PATTERNS OF BODY WEIGHT CHANGE IN RATS FOLLOWING NEONATAL HORMONE MANIPULATION: A "CRITICAL PERIOD" FOR ANDROGEN-INDUCED GROWTH INCREASES

By

M. F. Tarttelin1), J. E. Shryne and R. A. Gorski

ABSTRACT

The development of sexual behaviour and gonadal function is largely determined by the early postnatal hormone environment in the rat; testosterone propionate (TP) treatment in the neonatal female will stimulate development of predominantly masculine functional characteristics. On the other hand, removal of the testes from neonatal males results in feminization of these characteristics. It has been shown that an optimal neonatal steroid hormone environment is also essential for normal growth. We now report the effects of different doses of TP (10, 30, 90, or 270 μg) given on postnatal days 2, 3, 4, or 5 on growth as measured primarily by body weight. Only treatment in the 30–270 μg range on days 2 or 3 was effective in causing significant growth changes, however, these same doses caused sterility and impaired female sexual behaviour when given on days 4 or 5. Therefore, there appears to be a "critical period" before the fourth postnatal day when TP can affect processes leading to increased growth. Removal of the neonatal testes retards growth to the levels of the androgenized females. The ovaries of the female TP treated rats still have a restraining influence on growth since their removal produces an increment in body weight similar to, though not as great as, that of the normal ovariectomized rat. These findings suggest that neonatal TP ad-

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administration may possibly reduce the responsiveness of rats to the growth depressing effect of ovarian steroids by action at a site functionally different from that producing sterility and impaired sexual behaviour.

Much attention has been directed towards elucidating the effects of neonatal androgen treatment on the sexual development of the female rat. Particular emphasis has been placed on the changes in sexual behaviour and in ovarian function which tend towards the masculine pattern (Gorski 1971, 1974). Little comparable work has been done on other masculine characteristics such as the greater growth shown by male rats as compared to females. Two studies in particular analysed body weight (BWt) changes in the female rat following large doses of testosterone propionate (TP) in the neonatal period (Beatty et al. 1970; Bell & Zucker 1971). Both these studies showed that TP treatment of the female produced significant increases in growth compared to controls.

It is clear that there is a “critical period” for the effects of androgen on the brain as far as gonadal function is concerned which is dose and time dependent; small doses of TP are effective when given in the immediate postnatal period but less effective when given latter (Gorski 1968). Therefore, we thought it important to study the time/dose response to TP of body growth and to compare the results directly with the effects of androgen treatment on gonadal function and sex behaviour. Although BWt was used as a general index of growth, in the second part of the study daily food intake and body length at the end of the experiment were measured.

MATERIAL AND METHODS

Part I

Pregnant Sprague-Dawley rats of known fertilization date were housed in a temperature and light controlled (14 h light, 10 h darkness; lights off at 7 p.m.) room for one week before delivery. The day of delivery was designated day 1. Solutions of 10, 30, 90, and 270 µg TP were prepared with sesame oil so that each dose was contained in a final injection volume of 0.05 ml. The female pups were randomly chosen, at the time of birth, to receive injections of either oil or one of the doses of TP on day 2, 3, 4, or 5. The final experimental grouping is given in Table 1. The injections were made subcutaneously over the back using a one inch 26 gauge needle. The skin puncture was covered with collodium after withdrawal of the needle to avoid leakage. Animals were regrouped eight to a litter and arranged so that at least one control oil injected pup was in each litter. The pups were identified as to treatment by removing the distal phalanx of certain toes according to a coding system. The pups were weaned at three weeks of age, individually identified by ear numbers, weighed (correct to 1 g) and housed by litters and provided with Purina pelleted rat chow and tap water ad libitum. The rats were weighed at weekly intervals, and were examined daily from day 21 (D 21) for vaginal opening after which daily vaginal smears were taken and recorded. At 45 days of age and again at 90 days one ovary was examined by laparo-
Table 2.
Final numbers of individual rats in the various treatment groups.

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<th>Day</th>
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*TP, testosterone propionate.

tomy and the presence or absence of corpora lutea noted. By comparing the vaginal smear record and the laparotomy data for individual rats the incidence of sterility at D 45 and D 90 was determined.

