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Short communication

Testosterone enhances aggression of wild-type mice but not those deficient in type I 5α-reductase

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Abstract

Testosterone's (T) aggression-enhancing effects may be mediated in part by its 5α-reduced, 3-hydroxysteroid dehydrogenized metabolite 5α-androstane-3α,17β-diol (3α-diol). To test this hypothesis, in Expt. 1 gonadectomized (gdx) C21 mice were administered T, 3α-diol, or vehicle and were observed in the resident intruder test of aggression 1 h later. C21 mice administered androgens had significantly higher incidences of aggression than did vehicle-administered mice. In Expt. 2, wild-type mice and mice deficient in the 5α-reductase type I enzyme were administered T or vehicle and tested 1 h later in the resident intruder paradigm. Wild-type mice administered T had significantly shorter latencies and greater incidences of aggression than did 5α-reductase type I knockout mice administered T or vehicle-administered mice. Data from Expt. 1 are consistent with T and 3α-diol having similar aggression-enhancing effects, and results of Expt. 2 suggest that the inability to metabolize T to its 5α-reduced products may attenuate some aggression-enhancing effects of mice in the resident intruder test of aggression.

Theme: Neural basis of behavior

Topic: Hormonal control of reproductive behavior

Keywords: Neurosteroid; 3α-Androstanediol; Nongenomic; γ-Aminobutyric acid$_A$ receptor; *N*-Methyl-D-aspartate receptor; Fighting

Testosterone (T) can have activational and organizational effects on aggressive behavior. Gonadectomized (gdx) female or male mice show a reinstatement of aggressive behavior when T is administered [2,3,24,25,46]. Male mice are more sensitive than are female mice to androgen administration in adulthood [48] but perinatal androgenization of females results in a male-typical pattern of sensitivity to androgens [7,8,11,16].

Androgenic metabolites of T may enhance aggression through several mechanisms. Administration of an antiandrogen, a blocker of androgen activity, reduces the ability of T to induce aggression in some (SPF male mice) [21], but not all mouse strains [19,37]. Androgenic metabolites of T can be formed via metabolism by the 5α-reductase enzyme to dihydrotestosterone (DHT), which can then be metabolized by 3-hydroxysteroid dehydrogenase to 5α-androstane-3α,17β-diol (3α-diol), that can undergo conversion back to DHT. Testosterone and DHT can have similar aggression-enhancing effects, in some, but not all mouse strains [18,25,38,43,44] and have similar high affinities for intracellular androgen receptors (ARs) [9,22,23,35], whereas 3α-diol does not. 3α-diol is a very effective modulator of γ-aminobutyric acid (GABA)$_A$/benzodiazepine receptor complexes (GBRs) [14], but T and DHT are not [17]. As T and 3α-diol have different mechanisms, an important question is to what extent T's behavioral effects are attributable in part to actions of 3α-diol.

In Expt. 1, we tested the hypothesis that T and 3α-diol have similar aggression-enhancing effects when administered to C21 mice. In Expt. 2, the importance of T's metabolism on aggressive behavior was examined in 5α-

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reductase type I knockout mice. This enabled us to test the hypothesis that mice deficient in their ability to metabolize T would show less aggression than wild-type mice when administered T.

Although at present two isoforms of the 5α-reductase enzyme have been cloned and their distributions characterized [1,31], currently only the type I isoform, which is constitutively expressed in the rodent central nervous system at all stages of brain development [28], has been manipulated to develop a knockout model. The 5α-reductase type I knockout mice are a valuable research tool in which the expression of the type I 5α-reductase gene is perturbed, resulting in deficiencies in its protein product, the 5α-reductase type I enzyme [26,27]. In these knockout mice, the other isoform of 5α-reductase, type II, which is only transiently expressed in late fetal/early postnatal life, is intact and functional. Hence, Expt. 2, which utilizes 5α-reductase type I knockout mice, examined the importance of the 5α-reductase type I enzyme in mediating actions of T on aggressive behavior.

In Expt. 1, 22 adult, male C21 mice were obtained from Charles River Breeding Farms. For Expt. 2, B6, 129S-Srd5a1 ⟨tm1 Mahe⟩ male mice were derived from 10 breeder pairs (homozygous −/− father and heterozygous +/− mother) obtained from Jackson Laboratories (Bar Harbor, ME). The offspring cannot be differentiated by their phenotype; hence, polymerase chain reaction was used to determine the genotype of resulting offspring [36]. Subjects were either homozygous or −/− for the 5α-reductase type I enzyme (n=21), heterozygous or −/+ for the 5α-reductase type I enzyme (n=23), or were wild-type or +/+ for the 5α-reductase type I enzyme (n=59). All mice were group housed until surgery, after which time mice were individually housed with continuous access to Purina Rat Chow and water in their cages and were maintained on a 12:12-h reversed light/dark cycle.

