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The role of estrogens in androgen induced spontaneous activity in male rats.

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THE ROLE OF ESTROGENS IN ANDROGEN
INDUCED SPONTANEOUS ACTIVITY IN MALE RATS

A Thesis Presented

by

Edward J. Roy

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INDUCED SPONTANEOUS ACTIVITY IN MALE RATS

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ABSTRACT

Three experiments tested the hypothesis that testosterone may be aromatized to an estrogen to stimulate running wheel activity in rats. Aromatizable (testosterone propionate) and non-aromatizable (dihydrotestosterone propionate) androgens were compared with estradiol benzoate for the ability to induce running in castrated male rats. Dihydrotestosterone had no effect on running. Testosterone propionate increased running, but estradiol benzoate was more than one hundred times as effective. A relatively small dose of a specific estrogen antagonist, MER-25, was shown to attenuate the effects of both testosterone propionate and estradiol benzoate on male running. MER-25 did not affect the running of castrated, oil treated male rats and did not inhibit the running induced by food deprivation.

TABLE OF CONTENTS

	Page
ACKNOWLEDGEMENTS.....	iii
ABSTRACT.....	iv
LIST OF ILLUSTRATIONS.....	vi
GENERAL METHOD.....	2
EXPERIMENT I.....	3
Comparison of the effects of estradiol and aromatizable and non-aromatizable androgens on the running wheel behavior of castrated male rats	
EXPERIMENT II.....	5
The effect of an anti-estrogen on estradiol- and testosterone-induced running behavior	
EXPERIMENT III.....	8
The effect of an anti-estrogen on non-hormon- ally activated running behavior	
DISCUSSION.....	12
REFERENCES.....	19

LIST OF ILLUSTRATIONS

Figure	Page
1. Running wheel activity of castrated males treated with estradiol benzoate, testosterone propionate, dihydrotestosterone, or sesame oil vehicle.....	4
2. Effects of an anti-estrogen, MER-25, on running wheel activity induced by estradiol benzoate or testosterone propionate in castrated male rats.....	7
3. Effect of MER-25 on deprivation-induced running in ovariectomized female rats.....	10
4. Effect of MER-25 on spontaneous activity of castrated male rats.....	11

Castration is known to reduce the "vigor" of male rats, as indicated by a decrease in their activity in running wheels (Hoskins, 1925). This decrease in activity is presumably due to a withdrawal of androgens. The few attempts to demonstrate the importance of androgens for running wheel activity by the administration of exogenous testosterone to castrated males have been successful but have also produced certain anomalies. Asdell, Doorenbal and Sperling (1962) implanted pellets of testosterone propionate (TP) into castrated males and females, and found a definite increase in activity in females but an inconsistent effect in males, even with pellets containing as much as 20 mg TP. However, males were clearly responsive to pellets of estradiol benzoate (EB). Wang, Richter and Guttmacher (1925), in an attempt to demonstrate cyclicity in males, found that transplanted ovaries increased activity in males. More recently, Stern and Murphy (1971) demonstrated that 1 mg TP/day could restore pre-castration levels of activity in castrated male rats, but they were unable to block the effect of testosterone with the anti-androgen cyproterone acetate (10 mg/day).

These findings raise the possibility that testosterone is first aromatized to an estrogen, which in turn stimulates spontaneous activity. This suggestion has

been made previously for male rat copulatory behavior (McDonald, Beyer, Newton, Brien, Baker, Tan, Sampson, Kitching, Greenhill, and Pritchard, 1970). The hypothalamus of the rat is capable of aromatizing a small proportion of androstenedione to estrone (Naftolin, Ryan and Petro, 1972) or testosterone to estradiol (Weisz and Gibbs, 1974). If this is in fact the mode by which testosterone affects spontaneous activity in males, then: (1) estradiol should be more effective than testosterone in inducing running wheel activity in males; (2) a non-aromatizable androgen such as dihydrotestosterone propionate (DHTP; Ryan, 1960) should have no effect on activity; and (3) an anti-estrogen such as MER-25 (Lerner, Holthaus, and Thompson, 1958) should attenuate the effects of testosterone on activity.

GENERAL METHOD

The subjects were 63 male and 12 female Sprague-Dawley rats obtained from Charles River Breeding Laboratories. They were housed in Wahmann LC-33 activity cages and fed Purina Laboratory Chow ad libitum. Lights were on from 6 AM to 6 PM. Food intake was measured to the nearest 0.1 g daily at noon, body weight was measured every third day at 2 PM and injections were given

between 5 and 6 PM. Castrations were carried out under sodium pentobarbital anesthesia (Nembutal). Results were analyzed with the Student's t -test or the Fisher Exact Probability Test.

