Use of orchiectomy and testosterone replacement to explore meal number-to-meal size relationship in male rats

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Chai, Jia-Ke, Vladimir Blaha, Michael M. Meguid, Alessandro Laviano, Zhong-Jin Yang, and Madhu Varma. Use of orchiectomy and testosterone replacement to explore meal number-to-meal size relationship in male rats. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R1366–R1373, 1999.—Because food intake is a function of meal number and meal size and because gender-related hormones are involved in feeding regulation, we explored effects of orchiectomy and testosterone replacement on the relationship between meal number and size and changes in resulting feeding patterns in adult male rats, randomized into orchiectomy and sham-operation groups. A rat eater meter measured feeding indexes for 1 wk before and 2 wk after castration and during 8 days of testosterone replacement. Orchiectomy leads to an immediate change in the meal number-to-size relationship, resulting in 1) change in pattern of feeding; 2) a significant decrease in dark-phase meal number; 3) a significant increase in dark-phase meal size, but insufficient to offset decrease in meal number, so total food intake significantly decreased during dark phase; 4) no significant change in light-phase meal number; and 5) an increase in meal size leading to an increased food intake during light phase, which offset decreased food intake in dark cycle and resulted in no net significant change in food intake after orchiectomy. Testosterone replacement acutely reversed effects of orchiectomy on meal number-to-meal size relationship, restoring feeding pattern. Data suggest that androgens immediately influence the meal number-to-meal size relationship. The speed of onset seen after orchiectomy suggests that the influence of testosterone on food intake may also occur partially via a nongenomic effect.

male Fischer rats; food intake; rat eater meter

GENDER-RELATED HORMONES are involved in the regulation of food intake in rats (10, 44), hamsters (40), and mice (4, 29). Orchiectomy in the adult males decreases food intake, an effect reversed by systemic administration of testosterone in physiological doses. A different effect is seen in the female: ovariectomy induces hyperphagia accompanied by increased meal size and decreased meal number (5, 43). The alterations in females appear to correlate with changing estradiol concentrations, as shown in experiments with ovariectomized rats (5) and with estradiol replacement therapy (5, 44).

Much of the detailed investigation into the gonadal control of food intake has focused on its chronic effects for two reasons. First, estrogens and androgens are steroids with well known temporal genomic activity: the effect of estrogen withdrawal on food intake in the female rat is transient, whereas the effect of androgen withdrawal in the male rat is relatively permanent (29). Second, orchiectomy significantly decreases the rate of body weight gain, whereas total food intake is reported to be only slightly decreased or not at all (14, 29, 40). In contrast, ovariectomy results in profound increase of food intake (5). These findings suggest that a slower time course of androgen effects total food intake.

Changes in microstructure of feeding, as measured by a bar pressor technique 2 wk after orchiectomy in adult male mice, showed a slightly decreased food intake with a 3-day mean reduction in meal number (MN) and a significant increase in meal size (MZ; Ref. 29). Testosterone replacement produced a dose-related fall in MZ and a corresponding rise in MN. However, feeding-related behavior differs between mice and rats (28), and a bar press procedure, a trained conditional response, could result in an exceptionally higher occurrence of small meals. Moreover, a recent report indicates that some orchiectomy-related biochemical events, which may be associated with altered MN and MZ, occur already within 2 days of orchiectomy (27) and thus 1) are not restricted to the more delayed periods of observations previously reported and 2) suggest that testosterone may influence food intake, MN, and MZ via its nongenomic activity.

Rats regulate their daily food intake by varying either the size of a meal (MZ), the interval between meals (i.e., MN), or both. As pointed out by Becker and Kissileff (3), counterbalancing controls may exist so that a change in one will produce a compensatory change in the other to preserve a relative consistency of daily food intake. In the past, we demonstrated this reciprocity of MZ and MN via a series of internal and external perturbations (for review, see Ref. 19). To function as compensatory mechanisms, it is likely that MN and MZ are independently regulated in different yet connected anatomic sites of the brain, in a way analogous to the reciprocal innervation controlling spinal reflexes. Anatomic, electrophysiological, and pathophysiological data exist that show that, in the hypothalamus, as an example, the ventromedial nucleus (VMN) and the lateral hypothalamic area (LHA) interact to influence MN and MZ. Similar anatomic, electrophysiological, and pathophysiological data for the paraventricular nucleus (PVN) in relation to other hypothalamic nuclei are currently lacking. Thus the VMN and the LHA may well represent part, among other anatomic sites, of the putative food intake-regulating areas. Superseding the dualistic theory of...
food intake control (1), Panksepp (26) suggested that the recurrence of short-term and long-term satiety, mediated by the LHA and the VMN, respectively, determines food intake. We and others have updated Panksepp’s hypothesis by proposing that the LHA contributes to the modulation of MZ and the VMN to MN (12, 20, 21, 24, 39, 45, 46).