Mice were gonadectomized under sodium pentobarbital anesthesia (70 mg/kg) at approximately 55 days of age. At least 4 weeks following gdx, mice were injected with the assigned androgen, or vehicle, and behaviorally tested. Behavioral testing consisted of recording offensive aggression of experimental mice in the resident-intruder paradigm [10]. Briefly, an olfactory bulbectomized male (that would not initiate fights or retaliate but would reliably elicit aggression comparable to that of intact males; Expt. 1) or an intact stimulus male (Expt. 2) was left in the home cage of the experimental animal for 10 min [10]. During this time, the latency and incidence of aggressive behaviors (attacks, bites, threats, and tail rattles) initiated by the resident were recorded. Mice from Expt. 2 were subsequently used in another experiment to determine T's anti-seizure effects [15].

For Expt. 1, mice were randomly assigned to receive SC T (1000 μg in 0.1 cc; n=8), 3α-diol (1000 μg in 0.1 cc; n=8), or vehicle (propylene glycol; n=6), 1 h prior to behavioral testing. For Expt. 2, mice were randomly assigned within their genotypic group to receive SC T (1000 μg in 0.1 cc) or vehicle (propylene glycol), 1 h prior to behavioral testing. Mice deficient in the 5α-reductase type I enzyme administered T were not statistically different in their behavior regardless of whether they were homozygous (n=12) or heterozygous (n=13) for the 5α-reductase type I enzyme deficiency; therefore, these groups were combined to constitute the 5α-reductase type I knockout mice administered T (n=25; testosterone knockout). Following vehicle administration, there were no expected or observed differences in aggressive behavior as a function of genetic backgrounds of the mice; hence, the 26 wild-type, the nine homozygotes, and the 10 heterozygotes administered vehicle were combined to constitute the control group of vehicle-administered mice (n=45; vehicle control). The behavior of the testosterone knockout and vehicle control groups was compared to the 33 wild-type mice that were administered T (testosterone wild-type).

In both experiments behavioral differences as a function of androgen manipulation were analyzed using one-way analyses of variance (ANOVAs). Factors revealed as significant in the overall ANOVAs were further examined using Tukey's post hoc tests to ascertain group differences. Alpha level for statistical significance was $P \leq 0.05$.

In Expt. 1, androgen administration to C21 mice increased the number of aggressive acts compared to vehicle administration ($F(2,19)=17.244$, $P<0.01$). Notably, 3α-diol and T had similar aggression-enhancing effects (see Fig. 1).

In Expt. 2, the latency for the resident to initiate the first aggressive act towards the intruder varied significantly across groups ($F(2,110)=16.09$, $P<0.01$). Wild-type mice administered T had significantly shorter latencies to initiate

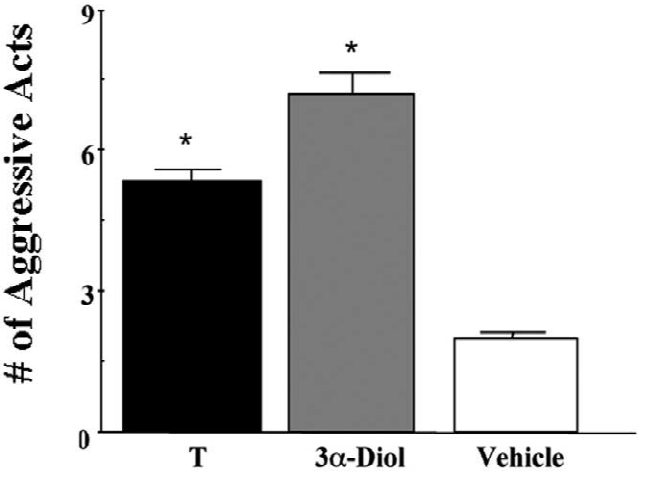

Fig. 1. Effects of testosterone, 3α-diol and vehicle on number of aggressive acts in male mice. Figure represents the number of aggressive acts (±S.E.M.), of C21 mice administered testosterone (black bars), 3α-diol (gray bars), or vehicle (open bars). *$P \leq 0.001$, significant difference from vehicle-administered mice.

the first aggressive act compared to 5α-reductase deficient mice administered T ($P<0.01$) or vehicle-administered control mice ($P=0.01$). The wild-type mice administered T had a significantly shorter average latency (129±28 s, S.E.M.) to the first aggressive act than did 5α-reductase deficient mice administered T (261±37 s), or vehicle-administered mice (342±24 s).