EXPERIMENT I

The first experiment compared the effects of EP, TP and DHTP on the running wheel activity of castrated male rats.

Procedure. Twenty adult males weighing 275-325 g were castrated and placed in activity cages. Baseline activity was measured for 22 days, and the animals were then divided into four groups ($n=5$ each) balanced according to daily running wheel activity during the last five days. The first group received 10 μ g EB/day for 24 days. The second group received 100 μ g TP for the first 12 days. The third group received 100 μ g DHTP/day for 12 days. When neither androgen significantly affected activity, TP and DHTP dosages were increased to 1 mg/day for the remaining 12 days. All injections were given daily just prior to lights off in 0.1 ml sesame oil.

Results. Estradiol benzoate dramatically increased the running of castrated male rats ($t=2.74$, $df=8$, $p<.02$) although the effect was not evident for several days and did not plateau until about 16 days (Figure 1). Testos-

Figure 1 Running wheel activity of castrated males treated with estradiol benzoate (EB, 10 μ g/day), testosterone propionate (TP), dihydrotestosterone propionate (DHTP), or sesame oil vehicle. The arrow indicates the beginning of treatment on day 7. TP and DHTP doses were 100 μ g/day for the first 12 days of treatment and 1 mg/day for the remaining days.

terone propionate also significantly increased activity ($t=2.90$, $df=8$, $p<.01$), but to a lesser extent. The estradiol-induced running levels were significantly higher than testosterone-induced levels ($t=2.14$, $df=8$, $p<.05$). For some animals testosterone increased running at a dose of 100 $\mu\text{g/day}$, but the response was not clear and statistically significant until after the dose was increased to 1 mg/day. In sharp contrast, DHTP had no effect on activity at either 100 $\mu\text{g/day}$ or 1 mg/day. Rather, the DHTP treated animals continued the gradual diminution of activity characteristic of castrated male rats. Examination of penile external morphology and the observation of occasional seminal plugs in rats of both DHTP and TP groups indicated that both androgens were exerting peripheral trophic effects.

EXPERIMENT II

The second experiment determined the effects of the anti-estrogen MER-25 on estradiol- and testosterone-induced running in castrated male rats.

Procedure. Thirty-one males were castrated and placed in activity wheels. After 24 days the rats were divided into five groups balanced according to the last seven days' activity. The five groups were given the following combinations of estradiol benzoate, testosterone

propionate, MER-25, and sesame oil vehicle:

1. 5 μ g EB plus oil (n=6)
2. 5 μ g EB plus 10 mg MER-25 (n=6)
3. 1 mg TP plus oil (n=6)
4. 1 mg TP plus 10 mg MER-25 (n=7)
5. Two injections of oil (n=6)

Each male received two daily injections in 0.1 ml sesame oil just prior to lights off. Injections were continued for 28 days. Since MER-25 was to be given daily, the dose of MER-25 chosen was small when compared to doses required to totally block the actions of estradiol on other behavioral and somatic responses (e.g., Shirley, Wolinsky, and Schartz (1968) used 40 mg to prevent mating behavior in cycling female rats, and Komisaruk and Beyer (1972) used 75 mg/kg to antagonize the effect of 2 μ g EB on vaginal cornification).

Results. The running levels induced by 5 μ g of EB were approximately one-half those induced by 10 μ g of EB in Experiment I, and activity levels of the 1 mg TP group were very similar to the 1 mg group in Experiment I. MER-25 attenuated the effects of both hormones (Figure 2). Based on individual means for the last 14 days of treatment, 10 mg of MER-25 significantly reduced the activity induced by 5 μ g EB (Fisher Exact $p=.030$) and also significantly reduced the activity induced by 1 mg TP (Fisher

Figure 2 Effects of an anti-estrogen (MER-25, 10 mg/day) on running wheel activity induced by estradiol benzoate (EB, 5 μ g/day) or testosterone propionate (TP, 1 mg/day) in castrated male rats.

Exact $p=.049$). The effectiveness of MER-25 varied among individuals. In the TP group, six of six animals increased activity above their baseline values, whereas in the TP plus MER-25 group, four of seven showed no increase above baseline. Four of the six controls did not increase activity above baseline. None of the MER-25 treated animals showed activity levels below those of the least active oil treated animals. The EB plus MER-25 group ran at significantly higher levels than the oil group ($t=2.34$, $df=10$, $p<.05$) but the TP plus MER-25 group was not significantly different from the oil group ($t=1.66$, $df=11$, $p>.05$).