Because gonadal hormones influence the hypothalamus and food intake, we hypothesized that immediately after orchectomy a change in food intake, MZ, and MN occurs. Such a change in feeding pattern may indirectly reflect the influence of testosterone’s action (genomic and nongenomic) on the VMN and LHA, among other hypothalamic nuclei. Thus the aim of our study was to use orchectomy and testosterone replacement in male Fischer rats to explore the MN-to-MZ relationship and thereby to gain insight, by inference, into the influence that testosterone may have on food intake regulation on the hypothalamus.

MATERIAL AND METHODS

Experimental Subjects

The study was approved by the Committee for the Humane Use of Animals at State University of New York Health Science Center at Syracuse; animals were cared for in accordance with the guidelines established by the National Institutes of Health. Fifteen male Fischer-344 rats (7–8 wk old; Charles River, Wilmington, MA; initial body weight 250–270 g) were housed in wire holding cages for 10 days to acclimatize them to constant study environmental conditions of a 12:12-h light-dark cycle (6:00 AM–6:00 PM), 45% relative humidity, and a room temperature of 26 °C. After acclimatization, the rats were individually placed in metabolic cages in which the supplied feeding cup situated at the end of a feeding tunnel is replaced by an electronic scale (ACREM; Ref. 18). Fresh coarsely ground standard rat chow (diet #5008; Ralston Purina, St. Louis, MO; approximate macronutrient composition in %: 49 carbohydrate, 27 fat, and 24 protein). No provisions were made for dietary self-selection either before or after orchectomy because this was not the aim of this study.

Automated Computerized Rat Eater Meter and Feeding Pattern Measurements

After acclimatization, the rats were individually placed in metabolic cages equipped with the automated computerized rat eater meter (ACREM; Ref. 18). Fresh coarsely ground standard rat chow and fresh water were provided each morning at 8:00 AM, and body weight was measured every 3 days. Briefly, the ACREM consists of commercially available metabolic cages in which the supplied feeding cup situated at the end of a feeding tunnel is replaced by an electronic scale balance, and two photoelectric cells are centered above the food dish. A real-time remote computerized data collection device integrates feeding activity as measured by the electronic scale and the photocells. The ACREM characterizes feeding activity of the rat by its access to the food cup, some of which included food consumption and some of which did not. A meal was defined as a bite or series of bites with food consumption preceded and followed by at least 5 min of no food consumption, whereas a sniff was defined as access to the food cup, associated with both olfactory and vibrissal exploration of the food cup, during which no food was consumed (18).

Food intake and feeding-related indexes were measured continuously and expressed per study period (e.g., per 24 h; per 12 h during dark period (6:00 PM–6:00 AM), or per 12 h during light period (6:00 AM–6:00 PM)). The indexes were meal number = total number of meals in each study period; meal size (g/meal) = total amount of food consumed per total meal number in each study period; and food intake (g) = amount of food consumed per study period.

Orchietomy and Sham Operation

After the baseline feeding pattern was obtained for all rats (days –8 to –1), eight rats were orchietomized at day 0 under general anesthesia (ketamine HCl 150 mg, xylazine HCl 30 mg, and acepromazine 5 mg; 0.6 ml/kg im of the mixture). A 1-cm skin incision was made at the tip of the scrotum; then a 5-mm incision was made into each sac at the tip of each testis, and the cauda epididymis was pulled out, accompanied by the testis and followed by the caput epididymis. The vas deferens and spermatic blood vessels were ligated, severed, and the testis were removed. In another seven male rats under anesthesia a sham operation was performed in which the testis and epididymis were only pulled out and then replaced and the blood vessels were left intact.

The rats were returned to their ACREMs after operation. Measurement of body weight, food intake, MN, and MZ were immediately started and continuously measured for the next 2 wk (day 0–day 13). After that, there was a hiatus of 14 days, during which the rats were kept in ACREMs but only the body weight and the total food intake were measured. This was followed by another 8-day ACREM period (days 27–34) during which testosterone replacement therapy was given.

