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Anabolic-Androgenic Steroids and Aggression in Castrated Male Rats

ANN S. CLARK[1] AND DIANA M. BARBER[2]

Department of Psychology, Dartmouth College, Hanover, NH 03755 USA

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CLARK, A. S. AND D. M. BARBER. *Anabolic-androgenic steroids and aggression in castrated male rats.* PHYSIOL BEHAV **56**(5) 1107–1113, 1994.—The resident-intruder paradigm of aggression was utilized to evaluate the aggression-inducing properties of two anabolic-androgenic steroid (AAS) compounds, methyltestosterone and stanozolol, in castrated male rats. Three weekly tests were conducted. On test week three, castrated males treated with methyltestosterone displayed levels of aggression equivalent to the levels displayed by castrated males treated with testosterone propionate on most of the behavioral indices assessed. In contrast, treatment with stanozolol at the dose used in this study was completely ineffective in eliciting aggressive behavior. AAS effects on aggression were mirrored by their ability to stimulate seminal vesicle growth. There were no effects of AAS treatments on the levels of locomotor activity. These findings highlight the heterogeneity of AAS effects on the nervous system and behavior and indicate that the psychological effects reported by human AAS abusers may depend upon the distinct chemical structures of the abused steroids.

Aggression Methyltestosterone Stanozolol Testosterone propionate Anabolic-androgenic Steroids

ANDROGENS have long been recognized as modulators of aggression in male rats (5,31). One paradigm which has been used to assess androgen effects on aggression in rats is the resident-intruder paradigm. Stereotypical patterns of behavior are exhibited by the resident male rat towards the intruder male during these encounters. Behaviors typifying these encounters have been described in detail by many authors (see 17 and 21 for a full description of the sequential analyses of aggressive encounters). For example, the resident male rat has been described as displaying hair raising, threat postures, leaping, and biting in interactions with intruder male rats (7). Other authors have referred to these behaviors as piloerection, lateral attacks, lunges and bites, respectively (3,11,12). Co-habitation with an intact female rat increases the likelihood that a male will display aggression towards a strange male rat (3,6). In addition, removal of the testes reduces the incidence of aggressive behavior by the resident male, while androgen replacement restores aggression to precastration levels (3,29). Testosterone and/or its metabolites are believed to be critical for the activation of aggression in the resident male (13,15).

The literature on androgen effects on aggressive behavior in humans is controversial (4,14,22). Self-administration of anabolic-androgenic steroids (AAS) has become a widespread drug abuse problem over the past decade (36). AAS are synthetic steroids which have both androgenic (masculinizing) and anabolic (protein-synthesizing) actions in the body (see 34, for review). Popular AAS have distinct chemical structures and metabolic fates, including the testosterone esters and alkylated testosterone analogues (34). Testosterone propionate (TP) is an example of one AAS whose androgenic actions in the CNS have been extensively researched. Unfortunately, very little is known about the influence of the majority of synthetic AAS on the brain or behavior. One side effect of AAS abuse which has frequently been reported in humans is an increase in aggression (19,26,33,35). In addition, spontaneous episodes of violent behavior have been shown to accompany AAS use in some individuals (27,32). Recently, a controlled double-blind study was conducted in which the AAS methyltestosterone was administered to normal adult male volunteers over a 2 wk period (30). Neuropsychological testing revealed a significant increase in measures of hostility and violent feelings during the high-dose period. Although physiological levels of naturally occurring androgens have been shown to influence the offensive aggression displayed by resident male rats (1,12,13) the effects of high doses of synthetic AAS on aggressive behavior in rats have yet to be examined (23). Therefore, the purpose of the present study was to characterize the aggression-promoting qualities of two synthetic anabolic-androgenic steroids, methyltestosterone and stanozolol, in castrated male rats. These two drugs were selected for study in part because the behavioral actions of these 17 α-alkylated steroids had not previously been investigated in rats. Secondly, not only are these two compounds among the most widely used, but, as mentioned above, a recent clinical report suggested that methyltestosterone may have neurobehavioral actions in humans (30).