EXPERIMENT III

Although MER-25 attenuated estradiol- and testosterone-induced running wheel activity, the possibility remains that this inhibition of activity might have been due to a non-specific toxicity rather than to any anti-estrogenic properties of MER-25. In Experiment III it was determined whether MER-25 affected non-hormonally activated running wheel activity or the high levels of activity induced by food deprivation.

Procedure. Part 1. Twelve female rats were ovariectomized, placed in running wheels, and allowed 20 days for activity to stabilize. They were divided into three

groups (n=4 each) and given the following treatments. Rats in group 1 were totally food deprived (but allowed ad libitum water) and injected with 10 mg/day of MER-25 for three days. Group 2 was food deprived and injected with the oil vehicle for three days. Group 3 was allowed free access to food and injected with oil vehicle for three days.

Part 2. Twelve male rats were castrated and placed in running wheels. After 12 days the rats were assigned to two groups balanced according to their baseline activity during the last 7 days. Six rats were given daily subcutaneous injections of 10 mg MER-25 for 28 days, and 6 rats were given daily oil injections. After injections began, two rats in the oil group became ill and were sacrificed; all of their data were excluded. After 28 days, injections were continued, and the rats were totally food deprived for two days to increase activity levels.

Results. Part 1. Females responded to food deprivation with activity levels similar to those of TP treated males in Experiment II. This response to food deprivation was not attenuated by MER-25 (Figure 3).

Part 2. Running wheel activity of castrated males was not affected by the estrogen antagonist, and their

Figure 3 Effect of MER-25 on deprivation induced running in ovariectomized female rats. Total food deprivation and injections (MER-25, 10 mg/day, or sesame oil vehicle) began on day 9.

Figure 4 Effects of MER-25 (10 mg/day) on spontaneous activity of castrated male rats.

fairly modest response to food deprivation (not shown) was not attenuated (Figure 4). MER-25 treated males averaged 1152 revolutions/day during the two days of deprivation compared with 946 revolutions/day for the oil treated males.

DISCUSSION

These results together with previously reported data suggest that testosterone must be aromatized before it enhances running wheel activity in male rats: (1) Estradiol benzoate was more effective than testosterone propionate in inducing running; (2) DHTP, a non-aromatizable androgen, had no effect on activity; (3) MER-25, a specific estrogen antagonist, attenuated the effects of both EB and TP on running; and (4) Stern and Murphy (1971) demonstrated that an anti-androgen, cyproterone acetate, would not attenuate the effects of TP on running. The suggestion that estradiol is more effective than testosterone was substantiated and quantified (Asdell and Sperling, 1963). The dose of TP used was one hundred times the dose of EB, yet EB still induced higher levels of activity. Thus, only small quantities of testosterone would need to be aromatized to an estrogen to stimulate running. Several reports of hypothalamic androgen aromatization have found quite low levels of conversion, on the order

of 0.01-0.1% (Naftolin et al., 1972; Weisz and Gibbs, 1974). It is not impossible that such small proportions, if aromatized at the site of action, could be of physiological importance. Furthermore, dihydrotestosterone, which has been found in rat hypothalamus in appreciable quantities after testosterone injection (Stern and Eisenfeld, 1971) and is taken up by the hypothalamus to the same degree as testosterone (Perez-Palacios, Perez, Cruz and Beyer, 1973), is nevertheless not the active metabolite of testosterone with respect to running behavior. DHTP had no effect on activity. Of course, it is possible that differences other than aromatizability could account for the differential effectiveness of TP and DHTP in stimulating activity. The results of Experiment II make this possibility seem rather unlikely.

The estrogen antagonist MER-25 attenuated the response to both estradiol and testosterone to similar degrees. Though the effects of MER-25 on testosterone- and estradiol-induced running were clear, they were not universal. Three rats given TP plus MER-25 did run at levels similar to those of rats given only TP, and two rats given EB plus MER-25 ran in the range of the EB group. Wide variations among individual responses to hormonal treatments are not uncommon on activity measures, especially with testosterone treatments. Asdell and Sperling

(1962) found definite responders and non-responders to TP pellets at doses from 1 mg to 20 mg (using only two animals per group). Hoskins (1925) reported that some male rats did not show a decrease in running activity after castration until 24 days post-operatively, whereas the activity of some males declined immediately. The reasons for individual differences are unknown.

