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Androgens, Estrogens and Their Anti-Hormones: Effects on Body Weight and Food Consumption

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EARLEY, C. J. AND B. E. LEONARD. *Androgens, estrogens and their anti-hormones: Effects on body weight and food consumption.* PHARMAC. BIOCHEM. BEHAV. 11(2) 211–214, 1979.—The estrogenic and androgenic effects on food-intake and body weight were examined over a 30-day period in male rats. From Day 8 to 21, animals were maintained on a 23-hr food-deprivation schedule in order to minimize possible between-group differences in food motivation. Food intake was measured during this period. From Day 22 to 23, animals were given free access to a fixed amount of food which was somewhat in excess to that consumed by each group during the previous 1-hr feeding period. Under this condition differences in body weight or weight gain could be assessed in terms of differences in metabolism since food-intake was the same for all groups. Body weights were measured about every 7th day. The effects of testosterone, dihydroxytestosterone and cyproterone acetate as found in this study would suggest that androgens increase food motivation, while testosterone may influence weight gain through its anabolic properties. Estrogen-treatment was found to decrease food-intake, body weight and weight gain. 19-Hydroxytestosterone, which is converted to estrogen in the brain but is without effect on peripheral systems (e.g., adrenals) was without effect on any of the measures studied. Cyproterone acetate had an estrogenic effect only on weight-gain while the anti-estrogen, nafoxidine, mimicked the estrogenic effect only for food-intake. The findings suggest that the estrogenic effects on food-intake and body weight may be due to two separate mechanisms.

Estrogen Androgen Testosterone Dihydroxytestosterone Cyproterone acetate Eating

IN a study by Gentry and Wade [4] testosterone was found to increase body weight and food consumption when administered at low to medium doses (<1 mg/kg/day of TP). At high doses (>1 mg/kg) however testosterone eventually reduced body weight and food-intake. Dihydrotestosterone (DHT), the androgen metabolite of testosterone also increased both measures but was less effective than testosterone. Also DHT at high doses did not lead to a decrease in these two parameters. On the other hand, estradiol administration was a potent depressor of body weight and food-intake. The authors concluded that the biphasic effect of testosterone was possibly due to an increase aromatization of testosterone to estradiol such that the estrogenic depressor effect finally overshadowed the androgenic stimulatory effect. Other investigations in this area similarly reported that androgens have stimulatory effects and estrogens, a depressor effect [5, 14, 21, 22, 23, 24]. However in considering the possible mechanisms whereby the hormones stimulate or depress body weight and food consumption both motivational and metabolic processes could be involved. For instance, an increase in food motivation due to androgens may increase food consumption and thereby have subsequent effects on body weight. Alternatively the hormones may act directly on body weight by altering metabolism. Testosterone is a potent anabolic steroid and estradiol exhibits some catabolic activity.

The aim of the present study was to explore this androgenic-estrogenic dimension exhibited by testosterone and attempt to delineate the possible motivational and metabolic aspects of the effect of testosterone. In the present study, food consumption was measured under a 23-hr food deprivation condition. Food deprivation by maximizing the hunger-drive should minimize any differences in food consumption under ad lib conditions. Since testosterone can be metabolized to DHT and estradiol (E2) and thereby exert an androgenic or estrogenic effect [13] the effects of DHT and E2 were tested in this study. An anti-androgen (cyproterone acetate) or an anti-estrogen (nafoxidine) was given in combination with testosterone to examine its estrogenic and androgenic component. Also testosterone was given in combination with a low dose of estradiol. If as Gentry and Wade [4] suggest, high doses of testosterone exert their depressor effects by way of an increase production of E2 then increasing the estrogen concentration itself should produce a similar reversal of testosterone's effects. Finally, 19-hydroxy-testosterone (19-OHT) which has minimal peripheral effects but is easily metabolized to E2 in the brain [8] was used to assess the CNS-peripheral effects of E2.