Male rats were divided into two groups and either castrated at D 2 or sham castrated. These males were weaned at the same time as the females, housed separately in the same environment and weighed weekly.

Body weight data through the first 18 weeks were subjected to a computer analysis. A frequency distribution was plotted to verify the suitability of the analysis of variance test. A one-way analysis of variance was conducted for data from each week taking first the days of treatment, i.e., D 2–D 5, and comparing the BWt of the groups given the different doses of TP. Then the analysis was repeated taking each dose of TP and comparing the various days of treatment. A t-test matrix was calculated for each group of data analysed so that at any week when there was a significant F value, the groups contributing to the significant differences could be identified.

To test sex behaviour, the females were ovariectomized at 18 weeks of age. Two weeks later the animals received 2 µg oestradiol benzoate (OB) for three consecutive days and 0.5 mg progesterone on the fourth day. The females were tested 4 h after progesterone with experienced males in a test arena. Each test consisted of 50 mounts by the male and the female's behaviour scored as a lordosis quotient (LQ: number lordosis responses/number of mounts × 100).

Part II

Based on the results obtained above, it was decided to study food and water intake and BWt patterns following ovariectomy in two groups of rats obtained from the previous study: a) 10 rats which received 90 µg TP neonatally and which were sterile by D 45; and b) 10 rats which received 10 µg TP and which were still exhibiting ovulatory cycles at D 45 but were sterile by D 90. A group of 10 oil injected control rats was also studied. Each of the TP treated groups was further divided into two sub-groups, one of which was scheduled for ovariectomy and the other to act as an unoperated control group. All 10 oil treated animals were scheduled to be ovari-
ectomized at the same time. The rats were housed in another room, similarly light and temperature controlled but isolated at all times from personnel other than the principal investigator. The rats were individually caged and provided free access to ground Purina rat chow in special feeders designed to prevent spillage. Tap water was available ad libitum in glass bottles. Food and water were weighed twice weekly but the data are expressed as mean weekly intake; the rats were weighed once weekly. They were allowed three weeks to adjust to the procedures before measurements were recorded; at this time the animals were 24 weeks old. Following three weeks of measurements, the appropriate animals were ovarioctomized under ether anaesthesia by a conventional flank technique. Three weeks later the rats were given daily subcutaneous injections of 3 µg OB in a volume of 0.05 ml of sesame oil for two weeks. Food intake, water intake, and BWt data were transformed into weekly percentage deviations from the three week preoperative period as described by Tarttelin & Gorski (1971), and were subjected to the same analytical methods as described earlier. Before sacrifice all rats were given a sex behaviour test as described above and had their nose-anal lengths measured under ether anaesthesia.

Table 2.
Statistical comparisons between body weights of the various treatment groups (10–270 µg testosterone propionate) compared with the oil treated controls on days 2 and 3 from weaning until the eighteenth week of age. There were no significant differences between any of the treatments on day 4 and 5.

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- NS
* sig. less than 0.05
** sig. less than 0.01
*** sig. less than 0.005
**** sig. less than 0.0005

180
RESULTS

Part 1

Females. – The tests of significance conducted on the BWt data are summarized in Table 2. There was no significant difference between the BWt of control rats given oil injections on D 2–D 5. TP was only effective in causing a significant increase in BWt over controls if given on D 2 or D 3. Ten µg TP was least effective, only causing significant BWt changes compared to controls during the 7–9 week period when given on D 2 ($P < 0.05$) and at the 18th week when given on D 3 ($P < 0.05$). Thirty µg was highly effective when given on D 2 causing significant increases in BWt over control rats at weeks 7–14 ($P < 0.005$). The weight difference was reduced slightly at weeks 15–16 ($P < 0.01$) and more so at weeks 17–18 ($P < 0.025$). On D 3, 30 µg TP was less effective, BWt reached significantly greater levels than control by the eighth week ($P < 0.05$).

Ninety µg TP gave a surprising result for which we have no explanation. This dose of TP was only temporarily effective when given on D 2, causing significant increase in BWt compared to controls from the 12–16th week

Fig. 1.

