factors also play roles in BW and appetite regulation [1,24,25]. In this study, the term *estrogens* was used when referring to endogenous estrogen [32].

2. Materials and methods

2.1. Animals

Sprague-Dawley (SD) female adult rats or pregnant SD rats were purchased and housed under controlled lighting (14 h light, 10 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.

2.2. Effects of chronic testosterone administration on pre-pubertal female rats

Female offspring of pregnant rats were used. The day of delivery was defined as postnatal day 0. On postnatal day 2, female pups were selected and randomized, and litter size was adjusted to 13–14 per dam. On postnatal day 21, the pups were weaned and housed four per cage. On postnatal day 23, the pups were randomly divided into control and testosterone-administered groups. Pups of the testosterone-administered group were implanted with a silas-