In Expt. 2, the number of aggressive acts initiated by the resident towards the intruder varied significantly across groups ($F(2,110)=11.11$, $P<0.01$). Wild-type mice administered T exhibited a greater number of aggressive acts compared to the number of aggressive acts initiated by 5α-reductase deficient mice administered T ($P<0.01$) or vehicle-administered control mice ($P<0.01$; see Fig. 2). Notably, 5α-reductase deficient mice administered T and vehicle-administered mice had a similar low incidence of aggressive acts.

The present findings supported our hypotheses and indicated that 5α-reduction may be important for some of T's aggression enhancing effects. The hypothesis that T and 3α-diol would have similar aggression-enhancing effects was supported. Indeed, T and 3α-diol administration similarly and significantly increased aggression compared to that seen following vehicle administration to C21 mice. This suggests that 3α-diol, T's 5α-reduced metabolite is at least as effective as T at enhancing aggression when administered to gdx, C21 mice. The hypothesis that mice deficient in their ability to metabolize T would show less aggression than wild-type mice administered T was also supported. When mice deficient in the type I 5α-reductase enzyme were administered T their latency to the initial aggressive act was significantly longer and the number of aggressive interactions were significantly fewer than that seen in gdx wild-type mice administered T, but latencies and number of aggressive acts were not significantly different from vehicle-administered mice. Together, these data suggest that T and 3α-diol can both enhance aggression and that T's metabolism by 5α-reductase may be involved in T's actions to enhance aggression of these mice.

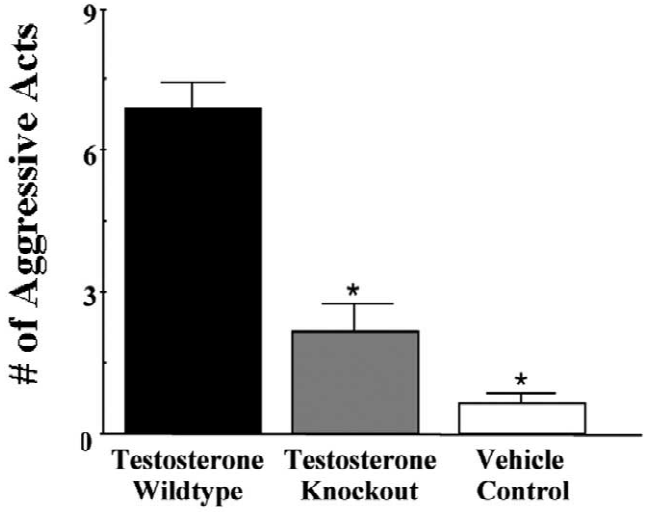

Fig. 2. Effects of testosterone administration on number of aggressive acts in wild-type and type I 5α-reductase male knockout mice. Figure represents the mean number of aggressive acts (±S.E.M.) of wild-type mice administered testosterone (black bars), mice deficient in type I 5α-reductase activity administered testosterone (gray bars), and vehicle-administered control mice (open bars). *$P\leq0.001$, significant difference from testosterone-administered wild-type mice.

Previous research supports the notion that T's 5α-reduced metabolites may enhance aggression. First, administration of 5α-reduced T metabolites, DHT [18,25,38,43,44] or 3α-diol, enhances aggression of mice [33,39]. Second, interfering with 5α-reduction attenuates androgens' aggression enhancing effects. For example, progesterone administration inhibits T-induced aggression by limiting T's 5α-reduction [18]. Third, different metabolites of T enhance androgen-induced aggression, but to various degrees of effectiveness. Notably, the efficacy of T's metabolites to induce aggression is not related to their ability to bind to ARs, but may be in part due to their ability to be 5α-reduced [25]. In support, androstenedione, an androgen with a low affinity for ARs [35] but which can act as a ligand at GBRs [17], administration to castrated Swiss Webster (but not CD) mice [12,24] or to hamsters [30], produces aggression similar to that of T administration.

