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Maternal testosterone and reproductive outcome in a rat model of obesity

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ABSTRACT

Global sex differences in obesity rates are persistent, suggesting the involvement of sex steroids. In addition, adipose tissue is a metabolic site for steroidogenesis. Here, we compared female reproductive parameters in a rat model of obesity, with the same parameters in its lean control strain, and tested for an association with integrated measures of corticosterone and testosterone. Steroids were extracted and quantified from 17 Otsuka Long Evans Tokushima Fatty (OLETF; an animal model for obesity) and 13 Long Evans Tokushima Otsuka (LETO; the lean control strain) hair samples that were collected after weaning offspring. The obese OLETF mothers had higher hair testosterone levels than the control LETO strain. Overall, testosterone, but not corticosterone, predicted litter sex ratios. Younger mothers with large litters and older mothers with small litters tended to have the highest sex ratios (i.e., male-biased litters). In the lean LETO strain, but not in the obese OLETF, maternal testosterone was positively associated with litter size and number of male pups. Corticosterone did not differ between the two strains and was not associated with testosterone or with reproductive parameters. This study suggests that long-term circulating testosterone is associated with female reproduction in multiple ways. The possible trade-off between litter size and sex ratio may be mediated by testosterone and influenced by body fat and composition, which influence the individual's well-being. Exploring the multiple roles of testosterone in females may also help explain the complex relationship between obesity and reproduction.

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1. Introduction

Obesity is associated with numerous health issues including diabetes, cardiovascular diseases, cancer, and reproductive disorders [1,2], such as menstrual dysfunction and anovulation [3]. The adipose tissue that is associated with obesity is an active metabolic site for glucocorticoids and sex steroids, e.g., converting androstenedione to testosterone [4]. Adipose tissue also has a significant role in the development and maintenance of polycystic ovary

syndrome, and 30 to 70% of women with polycystic ovary syndrome also suffer from obesity [5]. Worldwide, the prevalence of obesity has increased in the past few decades. In the United States of America, e.g., in 2009 to 2010, more than a third of the adult population were obese [6]. Because globally the prevalence of obesity is higher in women than in men [7], circulating sex steroids, such as testosterone, may be implicated.

Testosterone is an androgen produced by both sexes. In males, it is mainly produced by the testes and the adrenal cortex, whereas in females, it is produced by the ovary, placenta, and the adrenal cortex [8]. Although testosterone is involved in multiple roles including muscle and bone development, neuronal growth, and immune reaction [9],

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it is traditionally associated with, and studied in males. A study that was conducted in women aged 65 to 98 revealed that higher total testosterone levels were associated with metabolic syndrome, coronary heart disease, low levels of high-density lipoprotein cholesterol, and insulin resistance [10]. Testosterone may also be involved in female reproduction, by stimulating follicle growth and development [11], yet most studies have focused on the effects of progestins, estrogens, and glucocorticoids [12–14]. Recently, transdermal testosterone treatment in women improved live birth rate and multiple pregnancy outcomes by enhancing follicle responsiveness to follicle stimulating hormone [15]. On the other hand, high levels of testosterone may have a negative effect on fertility by delaying the onset of reproduction in females [16]. For example, female zebra finches (*Taeniopygia guttata*), injected with testosterone after laying their first egg, reduced their clutch sizes. This impact increased with testosterone doses [17]. In a study conducted on red winged blackbirds (*Agelaius phoeniceus*), most of the females that were treated with testosterone failed to nest and lay eggs [18]. The negative effect of testosterone on reproduction has also been documented in mammals. Richardson's ground squirrels (*Urocitellus richardsonii*) showed a negative correlation between circulating gestational testosterone and litter size [19], and in northern seals (*Callorhinus ursinus*), androgens negatively affected female fecundity by possibly causing embryonic delays [20].