[1] Requests for reprints should be addressed to Dr. Ann Clark, Department of Psychology, 6207 Gerry Hall, Dartmouth College, Hanover, NH 03755.
[2] Present address: Department of Ecology, Ethology and Evolution, University of Illinois, Urbana, IL 61801.

METHOD

Subjects

The subjects for this experiment were 51 Long-Evans male rats, weighing 300–370 grams at the start of the experiment, derived from stock from Harlan Sprague–Dawley (Indianapolis, IN) maintained in the Dartmouth College Psychology Department breeding colony. Animals in this colony are weaned at approximately 1 mo of age and housed in stable same sex groups of 6–10 animals prior to assignment to the experimental protocol. Male littermates from 8–10 litters were distributed equally amongst the resident male treatment conditions. Similarly bred Long-Evans female rats were used as cagemates in the aggression tests. All animals were housed in a temperature-controlled colony maintained on a 14:10 light/dark cycle (lights off 1400) with food and water freely available. Resident male rats were weighed weekly to assess treatment effects on body weight.

Surgery and Hormone Treatments

Resident male rats were castrated at approximately 90 days of age using aseptic technique under sodium methohexital (Brevital, 50 mg/kg) anesthesia 3 wk prior to the first aggression test. Daily SC injections of methyltestosterone (3 mg/day, $n = 12$), stanozolol (400 μg/day, $n = 8$), testosterone propionate (400 μg/day, $n = 15$) or the sesame oil vehicle ($n = 15$) were administered beginning on the day of castration. The doses of methyltestosterone and stanozolol were selected to mimic the dosages typical of a "heavy" steroid abuser (26,30). In pilot studies, we evaluated the effectiveness of testosterone propionate in stimulating aggression in castrated males. These studies revealed that a physiological dose of 200 μg/day (24), was marginally effective, while a dose of 400 μg/day reliably produced levels of aggression comparable to intact males, thus the 400 μg/day dose of testosterone propionate was used in the present study. After recovery from surgery, resident males were housed individually in hanging cages.

Aggression Testing

Two weeks after castration, resident male rats were transferred into a large arena (50 × 60 × 20 cm high, with a Plexiglas front and pine shavings on the floor, approved by the Dartmouth IACUC) within the animal colony where they were housed with an intact female rat. The female rat was between 75–90 days old at the time of pairing, but neither male or female animals had prior breeding experience. Aggression testing was begun one week after the male–female pairing, and continued for 3 wk. The aggression tests were conducted during the last one-third of the light portion of the light–dark cycle, as has been previously reported (1) to allow videotaping because we did not have access to low-light video equipment. Fifteen minutes prior to the aggression test, the female cagemate was removed to a separate hanging cage. At this time, an intruder male rat weighing 75–100 grams less than the resident male was injected with 0.50 mg diazepam (i.p). The purpose of using younger, smaller males as intruders was intended to encourage aggression by the larger resident males, as has been previously reported (1,7). The administration of this dose of diazepam has been shown by other investigators to minimize the defensive behaviors displayed by the intruders and to make the behavior of intruder males more consistent (1,2). During the first aggression test, each resident male was tested with a naive intruder male. On subsequent tests, experienced intruders were used, however resident-intruder pairings were unique on each weekly test.

Once the intruder rat was introduced into the resident's cage the aggressive behaviors displayed by the resident male during the fifteen minute test were recorded by an experimenter blind to the treatment conditions. The behaviors which were recorded have been described in detail elsewhere (7,11,12). These included: lateral attack and lunge attack frequency and duration, bite frequency, "on-top" duration, piloerection, and total attack duration. As described in (12), a lateral attack consists of the resident male moving into a lateral position, with the head and body curved toward the intruder male. The resident male moves sideways [the "threat posture" described in (7)] and often kicks or pushes the intruder male off balance. A lunge attack consists of a leap forward towards the intruder, often accompanied by a bite. Time "on top" refers to the time the resident male stands over or on top of the intruder male lying in a supine position. Piloerection on the resident male was scored on a scale from 0–4 with 0 representing no piloerection, 2 signifying partial piloerection or piloerection which was present for only part of the testing period, and 4 signifying complete piloerection which was maintained throughout the 15 min testing session. Videotapes of the aggression tests were reviewed for behavioral patterns and time measures by an experimenter blind to the treatment conditions of the animals. For purposes of comparison to other recent studies of resident–intruder aggression in which a composite aggression score was reported, we utilized the published formula to tabulate a composite score (composite aggression = sum of [the number of attacks + 0.2 (total attack duration) + number of bites + 0.2 ("on top" duration) + piloerection] for each resident male for each weekly test session. The composite aggression score is claimed to be a more stable measure of aggression than any of the individual indices by some authors (see 2, for discussion).