The disparity between androgens ability to enhance aggression and bind to ARs [12,22,32,35] and the inability of anti-androgens to specifically block androgen-induced aggression [5] suggests that androgens' aggression-enhancing effects may not be solely mediated by ARs. The ability of androgens to enhance aggression and bind to ARs is not positively correlated. Testosterone has a high affinity for intracellular ARs, but 3α-diol does not [9,35]. The present results indicate that T and 3α-diol have similar aggression enhancing effects (Expt. 1) and that attenuating T's metabolism to 3α-diol reduces T-facilitated aggression (Expt. 2). The notion that T and 3α-diol have similar aggression enhancing effects, but disparate affinities for ARs, and that attenuating T's metabolism to 3α-diol reduces aggression, suggests it is unlikely that these effects of T are solely due to actions at ARs. Further, the binding of DHT to ARs is not systematically related to its aggression enhancing effects [35,43]. There is also a lack of correlation between androgen-induced body and organ weight and aggression in female mice [47]. Testosterone propionate administered to adult mice altered the weight of the seminal vesicles but had no apparent effect on aggressive behavior [7]. Additionally, T is more effective than DHT at enhancing aggression while T has a lower affinity and dissociates more rapidly from ARs than does DHT [20,25,35]. Administration of anti-androgens does not inhibit androgen-induced aggression. Steroidal and non-steroidal anti-androgens, such as cyproterone, cyproterone acetate, and flutamide, which cause regression of the accessory structures, do not produce a significant decline in aggression when administered to male mice or gerbils

[19,37]. The ability of androgens with low affinities for ARs [35] but which are ligands of GBRs [17] to produce aggression suggest that some of androgen's actions may occur through non-AR substrates. The extent to which T's aggression-enhancing effects are mediated through actions at ARs and/or GBRs is the subject of ongoing investigation in our laboratory.

The present findings that T and 3α-diol can both enhance aggression in C21 mice and that disruption of 5α-reduction attenuates T's aggression enhancing effects are consistent with the hypothesis that metabolism to, or biosynthesis of, 3α-diol may be important for some of T's aggression-enhancing effects in mice; however, there are some methodological constraints which limit these interpretations. One concern regarding these studies is that there is considerable individual and cross genotype variability in androgen sensitivity and propensity for aggressive behavior of mice that has been reported in the literature [32,40,41,45]. This could have been addressed by performing post-castration, baseline screening for aggressive behavior, examining androgen levels, and/or incorporating multiple tests of aggression to assess this variable behavior. In view of these concerns, mice were gdx for 4–6 weeks prior to testing which produces low endogenous androgen levels across a number of genotypes [6]. As well, no direct comparisons have been made between the results of the two experiments because of the obvious differences in genotypes and other variables. Indeed, a strength of these studies may be the implication that 3α-diol had aggression-enhancing effects across genotypes.

Another methodological constraint related to genotype is that the limited availability of 5α-reductase type I knockout mice precluded having a sufficient number of animals with which to conduct dose-responsive experiments. Indeed, not only are effects of multiple dosages of androgens lacking, the one androgen dosage utilized was high, and likely pharmacological. Such a high dosage was utilized to maximize the likelihood effects would be observed 1 h 3α-diol's oxidation to DHT produced the mitigating effects on aggressive behavior. In Expt. 2, mice deficient in the 5α-reductase enzyme would have had limited production of DHT and 3α-diol; hence, one cannot rule out the possibility that DHT may be an active androgen in promoting aggression in mice. DHT has been reported to enhance aggression of male mice [4]; however, this is not seen in all strains of mice [42].

Second, the possibility of actions through ARs, despite the limited affinity of 3α-diol for ARs, cannot be ruled out. The high concentrations of 3α-diol utilized might have compromised the low affinity of 3α-diol, in physiological concentrations, for ARs [35]. However, there is little evidence that actions at ARs can account for aggression-enhancing effects. For example, administration of anti-androgens does not produce a significant decline in aggression when administered to some male mice [19,37] but has been reported to do so in others [21]. The aggression reducing effects of these anti-androgens may be independent of actions at ARs. Anti-androgens can alter GABA concentrations and may have effects through indirect actions on odor communication [5]. As well, mice with deficiencies in functional ARs do not show profound impairment in androgen-induced aggression [29].

Third, given the possibility that 3α-diol may have aggression-enhancing effects, it is also necessary to consider whether these effects on aggressive behavior reflect androgen-induced aggression. 3α-Diol is a neurosteroid and other neurosteroids have been demonstrated to alter aggression. Administration of neurosteroids, which are positive modulators of GBRs, have been demonstrated to increase aggression of CFW male mice [13], and those neurosteroids, which are negative modulators of GBRs, have been shown to inhibit aggression of Swiss strain male mice [34,49]. Consistent with this, 3α-diol, a positive modulator of GBRs, had aggression-enhancing effects. These actions of 3α-diol may be in part independent of androgenic activity and related more to actions at GBRs.

In summary, mice administered T or 3α-diol showed

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