Body weight at weekly intervals in animals treated with the indicated doses of testosterone propionate (TP) or oil on day 2 (D 2) of life. Statistical analyses of these data is presented in Table 2.
Table 2.

Fig. 2.

Body weight at weekly intervals in animals treated with the indicated doses of testosterone propionate (TP) or oil on day 3 (D 3) of life. Statistical analyses of these data is presented in Table 2.

(P < 0.05). On D 3, however, 90 μg TP was highly effective from week 5 (P < 0.01) reaching greater significance by the eleventh week (P < 0.0005) and maintaining this level through week 18. The dose of 270 μg TP was equally effective on D 2 or D 3 in promoting a highly significant increase in BWt (D 2, P < 0.005; D 3, P < 0.0005). Body weight data from D 2 and D 3 are illustrated in Fig. 1 and Fig. 2, respectively.

Because of an unaccountably high mortality in the D 4 oil injected controls only three animals survived. The small size of this group might have contributed to the absence of any significant difference between treatment groups and controls on D 4. Since there was no significant difference between any of the oil treated groups, we took a group of nine oil control rats at random from the total of 26 and ran an additional test of significance comparing the BWt of the various groups treated with androgen on D 4 to this artificially created control group. Marginal significance was only seen at weeks 2–5 with 10–90 μg TP. The mean BWt of rats treated even with the highest dose of TP were not significantly different from that of this artificial control group. Thus, the high mortality of D 4 control animals did not falsify the data. It is
clear, therefore, that treatment with doses of TP ranging up to 270 µg TP after the third postnatal day are not effective in causing increased BWt in the long term.

Dose interactions: By the 18th week, treatment on D 2 with 30 and 270 µg TP had caused significantly heavier BWt than 10 µg TP ($P < 0.05$, 30 µg;
Body weight at weekly intervals in intact males, males castrated at two days of age (fales), females given 90 μg testosterone propionate (TP) on day 3 and females given control oil injections. Statistical analyses in text.

\( P < 0.01, 270 \mu g \). Rats treated with 90 and 270 μg TP on D 3 were very highly significantly heavier than the 10 and 30 μg TP groups. There were no dose interactions on D 4 and D 5.

The incidence of sterility and the sex behaviour data are illustrated in Fig. 3, and are presented together with a summary of BWt at the 18th week for each different dose of TP and at each day of treatment. The incidence of sterility derived from examination of the ovaries exhibits the usual dose response relationship. The 10 μg TP dose became less effective when given at later postnatal ages in that the incidence of sterility at D 45, but not at D 90, decreased with increasing age at injection. This delay in the onset of the anovulatory condition with low doses of TP has been reported previously (Swanson & Van der Werff ten Bosch 1964; Gorski 1968). The higher doses
of TP produced sterility even when injected on D 4 or D 5. Analysis of the sex behaviour data showed a similar dose-time relationship. Ten \( \mu g \) TP was minimally effective in suppressing lordosis when given on any day. Thirty \( \mu g \) TP markedly inhibited lordosis when given on D 2 or D 3, but was less effective on D 4 or D 5. The higher doses of TP were effective when given on any day. Attention is drawn to the fact that 90 and 270 \( \mu g \) TP markedly suppress lordosis responsiveness when injected on D 4 or D 5.

**Males.** — Body weight of intact males and males castrated on D 2 (fales) (Gorski 1967) compared to similar data from females treated on D 2 with 90 \( \mu g \) TP or oil is illustrated in Fig. 4. The intact males were significantly heavier than the fales from weaning \((P < 0.05)\), and very highly significant different from all groups after the seventh week \((P < 0.0005)\). The fales were significantly heavier than females treated with 90 \( \mu g \) TP from the eighth week onwards \((P < 0.05)\), but they were only significantly heavier than the high dose TP group from weeks 8–11. There was no difference between the 270 \( \mu g \) TP group of females and the fales after the 11th week.