Locomotor Activity

To assess the possible contribution of AAS-induced changes in activity to the measures of aggression, weekly tests of locomotor activity were also conducted during the study period. All rats had been habituated to the locomotor activity apparatus. During the locomotor activity test, the resident male rat was placed in a large rectangular Plexiglas arena which was marked with a floor grid of 35, 12 cm × 12 cm squares. An observer blind to the treatment conditions of the animals recorded the number of grid lines crossed by the rat during the three minute observation period. The activity tests were conducted during the last one-third of the light portion of the light/dark cycle, which corresponded to the time of the weekly aggression tests.

Seminal Vesicle Weights

At the conclusion of the behavioral studies, the resident males were sacrificed by asphyxiation with CO_2 and their seminal vesicles removed and weighed.

Statistical Analysis

Each measure of aggression, except piloerection, was subjected to an two-way ANOVA with repeated measures. Posthoc comparisons were made using the Newman–Keuls test. The nonparametric piloerection data were evaluated using a Kruskal–Wallis one way-ANOVA for each test day followed by Mann–Whitney *U*-tests for comparison of the means

of specific treatment groups. Statistical significance was defined as $p < 0.05$.

RESULTS

Body Weight

There were no measurable effects of hormone treatment on body weight. Each of the four treatment groups, including the oil-treated controls, showed a significant increase in body weight over the 6 wk observation period [$F(5,230) = 279.9, p < 0.05$]; (See Fig. 1). The interaction between treatment and test week did not attain statistical significance.

Individual Aggression Indices

In general, hormone treatment effects on the individual aggression measures were modest. By test week three, with the exception of attack latency, the rank order by treatment group of the behavioral frequency of the aggressive measures (from more frequent to less frequent) was methyltestosterone > testosterone propionate > oil > stanozolol, although in many cases the differences between groups were not significant. There was a significant overall main effect of hormone treatment on the frequency of bites [$F(3,46) = 4.4, p < 0.05$] and lunge attacks [$F(3,46) = 3.77, p < 0.05$]. Piloerection scores were also significantly elevated in males treated with methyltestosterone or testosterone propionate relative to the oil-treated controls ($p < 0.05$). Surprisingly, in the present study, hormone treatment had no significant effect on the frequency of lateral attacks [$F(3,46) = 0.87$, n.s.]. In addition, no significant effects of treatment were observed on attack latency, on-top time, or total attack time (Fig. 2). No significant interactions between test week and treatment were present for the individual indices of aggression.

Composite Aggression Scores

In the interest of comparing our results to other published reports, a composite aggression score was calculated for each of the three weekly aggression tests based on the observations made during the actual test and confirmed by videotape review (Fig. 2). Statistical analysis of the aggression data revealed a significant main effect of both hormone treatment [$F(3,46) = 5.2, p < 0.05$] and test week [$F(2,92) = 36.4, p < 0.05$] on the composite aggression score. A significant interaction between treatment and test week was also observed [$F(6,92) = 3.39, p < 0.05$]. To further analyze these results, a one-way ANOVA, followed by posthoc Newman–Keuls tests, was conducted on the weekly composite aggression scores. On test week one, no group differences were statistically significant. On test week two, resident male rats treated with methyltestosterone had composite aggression scores which were slightly, but not significantly, elevated relative to the composite aggression scores of the oil-treated controls. On test week three, composite aggression scores for rats treated with methyltestosterone or testosterone propionate were significantly higher than the scores for the oil-treated controls (Newman–Keuls, $p < 0.05$). The difference between the composite scores of the methyltestosterone-treated males and the testosterone propionate-treated males on test week three did not attain statistical significance. Throughout the test period, there were no differences between the composite aggression scores of males treated with stano-