Testosterone Replacement

Testosterone (testosterone enanthate, BTG Pharmaceuticals, Inselin, NJ) was administered in eight orchietomized rats according to the dose schedule of Gentry and Wade (10). A dose of 0.2 mg testosterone in 0.1 ml corn oil was given daily at 8:30 AM for 8 consecutive days by intramuscular injection. Sham-operated rats had daily intramuscular injections of 0.1 ml corn oil.

Statistical Analysis

The feeding indexes of MN, MZ, and food intake were analyzed separately for 24 h, for light-phase, and for dark-phase feeding. All data are expressed as means ± SE. ANOVA was used to analyze the time course data within the groups. The two-tailed Student’s t-test was used to compare findings between orchietomized rats and sham-operated controls and between findings from hormone replacement in orchietomized rats with those from sham-operated controls injected with a vehicle. A statistically significant difference was considered as a probability < 0.05. Within groups, t-tests were also used to compare the pooled mean data from days –8 to –1 (preoperation) with days 3–13 (postoperation). Because the feeding pattern normalized within 3 days during testosterone injection in orchietomized rats, the data from the 8-day testosterone and/or vehicle treatment period were pooled from days 30 to 34 (testosterone replacement), without the first 3 injection days.

RESULTS

MN

Before operation. As shown in Fig. 1, before operation (orchietomy or sham operation) there was no difference between the two groups in 24-h, dark-phase, or light-phase MN.

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After operation. Immediately after operation, 24 h MN decreased in both groups, probably secondary to the effects of anesthesia. However, the decrease in MN was significantly lower in the orchietomized group compared with the control group. Control rats recovered from operation by day 3. From day 3 to day 13, MN did not significantly change in sham-operated controls. In orchietomized rats it decreased significantly (P < 0.01) and was also significantly lower than in the controls (P < 0.01; Fig. 1). Immediately after operation, dark-phase MN decreased in both groups, but was significantly lower in the orchietomy group than in the control group. In orchietomized rats after day 3 (when the rats had recovered from operation) and until day 13, dark-phase MN decreased significantly compared with control and preoperative values (P < 0.01). Sham-operation had no effect on dark-phase mean MN, which did not change significantly compared with preoperative values (Fig. 1). Light-phase MN increased postoperatively in both groups (P < 0.05 in sham-operated group; not significantly in orchietomized rats; Fig. 1).

MZ

Before operation. As shown in Fig. 2, mean 24-h, dark-phase, and light-phase MZ were all similar in both groups preoperatively.

After operation. Immediately after operation, mean 24-h MZ decreased in orchietomized rats. After day 3 and until day 13, daily MZ increased in orchietomized rats (P < 0.01 compared with controls and to preoperative values), but did not change in sham-operated rats (Fig. 2). Immediately after operation, daily MZ decreased in orchietomized rats. After day 3 and until day 13 dark-phase MZ increased in orchietomized rats (P < 0.01 compared with control and preoperation), but did not change in sham-operated rats (Fig. 2). After day 3 and until day 13 light-phase MZ increased in orchietomized rats (P < 0.05 compared with control; P < 0.01 compared with preoperatively), but did not change in sham-operated rats (Fig. 2).

Food Intake

Before operation. Figure 3 shows that mean 24-h and mean 12-h dark- and light-phase food intake did not differ between orchietomized rats and sham-operated controls.

After operation. Immediately after operation, mean 24-h food intake decreased in both groups but was significantly lower in the orchietomy group. After day 3 and until day 13 daily food intake was slightly lower in orchietomized rats than in sham-operated controls (P = 0.09; Fig. 3). Dark-phase food intake decreased immediately after operation in both groups and was significantly lower in the orchietomy group.

After day 3 and until day 13 mean postoperative dark-phase food intake was significantly lower in orchietomized compared with sham-operated rats (P < 0.01). Compared with the preoperative period, dark-phase food intake after operation was significantly lower in both orchietomized rats (P < 0.05) and sham-operated controls (P < 0.05; Fig. 3). Immediately after operation, light-phase food intake decreased in both groups and was significantly lower in the orchietomy group. Compared with preoperative values, after day 3 and until day 13 mean light-phase food intake was increased in both groups (P < 0.05). The light-phase food intake was significantly higher on days 6, 10, 11, and 13 in orchietomized compared with the sham-operated rats; mean postoperative light-phase food intake comparisons had borderline significance (P = 0.054; Fig. 3).