![Fig. 5.](image)

Mean body weight (± standard error) of rats beginning at 24 weeks of age but which were given 90 \( \mu g \) testosterone propionate (solid circles) or oil (open diamonds) on day 3. The animals were ovariectomized at OvX and treated for two weeks (at horizontal bar) with oestradiol benzoate (3 \( \mu g \)/day).
Fig. 5 compares mean BWt of rats treated with 90 μg TP with oil treated controls. At the outset of this portion of the study the TP treated rats were significantly heavier than the oil treated rats ($P < 0.005$) and this difference was maintained throughout the experiment although the levels of significance were reduced at the end of the illustrated period ($P < 0.025$). After ovariectomy (OvX) the BWt of the TP group and controls changed in the same direction. The most significant finding was that the oil treated rats reached the preoperative BWt level of the androgen treated group. Following OB treatment both androgenized and control rats lost weight. For an accurate comparison of the rates of change of BWt a data transformation to percentage change from the mean preoperative level is given in Fig. 6. Fig. 6 also includes data from rats treated with the low dose of TP. Half of the 90 μg TP group ($N = 4$) and the 10 μg TP groups ($N = 5$) were left intact to serve as controls.

Fig. 6.
Weekly body weight data from the ovariectomized (OvX) rats illustrated in Fig. 4 expressed as the per cent deviation from the three week preoperative period. Similar data from sham operated androgenized rats are included for comparison. The horizontal bar indicates the period of treatment with 3 μg oestradiol benzoate per day in the OvX rats and daily oil treatment in the sham operated groups.
Statistical analyses in text.
Weekly food intake of the animals illustrated in Fig. 5, expressed as the mean per cent deviation from the three week preoperative period. Treatment and symbols identical to Fig. 5.

for OvX groups (10 μg TP, N = 5; 90 μg TP, N = 5; oil, N = 5). Oil treated rats grew significantly more than the 90 μg TP rats at each week following OvX (P < 0.05). After OB treatment there was no significant difference between the oil and 90 μg TP groups. Oil treated rats were not different from the 10 μg TP group at any time. Rats treated with 10 μg TP increased their BWt significantly more than those treated with 90 μg TP after the second week (3rd week, P < 0.02; 4 the week, P < 0.001), but following OB treatment there was no longer any significant difference between these two groups. The intact TP treated group of animals were not significantly different from each other but were significantly different from all other groups after the first post-OvX week until OB treatment which eliminated the differences between groups.

Food and water intake plotted as the percentage deviation from the three week preoperative mean is illustrated in Figs. 7 and 8. Prior to OvX there was no difference between groups. Following OvX, food intake in the TP and oil treated groups rose significantly above intact TP treated rats at the second post-OvX week (P < 0.005 for TP treated rats; P < 0.05 for oil treated rats) but treatment with OB caused a rapid return to intact levels (Fig. 7). Water
Weekly water intake of the animals illustrated in Figs. 5 and 6, expressed as the mean per cent deviation from the three week preoperative period. Treatment and symbols identical to Fig. 5.

intake was not different in any of the groups prior to OvX. Following OvX, water intake of TP treated rats fell and was significantly lower than that of the intact TP rats ($P < 0.005$ for 90 µg TP; $P < 0.01$ for 10 µg TP). Following OB treatment, the water intake rose to intact rat levels. The oil control OvX rats showed an increased water intake following OB treatment which rose significantly above all groups ($P < 0.005$).

At the end of this experiment all rats were anaesthetized with ether and their nose-anal lengths measured. Body length in the two groups treated with TP were similar (90 µg TP, 23.2 ± 0.4 mm; 10 µg TP, 23.4 ± 0.1 mm) and significantly greater than in the oil treated group (22.1 ± 0.3 mm; $P < 0.05$, 0.005, respectively).