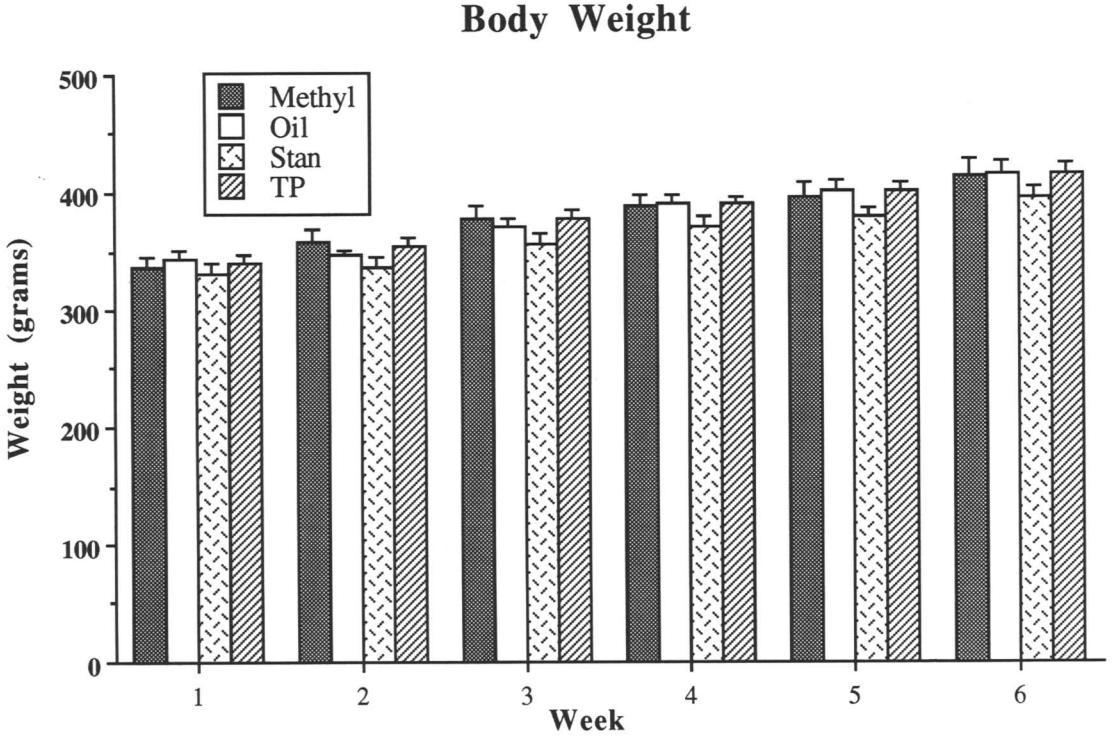

FIG. 1. Body weight was measured weekly throughout the study period. No differences in body weight were observed as a consequence of hormone treatment. Error bars represent SEM. Abbreviations: Methyl = methyltestosterone; Stan = stanozolol; TP = testosterone propionate.