Body Weight

Table 1 summarizes changes in mean body weights after orchietomy, sham operation, and after testosterone replacement therapy. Body weights were the same in the orchietomized rats (266 ± 2 g) and sham-operated controls (266 ± 2 g) at the time of operation (day 0). However, significantly lower body weight was observed in orchietomized rats compared with the sham-operated controls as soon as day 3 after operation (P < 0.01). The average daily body weight gain between
day 3 (after the rats had recovered from operation) and day 24 was significantly lower in the orchiectomized rats compared with the sham-operated controls (1.0 ± 0.2 vs. 2.1 ± 0.2 g; P < 0.01). When the ∼10 g loss of weight from the operative specimen (testes, epididymis, and part of the vas deferens) is taken into account, there was a body weight difference of 31 g between the two groups at day 24.

Testosterone Replacement

Figure 4 summarizes the changes in mean 24-h food intake and feeding pattern that occur with testosterone replacement compared with the indexes measured preoperatively and operatively.

When orchiectomized rats were treated with testosterone as shown in Fig. 4, the 24-h mean MN was not significantly different from the controls, but it remained lower than preoperative values in both groups (P < 0.01; Fig. 4). No significant difference in dark-phase MN was observed in orchiectomized rats supplemented with testosterone compared with controls (6.8 ± 0.7 vs. 6.5 ± 0.6 meals/12 h). The dark-phase mean MN during the replacement period was significantly lower than preoperative values in both groups (P < 0.01). Light-phase MN was not different between the orchiectomized rats treated with testosterone and the controls (5.0 ± 0.4 vs. 4.8 ± 0.5 meals), nor was it different compared with preoperative values.

Mean daily MZ did not differ between orchiectomized rats treated with testosterone and sham-operated controls injected with vehicle, but it increased over preoperative values in both groups (P < 0.05; Fig. 4). Mean dark-phase MZ did not differ between orchiectomized rats treated with testosterone and sham-operated controls injected with vehicle (1.4 ± 0.1 vs. 1.5 ± 0.2 meals), nor was it different from preoperative values in both groups. Mean light-phase MZ did not differ between orchiectomized rats treated with testosterone

Fig. 2. Effect of orchiectomy on meal size (MZ; means ± SE) in orchiectomized rats (n = 8) and sham-operated controls (n = 7). MZ was measured during 24 h (top), during dark period (6:00 PM–6:00 AM; middle), and during light period (6:00 AM–6:00 PM; bottom). Operation was performed at day 0 as indicated with vertical line. Significance: *P < 0.05 orchiectomized vs. sham-operated rats.
and sham-operated controls injected with vehicle, but it was significantly increased over preoperative values in both groups (1.3 ± 0.1 and 1.5 ± 0.1 meals; P < 0.01).

Daily food intake in orchiectomized rats treated with testosterone was not significantly different compared with controls treated with vehicle only and to preoperative values (Fig. 4). After testosterone treatment, dark-phase food intake was not significantly different from sham-operated controls injected with vehicle (9.1 ± 0.5 vs. 9.4 ± 0.4 g). In both groups, food intake in the testosterone-replacement period was significantly lower than the preoperative values (P < 0.05). The light-phase food intake was similar in testosterone-replaced rats and in controls (6.2 ± 0.3 and 6.8 ± 0.5 g).

In orchiectomized rats, body weight increased with testosterone replacement therapy to 272 ± 5 g at day 33 (Table 1), which was still significantly lower than the body weight in sham-operated rats (314 ± 4 g; P < 0.01). Body weight gain between days 27 and 33 slightly increased in the orchiectomized rats with testosterone replacement therapy but did not differ significantly between groups (1.2 ± 0.3 vs. 1.7 ± 0.3 g).

**DISCUSSION**

In young adult male Fischer-344 rats, the ACREM was used to measure the immediate changes in daily, as well as the dark- and the light-phase MN, MZ, and total food intake before and after orchiectomy and then after testosterone replacement. Our findings confirmed and extended previous observations that the orchiectomized male rat significantly decreases its rate of body weight gain with slight or no decrease in daily food intake and that testosterone administration reverses the orchiectomy effect on body weight gain (10, 14, 29, 40).