METHOD

Animals

Ninety-six male Sprague-Dawley rats weighed 230–260 g prior to castration. Two days after surgery all animals were randomly assigned to treatment groups and housed 4 per cage. Each hormone treatment group consisted of 12 animals. The animals were maintained on an alternating light cycle (0700–1700 hr light phase) and were given free access to water throughout the experimental period.

Procedures

The experiment was scheduled over 30 consecutive days, with Day 0 representing the day of castration. Until Day 8, animals were under ad lib food conditions in the home cage. From Day 8–21 all animals were placed on a 23-hr food deprivation schedule with the 1-hr feeding period commencing at 1800 hr. During this 1-hr feeding period the animals were removed from their home cage and were placed in testing cages with 2 animals occupying each test cage. Thus the animals were fed in pairs, giving 6 paired-consumption values per treatment group. The animals were returned to their home cages after 1 hr. Following a period of adaptation (Day 8–15) to these experimental conditions, the amount of food consumed during these 1-hr periods was recorded over 5 consecutive days (Day 16–20). An average (g/day/pair) of the food intake for these 5 days was calculated. The average consumption scores were then used to establish the mean consumption value for each treatment group. From Day 22–30 animals were maintained in their home cage and were given access to 100 g of food at 1800 hr. The animals were permitted to finish the full amount of food thus establishing a fixed intake of food. The 100 g of food is in excess of the previous daily intake (80 g/4 animals, see Results). Since the intake of food is roughly equivalent across all groups, any difference in weight gain arising between treatment groups can be associated with differential metabolism rather than differential intake. The weight of each animal was measured on Day 0, 2, 8, 15, 22 and 30. The difference between individual weights for Day 22 and Day 30 was tabulated in order to provide an index of the rate of change in body weight under fixed food-intake conditions.

Treatment Schedule

All injections were given SC in 0.1 ml of arachis oil. Castrated controls (CAST) received 0.1 ml of oil only. All hormone/oil treatments were given daily between 0800–1000 hr commencing on the second day post-operative. The following hormones were used: testosterone propionate (TP), dihydrotestosterone propionate (DHTP), 19-hydroxytestosterone propionate (19-OHTP), estradiol propionate (E2P), cyproterone acetate (CYP), and nafoxidine (NAF). TP, DHTP, and 19-OHTP were administered in a dose of 300 μg/rat/day. E2P was administered separately in a dose of 10 μg/rat or in conjunction with TP in a dose of 2 μg/rat. The antiandrogen (CYP) or the anti-estrogen (NAF) were administered in combination with TP in a dose of 1 mg/rat. TP when administered in conjunction with other hormones was given in a dose 300 μg/rat.

RESULTS

The variation in body weight under different treatment conditions from Day 0 to Day 30 are given in Fig. 1. The

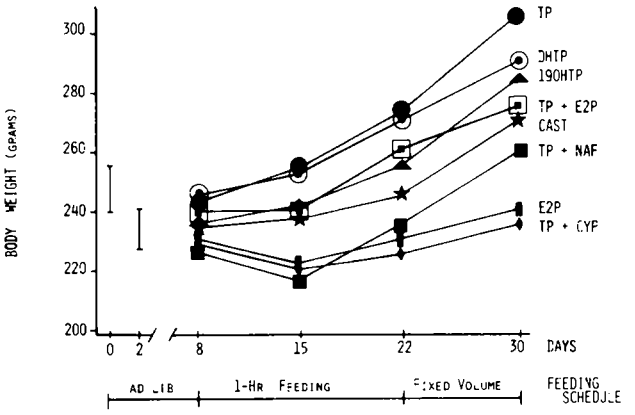

FIG. 1. The mean body weights (N = 12) for each treatment group are given for Day 8, 15, 22 and 30. The body weights for Day 0 and 2 are represented on the graph as the range or spread of group means. Thus the mean values of all treatment groups are within the ranges marked on the graph. There was no significant difference between treatment groups for Days 0, 2 or 8. The line beneath the graph gives the period during which a particular feeding schedule was in use. All treatment groups were compared with CAST using the Student's *t*-test (two-tailed): TP, DHTP, TP+CYP, and E2P groups differed from CAST ($p<0.05$) on Day 15, 22 and 30. TP+NAF group on Day 15 and the TP+E2P on Day 22 were found to differ from the CAST group ($p<0.05$).