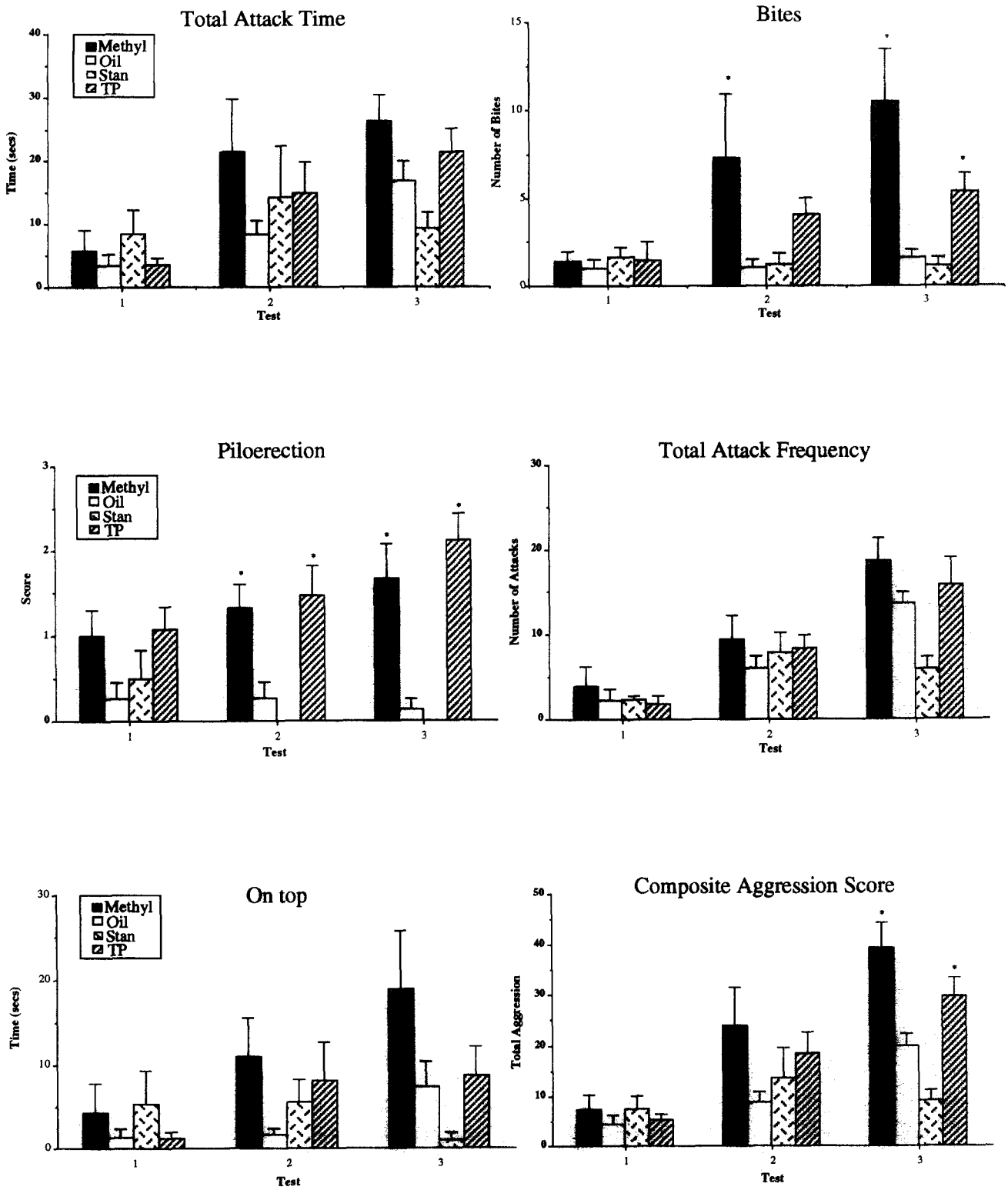

FIG. 2. Individual and composite measures of aggression measured in castrated male rats receiving different hormone treatments. Asterisks indicate group means which were significantly different from the oil control ($p < 0.05$).

zolol and the oil-treated controls. Interestingly, while the methyltestosterone, oil, and testosterone propionate-treated animals all showed a significant increase in composite aggression scores over the 3 wk of testing, no significant changes in the levels of composite aggression were noted during this time period in the male rats treated with stanozolol.

Locomotor Activity

Three weekly tests of locomotor activity were conducted during the study period. No significant main effect of hormone treatment on activity was observed. As expected, there was a significant effect of test week on locomotor activity [$F(3,24) = 2.22$, $p < 0.05$]; activity levels decreased in general over the three week test period as the rats acclimated to the test apparatus (data not shown). The interaction between hormone treatment and test week was not significant.

Seminal Vesicles

At the conclusion of behavioral testing, the resident male rats were sacrificed and their seminal vesicles removed and weighed. One-way ANOVA revealed a significant effect of hormone treatment on seminal vesicle weight [$F(3,46) = 29.5$, $p < 0.05$]. Posthoc Newman–Keuls tests revealed that male rats treated with methyltestosterone or testosterone propionate had seminal vesicle weights which were significantly elevated relative to the oil-treated controls ($p < 0.05$). The weights of seminal vesicles removed from males treated with stanozolol did not differ from the vehicle-treated controls (Fig. 3).