Our study extends information concerning the microstructural changes that occur acutely in the immediate post-orchiectomy period. After orchiectomy and testosterone replacement, the immediate change in the MN-to-MZ relationship that occurred is described in RESULTS.
Table 1. Effect of orchiectomy and testosterone replacement therapy on body weight in orchiectomized rats and sham-operated controls

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Days</th>
<th>Orchiectomized Rats, g</th>
<th>Sham-Operated Controls, g</th>
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</thead>
<tbody>
<tr>
<td>Preoperation</td>
<td>−9</td>
<td>246 ± 2</td>
<td>246 ± 2</td>
</tr>
<tr>
<td>−6</td>
<td>253 ± 3</td>
<td>254 ± 1</td>
<td></td>
</tr>
<tr>
<td>−3</td>
<td>259 ± 2</td>
<td>260 ± 3</td>
<td></td>
</tr>
<tr>
<td>Operation</td>
<td>0</td>
<td>266 ± 2</td>
<td>266 ± 2</td>
</tr>
<tr>
<td>3</td>
<td>238 ± 3*</td>
<td>259 ± 3</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>244 ± 4*</td>
<td>273 ± 3</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>248 ± 4*</td>
<td>280 ± 3</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>251 ± 2*</td>
<td>285 ± 3</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>256 ± 3*</td>
<td>294 ± 3</td>
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<td>18</td>
<td>259 ± 3*</td>
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<td>21</td>
<td>260 ± 3*</td>
<td>302 ± 2</td>
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</tr>
<tr>
<td>24</td>
<td>263 ± 4*</td>
<td>304 ± 3</td>
<td></td>
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<tr>
<td>Testosterone replacement therapy</td>
<td>27</td>
<td>266 ± 4*</td>
<td>306 ± 3</td>
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<tr>
<td>30</td>
<td>268 ± 4*</td>
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</tr>
<tr>
<td>33</td>
<td>272 ± 5*</td>
<td>314 ± 4</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE (n = 8 for orchiectomized rats, n = 7 for sham-operated controls). Operation was performed at day 0. Testosterone replacement therapy (0.2 mg daily im) was started at day 28 in orchiectomized rats; sham-operated rats were injected with vehicle. Significance * P < 0.01 orchiectomized rats vs. sham-operated rats.

The modulatory effects of orchiectomy on the meal patterns of number and size are similar to those reported after total liver denervation (32) or olfactory bulbectomy (17), when compensatory changes of MN and MZ resulted in no net effect on daily food intake. Thus the present evidence supports the widely recognized concept that MN and MZ are tightly coupled to maintain the homeostasis of food intake, and, by inference, it suggests the existence of a close functional link between the hypothalamic areas influencing MN and MZ. Data have been generated suggesting that the changing levels of the neurotransmitters dopamine and serotonin in the LHA and in the VMN, among other events in other hypothalamic nuclei, such as the PVN, play a role in influencing hunger and in influencing satiety (12, 25, 39). Changing dopamine levels in the LHA correlate with changes in the size of the meal (20, 45), whereas changes in dopamine levels in the VMN related to the intermeal interval, i.e., MN (21, 46).

The role of the VMN as a target site for testosterone is well documented, although its relationship in influencing the microstructure of food intake still needs to be completely detailed. When implants of testosterone propionate (TP) are used, 5α-dihydrotestosterone (DHT) propionate and 17β-estradiol, in the VMN and anterior hypothalamus-preoptic area in castrated male rats, it was shown that TP may act directly in the hypothalamus to influence food intake in male rats (23). These data suggest that aromatization of testosterone to estrogens is related to the central effects of TP on food intake, because estradiol treatment tended to be more effective than TP in reducing food intake. In contrast, treatment with DHT propionate, a nonaromatizable androgen, failed to have any effect on food intake even at a very high dose of 20 mg/day (28). Furthermore, hypothalamic implants of estradiol benzoate in male rats reduced food intake, whereas ovarian transplants in castrated male rats suppressed weight gain compared with intact male rats; after removal of the ovarian grafts, body weight increased once more (2).