TABLE 1

CONSUMPTION AND WEIGHT GAIN

	Food Consumption (g)[a]	Weight Gain (g)[b]
TP	37.1 ± 0.6*	31.8 ± 5.0
DHTP	37.5 ± 0.9*	20.1 ± 4.0
19OHTP	34.7 ± 0.9	29.2 ± 6.0
TP + E2P	33.2 ± 0.6	14.7 ± 2.5*
TP + CYP	31.7 ± 0.3	10.1 ± 2.5*
TP + NAF	25.9 ± 0.4*	25.3 ± 6.0
E2P	26.4 ± 0.3*	10.0 ± 3.5*
CAST	32.8 ± 0.6	25.0 ± 4.0

*$p<0.05$ compared with CAST.

[a]The Mean (± SEM) consumption of 6, paired mates averaged over the 5 day period (Day 16–20).

[b]The mean difference (± SEM) between the animals' weight on Day 22 and 30. Values are representative of 12 determinations.

effects of hormone treatment on food intake and weight gain are given in Table 1. From Day 15 onward both the TP and DHTP groups began to exhibit greater body weights than the CAST group. The food consumption (see Table 1) was also markedly higher in these two groups than in CAST. E2P in combination with TP was effective in reversing or antagonizing the effects of TP. Under this condition neither body weight nor food consumption was noticeably different from CAST, except on Day 22. On the other hand, E2P treatment alone substantially blocked the weight gain and reduced food consumption. However, 19-OHTP, the estrogen precursor had no substantial effect on any of the parameters measured.

CYP was found to be a potent antagonizer of weight gain, maintaining weights well below that found in castrated animals. Although blocking weight gain to a similar degree as E2P (alone) treatment, CYP+TP treatment reduced consumption values to those found in the CAST group. The effects of NAF+TP were initially one of reduced body weight as seen on Day 15. But on Day 22 and 30 the weights of the NAF+TP group increased and were not significantly different from those found with the CAST group. The consequences of NAF+TP treatment on food consumption was one of reduction. Finally, although the amount of food consumed was the same for all treatment groups from Day 22–30, the TP+E2P, TP+CYP, and E2P groups demonstrated significantly less of a weight gain compared with CAST.

DISCUSSION

Estrogenic Effects

E2P was found to reduce body weight and food intake and to antagonize the stimulatory effects of TP on these responses. These results support the findings and conclusions of Roy and Wade [22] and Gentry and Wade [4]. When food consumption was fixed between Day 22 and 30, most groups showed an increase in body weight of 25–30 g. The E2P group showed only a 10 g increase and the TP+E2P group showed an increase of less than 15 g. Thus E2P in general decreases the rate of body growth by factors other than food intake. The study of Mook *et al* [17] suggests that the integrity of the adrenals is essential for increased eating and growth that accompanies ovariectomy. That estrogens themselves have a direct influence on adrenal production has been substantiated by several investigators [3,11]. Other effects of estrogen, such as causing a decrease in glycogen and cholesterol concentrations, have also been reported [11]. Thus the apparent effects of E2P on body weight appear to be of metabolic origin of which adrenal production, or glycogen and cholesterol storage may be contributing factors.

Nafoxidine

Hypothalamic implants of E2 have been found to reduce food intake [1, 7, 25]. Furthermore the anti-estrogens, when implanted in the hypothalamus show estrogenic, not anti-estrogenic, effects on food intake [2,21]. Thus the similarity of E2P and NAF treatment on food intake may be related to their similar action on the hypothalamus. Several other studies have reported the effectiveness of systemically administered anti-estrogens on reducing food intake and body weight [15, 16, 22]. However from the present study it would appear that the reduction in body weight may be a secondary consequence of decreased food intake. When the effects of food intake were controlled by using fixed amounts of food, the body weights of the NAF+TP group increased rapidly. Thus NAF appears to mimic E2P effects on food consumption but it does not have similar effects on metabolism.