DISCUSSION

The present study examined the effects of AAS on aggressive behavior and activity in adult castrated male rats. In addition, the androgenic potency of hormone treatments in stimulating seminal vesicle growth and overall body weight were determined. One contribution of the findings reported here is the observation that at the dosages used in this study the effects of two AAS differed markedly in regard to their ability to stimulate aggression in castrated male rats.

While many athletes and body builders take AAS with the intention of improving strength, performance and muscle mass (36), controlled studies examining AAS effects on body weight gain in humans have produced inconsistent results (18). Similarly, weight gain was not observed in intact male rats treated for approximately 6 wk with either nandrolone decanoate or stanozolol (8,37). Because the present study was conducted using castrated male rats, our results cannot be directly compared to the data from human studies and studies in intact male rats. Other researchers have reported increases in body weight in castrated male rats treated with androgens relative to oil-treated controls (9,16,20). We failed to observe any significant effect of the AAS treatments administered in our experiments on weight gain in castrated male rats during the 6 wk study period. It has been suggested that time since castration, steroid dose, timecourse and target-tissue metabolism of AAS all contribute to the observed effects of AAS on weight gain (16). Clearly, further studies need to be done in which a variety of AAS compounds are administered to castrated and intact male rats under conditions where diet and exercise are also manipulated, to have a complete understanding of the effects of AAS on body composition and physiology in human abusers.

The effects of AAS treatments on seminal vesicle growth were also determined. Seminal vesicle stimulation is routinely used as an index of the androgenic potency of steroid compounds in peripheral tissues. We were particularly interested in whether the actions of the AAS on this peripheral organ would mimic their effects on aggressive behavior. While both the methyltestosterone and testosterone propionate treatments stimulated seminal vesicle growth above the oil-treated controls, stanozolol had no effect on seminal vesicle weight. In a follow-up study, we administered a range of doses of stanozolol (200–1000 μg/day) and determined seminal vesicle weights. At all doses, we failed to observe any stimulation of seminal vesicle growth by stanozolol (Clark, unpublished). Ongoing studies in our laboratory are exploring the potency of these different AAS compounds at brain steroid receptors. Although no previous analysis of these synthetic AAS compounds at brain receptor targets have been conducted, there are some data elucidating the actions of these compounds at peripheral sites. These data show stanozolol to have a much lower relative binding affinity for the rat prostate androgen receptor than either methyltestosterone or testosterone (28). Thus, one possibility that remains to be determined is whether a similar difference in relative binding affinity to brain androgen receptors could account for the different aggression promoting qualities of these AAS.

Locomotor activity did not appear to be influenced by AAS treatment. Thus, AAS effects on aggression cannot be attributed

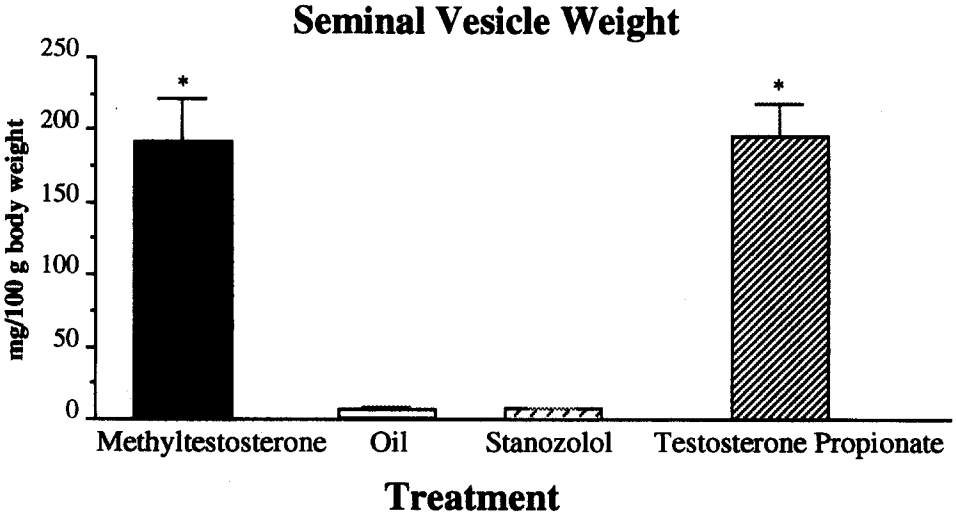

FIG. 3. Seminal vesicle weights were determined in castrated male rats sacrificed after 6 wk of treatment with different hormone regimens. Weights are expressed as mg dry weight per 100 g body weight. * $p < 0.05$ vs. oil control.