The VMN of the male rat contains neurons with receptors for testosterone, DHT, and estradiol (38), neurons that accumulate testosterone and estradiol. Testosterone acts genomically as an androgen on specific neural androgenic receptors, whereas neurons within the brain are able to metabolize circulating testosterone into neurally active metabolites. Testosterone is converted via aromatase to 17β-estradiol through the activity of a specific androgen binding cytochrome P-450 enzyme and to DHT by 5α-reductase (7). These gonadal steroid hormones may affect ingestive behavior via an influence on neurotransmitters in several hypothalamic nuclei, such as the PVN.
different ways: 1) nongenomic effects on pre- or postsynaptic membranes alter permeability to neurotransmitters or their precursors or the functioning of neurotransmitter receptors; 2) genomically, by altering the synthesis of proteins that may participate in pre- or postsynaptic events after axonal or dendritic transport.

Consistent evidence indirectly supports the possible nongenomic effects of testosterone on the VMN in modulating feeding patterns. The VMN neurons contain different subgroups of neurons, projecting to the central gray, with specific sensitivity to metabolites of testosterone (42). Mean threshold of excitation decreases after orchietomy, but reverses with either TP or DHT. This increased excitability of the VMN neurons after orchietomy could possibly explain the early satiety and hence lower food intake and body weight. Supporting this inference are data showing that castration reduces (36) and testosterone replacement restores VMN concentrations of neuropeptide Y (NPY) (37), a well known orexigenic neuropeptide, whose mechanism of action is based on the modulation of neuronal excitability (8). Furthermore, most of the factors influencing food intake, including interleukin-1 (30) and leptin (41), share with NPY the same mechanism of action. This indicates that modulation of neuronal excitability might represent the final pathway common to different factors in the control of food intake (15). In the ovariectomized female rat, the reverse occurs: delayed development of satiety and hence increased food intake and body weight gain. This gender difference in the biological response to castration might be explained by the anatomic (16) and functional (35) differences existing between male and female VMN.

The genomic effects of gonadal steroids on food intake are yet to be demonstrated, but they likely occur. Dopaminergic neurons play a critical role in multiple brain function, including eating activity. Tuberoinfundibular dopaminergic activity, a pathway involved in the regulation of prolactin, increases 2 wk after orchietomy and declines in castrated male and female rats after 2 wk of testosterone or estradiol replacement, respectively (11). Furthermore, in the male rat, dopamine turnover increases in the median eminence 1–2 wk after orchietomy and decreases after testosterone replacement (11). The delayed occurrence of changes in dopamine activity suggests the involvement of a genomic mechanism, and recently it has been shown that the efficacy of dopaminergic neurotransmission is regulated by a phosphoprotein DARPP-32 (9).

The effects of testosterone and gonadal steroids on LHA activity in controlling food intake are considerably less clear. However, a recent report showed that the anorexic effects of dehydroepiandrosterone in Zucker rats are mediated by changes in serotonin and dopamine levels within the LHA (31).

The catechol estrogens are unique. Because of the steroid structure they act similar to estrogens, while, via the catechol structure, they act similar to and compete with catecholamines. Cathechol estrogens are potent inhibitors of tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis, and of catechol-O-methyl transferase, an enzyme involved in the inactivation of norepinephrine and dopamine. They compete for membrane dopamine binding sites, which results in a net increase in dopamine levels. They also block the accumulation of dopamine and norepinephrine in the rat brain synaptosomes (13) and directly inhibit α-adrenergic or dopamine receptors (22). The VMN (2) and the PVN (6) have also been implicated as neural sites mediating the effects of estrogen on feeding. The catechol estrogens appear to be the biochemical link between estrogens and catecholamines in the central nervous system and probably modulate the circadian rhythm in feeding via effects on the neurotransmitters.

Perspectives

On the basis of the sum of our data and the cited studies from the literature, we reason that the immediate effects of testosterone on food intake that we observe in the male rat occur probably via testosterone's nongenomic activity, likely brought about by testosterone’s metabolism to estradiol. We postulate that some of the estradiol is metabolized in the hypothalamus to catechol estrogen, which has dopaminergic-like activity. The evidence in favor of this postulate is (a) testosterone can be metabolized into estradiol in various tissues including hypothalamus and adipose tissue; (b) the levels of aromatase are significantly higher in males than in females and in the anterior hypothalamus and the VMN (34), in the nucleus of stria terminalis, the medial preoptic nucleus, and medial and cortical amygdala (33); (3) progesterone reduces the weight-reducing effect of a high testosterone dose similar to its reversal of the weight-reducing effect of estradiol; (4) high doses of DHT (nonaromatizable androgen) do not suppress weight gain in male rats; and finally, (5) testosterone reduces body weight by reducing adipose tissue mass.

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