Testosterone may also be associated with an increased sex ratio (i.e., male-biased litters). For example, a study on field voles (*Microtus agrestis*) found that high preconception-circulating testosterone was associated with male-biased litters [21], and a study in Barbary macaques (*Macaca sylvanus*) revealed that females with higher preconception fecal androgens produced more males compared to females with lower testosterone concentrations [22]. Although the mechanism is not clear, Trivers and Willard suggested that parents should adjust their offspring's sex ratio according to maternal conditions (among other), to increase reproductive success. Thus, mothers in a good condition are expected to produce male offspring, whereas mothers in a poor condition are expected to produce females [23]. Another option is that testosterone may contribute to maternal dominance behavior, affecting maternal condition, and consequently offspring sex ratio [22].

Exploring the multiple roles of testosterone in females may also help explain the complex relationship between obesity and reproduction. Most animal models for obesity are mice and rats, although most mammals in captivity can also become obese [24]. A prominent model for obesity, which we used in our study, is the Otsuka Long Evans Tokushima Fatty (OLETF) laboratory rat which lacks the cholecystokinin 1 receptor for the satiety hormone cholecystokinin [25]. Otsuka Long Evans Tokushima Fatty's lean control strain is the Long Evans Tokushima Otsuka (LETO) rat. Otsuka Long Evans Tokushima Fatty rats share many characteristics with human obesity [26]. As in human obesity, OLETF rats are prone to diet-induced overeating, resulting in increased obesity. They prefer palatable diets and do not have a primary deficit in leptin signaling. Otsuka Long Evans Tokushima Fatty rats have an increased body fat percentage and larger adiposities compared with LETO

controls. Dams' activity levels are not significantly different between the two strains [27], however, in the past, we have documented multiple differences in maternal behavior between OLETF and LETO dams [27–30]. In this study, we quantified integrated testosterone and corticosterone levels that represent long-term circulating concentrations in OLETF and LETO rats and examined their association with reproductive parameters (i.e., litter size and sex ratio). Given that androgen production rates are elevated in obese women due to adipose tissue conversion of androstenedione to testosterone [4], we hypothesized that OLETF rats, with higher fat mass, would exhibit higher testosterone levels. We also predicted that the obese OLETF and the lean LETO might show different patterns of association between testosterone and reproductive parameters.

2. Methods

2.1. Subjects

We studied 17 OLETF and 13 LETO lactating female rats aged 160.7 ± 56.13 (76–276) days that had 1.6 ± 0.56 (1–3) litters. There was no difference in mean maternal age and mean number of gestations between the two strains. Animals were raised in the colony at the Gonda Brain Research Center at Bar Ilan University, Ramat Gan, Israel, under a 12:12-hour dark-light cycle and a constant room temperature of 22 ± 2 °C. Rats were housed in polypropylene cages ($38 \times 21 \times 18$ cm). Water and standard chow were ad libitum.

Once pups were weaned, at the age of 21 to 22 days, over a period of 14 months, the number of males and females in a litter was noted, and sex ratio was calculated as the number of males divided by the total litter size (i.e., male and female offspring). We note that pup attrition from birth to weaning in our colony is minimal, and we do not have evidence of OLETF-LETO differences in pup attrition. Similarly, we have no evidence of infanticide directed toward newborns of a specific sex.

Bar Ilan University's Animal Use and Ethics Committee did not require formal approval for this study, as hair was sampled from the existing breeding colony, and not from experimental animals, and the hair-cutting procedure is noninvasive.

2.2. Steroid quantification

Hair integrates steroids over time of growth (i.e., weeks and months), thus levels are not affected by the momentary stress of handling [31]. Hair collection in the laboratory is relatively noninvasive, and the use of scissors does not cause pain or infection to the animal or researcher. In addition, hair steroids reflect free (i.e., unbound) steroids, which are assumed to be more relevant to behavior [32]. Therefore, hair-testing is an appropriate matrix for examining the relationship between endogenous steroids and reproductive outcomes. Measurements of hair growth rate of the two strains at two time points showed similar rates (pilot study, see [supplementary information](#)). Maternal hair was cut once pups were weaned. Earlier hair collection (i.e., postpartum) might have stressed the mother and

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