to nonspecific AAS-induced increases in general activity. Our results agree with the failure to observe effects of a different AAS, nandrolone decanoate, on general locomotor activity in either intact or castrated male Wistar rats (25), and the observation that the administration of 3–5 mg/kg/day of testosterone propionate to intact male rats did not produce increased open-field activity (10). Recently, administration of methyltestosterone to human subjects on a daily basis failed to change daily activity scores as measured by a wrist monitor (30).

In the present study, aggressive behavior was measured after a single dose of two different AAS. While the conclusions one can draw in the absence of a complete dose–response analyses are limited, these results suggest distinct effects of AAS treatment on the stimulation of aggression. On test week three, in agreement with published studies, castrated male rats treated with testosterone propionate showed a significant elevation in aggression relative to the oil-treated controls. Interestingly, at the doses used in this study which were selected to mimic human abuse levels, the AAS methyltestosterone and stanozolol were found to have very different effects on aggression in resident males. Treatment with methyltestosterone was as effective as testosterone propionate in inducing aggression in resident males on the third weekly test. In addition, males treated with methyltestosterone had slightly elevated levels of aggression, relative to controls, on test week two. In contrast, treatment with stanozolol at a dose of 400 μg/day was ineffective in stimulating aggression in resident male rats.

The results from the individual measures of aggression were variable. In agreement with previous reports, we observed a significant increase in piloerection across test weeks in castrated resident male rats given replacement therapy with testosterone propionate. Piloerection was also significantly elevated relative to the oil controls in male residents treated with methyltestosterone. In contrast, male residents treated with stanozolol showed little piloerection. The frequency of lunge attacks and bites was significantly elevated in male resident rats treated with TP or methyltestosterone. No significant differences between the controls and hormone-treated rats were observed in the frequency of lateral attacks, the duration of total attack or "on-top" time. Although we observed piloerection and lateral attacks in the resident male rats treated with TP and methyltestosterone, in general the levels of aggression stimulated by hormone treatments in our laboratory were slightly lower than those previously reported (3). Several factors may underlie this discrepancy. First, our castrated males were raised in stable same-sex groups of 6–10 males from weaning, lessening their exposure to strange males, an experience which has been shown to elevate aggression levels (3). Second, our oil-treated control group showed an increase in aggression, particularly on test week three. This may have contributed to the failure of some individual aggression measures to attain statistical significance, and others have occasionally seen a high level of aggression in castrated oil-treated male rats (3). It is also possible that the repeated handling and daily injections administered to the rats in our experiment, as opposed to the use of Silastic tubing in other experiments (1,2), somehow contributed to the lessening of aggressive tendencies in our animals. Finally, we tested our animals for aggression in the late portion of the light period of the light/dark cycle, as has been utilized in previous aggression experiments (1,2). It remains a possibility that higher levels of aggression would be observed in the dark phase. We are currently assessing the role these variables may play in the assessment of resident-intruder aggression in our laboratory.

As mentioned earlier, there is considerable discord surrounding the role of androgens in human aggression. While the present study begins to establish some of the neurobiological actions of AAS in the rat, of considerable importance is the information to be gained from extensive dose–response analyses of AAS effects on aggressive behavior in animals, as well as examination of the potential cellular mechanisms underlying their behavioral actions. The present study utilized castrated male rats to provide a direct assessment of AAS effects on the brain in the absence of gonadal secretions. This approach provides information on the efficacy of these drugs as androgens in the brain. One goal of the present study is to begin to characterize the individual actions of doses and compounds routinely self-administered by AAS users. By characterizing the potency of individual compounds on aggressive behavior and brain steroid receptors in animals, these studies may contribute to our understanding of the complex actions of these drugs on the human brain and behavior.

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