**DISCUSSION**

The present data confirm earlier reports of *Beatty et al.* (1970) and *Bell & Zucker* (1971) that treatment with TP causes increased BWt. However, the present study indicates that this response is dose dependent. The low dose of 10 µg TP is only effective in producing increased BWt compared to controls during the early growth period when given on D 2, and this difference does not reach great significance. The higher doses are more effective on both D 2
and D 3. The interesting finding is that there is no effect of the high doses of TP when given on D 4 and D 5. Bell & Zucker (1971) reported that a much higher dose (1 mg TP) given at D 5 was an effective growth stimulator. Beatty et al. (1970) injected 1.5 mg TP on D 3 and also produced significant growth increases. Our results with smaller amounts of TP suggest that there is a "critical period" when the neonatal rat is particularly sensitive to an action of TP which modifies growth processes. The existence of a similar critical period for the effects of TP on gonadotrophin secretion and sex behaviour is widely recognized. A further point worthy of note is that the higher doses of TP, although having no effect on growth when given on D 4 or D 5, nevertheless still induce androgenization, that is, anovulatory sterility, constantly cornified vaginal smears, and the absence of sexual receptivity. Since there is no indication that the polyfollicular ovaries from persistent oestrous rats treated on D 4 or D 5 have a different secretory pattern than those from animals treated with TP on D 2 or D 3 (both groups display constant vaginal oestrus), the growth stimulating properties of TP appear to act independently of mechanisms affecting reproductive activity, and are therefore also independent of the persistent oestrous condition per se.

However, the second part of this investigations demonstrates that the sterile ovary still has a restraining influence, since the BWt does increase in the TP treated rat following ovariectomy. Sensitivity to large exogenous amounts of OB is not lost and both TP and oil treated rats respond similarly with a depression in BWt. Beatty et al. (1970) demonstrated the same phenomenon by treating rats with OB at the time of OvX and finding that the weight increase which normally follows OvX was inhibited. An interesting observation in our experiment is that there appears to be a difference in the relative growth response following OvX between groups treated with the high and low dose of TP. Thus, rats treated with oil or 10 µg TP did not differ from each other, but they both gained weight faster than the group treated with 90 µg TP. The number of animals in this part of the experiment is small and this important finding must be replicated, but it would appear that the higher dose of TP does reduce the BWt gain following OvX. The data of Bell & Zucker (1971) are not directly comparable since they used larger amounts of TP (1 mg) on D 5, but they also concluded that there was a reduced growth response in TP treated females following OvX.

Food and water intakes show much the same pattern independent of treatment. Food intake rises following OvX and falls again when OB is given. Water intake of androgenized rats, when expressed on a weekly basis, falls after OvX and rises towards normal levels following OB treatment. The oil treatment group showed a greater increase in water intake following OB than did the TP treated group. A long-term effect of OB in increasing water intake in OvX rats has been reported elsewhere (Tarttelin & Gorski 1973).
If one postulates that neonatal TP treatment, at least at certain doses, reduces the effect of oestrogen on the hypothalamic mechanisms involved in growth stimulation, then this could account for the smaller growth changes in TP treated rats following OvX. The suggestion that there is a reduction in the oestradiol binding ability of the hypothalamus of the androgenized rat supports this postulate (Flerkó et al. 1967; Tuohimaa & Niemi 1972; Vertes et al. 1973). In other words, rats given TP neonatally may grow at a rate which is less impaired by the normal endogenous levels of oestrogen. In this regard, very high levels of oestrogen are needed to depress BWt in males (Sullivan & Smith 1957). If this postulate is valid, then one would expect rats that were neonatally OvX to grow at the same rate whether or not they were given TP neonatally. Bell & Zucker (1971) found that following neonatal OvX, there were smaller differences between TP and oil treated groups than in the case of intact treated rats; but they reported that TP treatment still produced significantly increased BWt 110 days after treatment. However, we have found that following neonatal OvX, there is no significant BWt difference between TP and oil treated groups (Tarttelin et al. 1973), even at 24 weeks. Moreover, there were no significant differences in nose-anal length between neonatally OvX rats given TP or oil treatment.

We conclude that our investigation supports the concept that dose dependent TP treatment at a "critical period" in the first three days of life reduces the responsiveness of BWt regulating mechanisms to feedback of gonadal steroids. If this is a hypothalamic effect, the areas involved are apparently functionally unrelated to the areas responsible for gonadotrophin and sex behaviour control, since these three processes can be individually altered by appropriately timed injection of androgen.

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REFERENCES


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