19-Hydroxytestosterone

19-OHTP had no effect on any of the parameters studied, yet 19-OHTP has been found to exert a potent effect on other estrogenic behaviors [6, 8, 18, 19, 20]. Implants in the hypothalamus will also induce estrogenic behaviors (e.g., sexual behavior [8]). Therefore if the systemic administration of E2P and NAF is associated with a direct effect on the hypothalamus, why does 19-OHTP not have a similar effect? One possible explanation is that E2P and NAF are exerting their effects on some other area where 19-OHTP can not be aromatized to estrogen. From the study by Lieberburg and McEwen [13] it would appear that unlike the hypothalamus, pre-optic area or other cortical areas, the pituitary has virtually no capacity to aromatize testosterone to estrogen. Therefore 19-OHTP would not be expected to have a direct influence on the pituitary system while E2P and NAF would have an effect. Kurl and Morris [12] investigated the in vivo dose response effects of three commonly used anti-estrogens on depletion of estrogen receptors in the uterus, pituitary, hypothalamus and amygdala. The results of the study indicate that the doses of anti-estrogens commonly reported to reduce body weight have negligible effects on estrogen receptors in the hypothalamus and amygdala but were effective with uterus and pituitary receptors. Thus the loss of weight commonly found with anti-estrogens and estrogens may in part be related to a direct effect on the pituitary.

Androgenic Effects

In keeping with the findings of Gentry and Wade [4] both DHTP and TP increased food consumption and body weight. However, unlike the findings reported by Gentry and Wade the present results did not show any distinct difference between TP and DHTP treatments. In their study the changes in body weight were concomitant with the changes in food intake in all cases. In the present study, there was no differences in body weights possibly as there was no difference in food intake. DHTP appears to stimulate food intake but it seems less effective in maintaining body growth. By Day 30 the weights of the TP group were somewhat higher and the weight-gain greater compared with the DHTP group, yet food consumption was virtually the same for both of these groups. This difference in metabolism may be due to the greater anabolic effects of TP. A similar conclusion was given by Gentry and Wade [4] for the differences in body weight found in their TP and DHTP animals. The inverted U-shape effect found with increasing higher doses of testosterone was suggested to be due to an increase in aromatization of testosterone to estrogen [4]. Therefore the depressor effect of testosterone would represent an increasing depressor effect of E2 on body weight and food consumption. The effect of TP+E2P would support this argument. With regards to metabolism and body weight, E2P was suggested to influence adrenal function. The finding that with increasing higher doses of testosterone an inverted U-shape effect is exerted on adrenal function [9] is therefore of particular interest.

Cyproterone Acetate

The effects of TP+CYP may be viewed as a direct effect of CYP on body weight plus an anti-androgen effect on food consumption. Vilberg, Revland and Beatty [24] found that CYP treatment reduced body weight in castrated, castrated+TP, and sham animals but was without effect on castrated+adrenalectomized animals. Thus CYP acts on body weight somewhat independently of its "anti-androgen" action. Vilberg *et al.* [24] suggested that the effects of CYP on body weight may in part be mediated through its effects on adrenocortical function. This interpretation is interesting in light of the similarity of CYP and E2P effects on body weight

and the suggested effects of both hormones on adrenal function. With regards to food intake, the TP+CYP group was not distinguishable from CAST. CYP treatment appears to have antagonized the TP effect on food intake. The study by Vilberg *et al.* [24] demonstrated that unlike its effect on body weight, when given alone to CAST animals CYP has no effect on food intake. Therefore the results would suggest that the influence of CYP on food intake is an anti-androgen effect and not a direct effect like its effect on body weight. This finding in conjunction with TP and DHTP effects would suggest that androgen may facilitate some aspect of food motivation.

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