It is highly unlikely for several reasons that MER-25 decreased running by inducing a general malaise rather than inhibiting the actions of testosterone. First, the dose of MER-25 which inhibited testosterone-induced activity had no effect on the activity of castrated, non-hormonally treated males. Second, the mean level of activity of the TP plus MER-25 group was higher than the oil control level. More specifically, of those rats for whom MER-25 clearly antagonized the effects of testosterone, none ran below control levels. Third, although MER-25 affects weight regulation in an estrogenic fashion (Roy and Wade, unpublished data), food intake of the TP plus MER-25 group was the same as that of oil treated controls during the time when its testosterone-antagonizing effect was most evident (28.8 g/day compared to 28.5 g/day for the last 14 days of treatment). Fourth, rats receiving MER-25 are capable of running at higher levels in response to non-hormonal

stimulation. Kennedy (1964) previously used deprivation-induced running to differentiate between a general impairment of activity and a specific impairment of estradiol-induced activity. Females receiving 10 mg/day of MER-25 showed running responses to deprivation identical to control deprived rats. Extended treatment with MER-25 does not alter this capability, since groups of males injected with 10 mg/day or oil for 30 days and food deprived for the last two days showed similar increases in their running wheel activity. Finally, a learned aversion to saccharin-flavored water did not develop when it was twice paired with injections of 125 mg/kg of MER-25 (Roy and Wade, unpublished observations). This supports the contention that the inhibition of hormonally induced running is not due to a general illness.

The data reported here for running behavior are analagous to earlier reports related to the possible involvement of aromatization in the mediation of male sex behavior in rats. Castrated males treated with EB will display aspects of male sex behavior, including mounting, intromission patterns, and occasionally ejaculatory behavior (Beach, 1942; Pfaff, 1970; Sodersten, 1973). Estradiol-induced male sex behavior

is more complete when penile and accessory organ atrophy is reversed by concurrent administration of DHTP (Baum and Vreeburg, 1973; Feder, Naftolin and Ryan, 1974; Larsson, Sodersten, and Beyer, 1973), yet DHTP by itself will not maintain male sex behavior in rats (Feder, 1971; McDonald et al., 1970). These data are consistent with an aromatization hypothesis, but the report of Whalen, Battie and Luttge (1972), which to date is the closest analogy to Experiment II (in which an anti-estrogen attenuated the effects of TP) did not support the hypothesis for male sex behavior in males. Even if aromatization is of physiological importance in the induction of sex behavior in male rats, caution is still advisable with regard to generalizations to other species. Feder et al. (1974) point out that DHTP alone will maintain male sexual behavior in guinea pigs (Alsum and Goy, 1974), as it will in rhesus monkeys (Phoenix, 1974). The data are more clear-cut for aromatization being involved in the hormonal induction of spontaneous activity. This suggests the possibility that aromatization may contribute to the induction of sex behavior by increasing levels of arousal, like electrical shock (Barfield and Sachs, 1968; Cagguila and Eibergen, 1969).

Biochemical experiments in conjunction with behavioral analyses will be required to resolve whether and when

aromatization plays a physiological role in the behavioral actions of testosterone. At the cellular level, there are at least two ways in which MER-25 could have antagonized the action of testosterone on spontaneous activity. The first involves the initial uptake of testosterone, in which case MER-25 would be acting as an anti-androgen. Estradiol competes with testosterone for uptake by brain tissue (McEwen, Pfaff and Zigmond, 1970), and it is possible that MER-25, because of its stereochemical similarity to an estrogen, could inhibit the uptake of testosterone. Peripherally MER-25 apparently does not affect the initial uptake of testosterone, since it does not in general antagonize the trophic effects of testosterone on the prostate gland and seminal vesicle of males and does not antagonize testosterone's uterotrophic effect in females (Lerner et al., 1958; Lerner, Hilf and Harris, 1968). Conversely, the androgen antagonist cyproterone does inhibit the uptake of testosterone by the brain (McEwen et al., 1970; Stern and Eisenfeld, 1971), but does not alter testosterone's effect on running (Stern and Murphy, 1971). It is unlikely that MER-25 would inhibit the uptake of testosterone to a greater extent than the anti-androgen. The second possibility is that testosterone is aromatized to an estrogen by the brain, and MER-25 competes with the

estrogen. Labelled testosterone has not yet been localized in the nuclei of brain cells of rats (McEwen, Deneef, Gerlach and Flapinger, 1974). This is consistent with the possibility that small proportions of testosterone are aromatized and then taken up by the nuclei. If this is the case, MER-25 would be expected to have little inhibitory effect on testosterone uptake by whole tissue, but a clear effect on the localization of products of aromatization. The behavioral evidence supports this hypothesis.

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