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'Roid rage in rats? Testosterone effects on aggressive motivation, impulsivity and tyrosine hydroxylase

Ruth I. Wood *, Abigail Armstrong, Vlad Fridkin, Vivek Shah, Allison Najafi, Michael Jakowec

Department of Cell and Neurobiology, Keck School of Medicine at the University of Southern California, Los Angeles, CA 90033, United States

HIGHLIGHTS

- We tested effects of chronic, high-dose testosterone on aggressive motivation and impulsivity in male rats.
- Testosterone did not enhance motivation for aggression, but did increase fighting.
- Testosterone reduced impulsivity in a delay-discounting test for food reward.
- Testosterone selectively reduced levels of tyrosine hydroxylase in caudate-putamen.

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ABSTRACT

In humans and animals, anabolic-androgenic steroids (AAS) increase aggression, but the underlying behavioral mechanisms are unclear. AAS may increase the motivation to fight. Alternatively, AAS may increase impulsive behavior, consistent with the popular image of 'roid rage. To test this, adolescent male rats were treated chronically with testosterone (7.5 mg/kg) or vehicle and tested for aggressive motivation and impulsivity. Rats were trained to respond on a nose-poke on a 10 min fixed-interval schedule for the opportunity to fight in their home cage with an unfamiliar rat. Although testosterone increased aggression (6.3 ± 1.3 fights/5 min vs 2.4 ± 0.8 for controls, $p<0.05$), there was no difference in operant responding (28.4 ± 1.6 nose-pokes/10 min for testosterone, 32.4 ± 7.0 for vehicle). This suggests that testosterone does not enhance motivation for aggression. To test for impulsivity, rats were trained to respond for food in a delay-discounting procedure. In an operant chamber, one lever delivered one food pellet immediately, the other lever gave 4 pellets after a delay (0, 15, 30 or 45 s). In testosterone- and vehicle-treated rats, body weights and food intake did not differ. However, testosterone-treated rats chose the larger, delayed reward more often (4.5 ± 0.7 times in 10 trials with 45 s delay) than vehicle controls (2.5 ± 0.5 times, $p<0.05$), consistent with a reduction in impulsive choice. Thus, although chronic high-dose testosterone enhances aggression, this does not include an increase in impulsive behavior or motivation to fight. This is further supported by measurement of tyrosine hydroxylase (TH) by Western immunoblot analysis in brain regions important for motivation (nucleus accumbens, Acb) and executive function (medial prefrontal cortex, PFC). There were no differences in TH between testosterone- and vehicle-treated rats in Acb or PFC. However, testosterone significantly reduced TH (to $76.9 \pm 3.1\%$ of controls, $p<0.05$) in the caudate-putamen, a brain area important for behavioral inhibition, motor control and habit learning.

1. Introduction

Anabolic-androgenic steroids (AAS) are performance-enhancing substances. Misuse of AAS by athletes is widely acknowledged, but potential health risks are not well-understood. These include not only cardiovascular, hepatic and reproductive dysfunction, but also alterations in brain and behavior. Many AAS users meet DSM criteria for psychoactive substance dependence, including continued use despite negative side effects, and withdrawal symptoms when steroids are discontinued [1]. However, unlike other illicit drugs, AAS have only a limited capacity to cause acute intoxication or other immediate physiologic responses [2]. Instead, a potential danger of AAS abuse reflects the increased likelihood that users will engage in behaviors that pose significant risks to themselves and others. Steroid use has been implicated in several violent murders [3–6]. Similarly, in surveys of current users and in prospective studies of human volunteers, increased aggression is the most consistent behavioral effect of high-dose AAS exposure in humans [7–16]. This has given rise to the image of "roid rage": a sudden and exaggerated aggressive response to a minimal

* Corresponding author at: Department of Cell and Neurobiology, Keck School of Medicine at the University of Southern California, 1333 San Pablo St., BMT 408a, Los Angeles, CA 90033, United States. Tel.: +1 323 442 1980; fax: +1 323 442 3158.
E-mail address: riw@usc.edu (R.I. Wood).

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provocation. Roid rage is recognized in popular media [17], in body-building circles [7,18,19], and in clinical literature [3–6].

Investigating AAS use in humans is complicated by the user's motivation for increased strength and muscle mass [1,2]. Animal studies can explore consequences of AAS in an experimental context where appearance and athletic performance are irrelevant. Such studies show that AAS are rewarding, as demonstrated by self-administration [20–29] and conditioned place preference (CPP) [30–37]. Furthermore, AAS stimulate social behavior, particularly mating and aggression [20,38–42]. In a resident–intruder test, attack latency by the steroid-treated home-cage male is reduced, and the composite aggression score increases [40]. With additional stimulation (tail pinch), steroid-treated males will attack anestrous females [41,42].

The present study investigated potential underlying causes of AAS-induced aggression in rats, including increases in impulsivity and aggressive motivation. Loss of impulse control is one of the generally-accepted, but relatively untested, features of roid rage. According to this model, a small provocation (introduction of an intruder into the home cage) in a rat treated with AAS would produce an exaggerated behavioral response (short-latency attack). Alternatively, androgens may enhance aggressive motivation. Agonistic behavior is rewarding when you win. Animals will work for the opportunity to attack an intruder [43,44], and show CPP for an environment where they previously won fights [45]. Since androgens promote fighting and fighting is rewarding, it is reasonable to expect that chronic exposure to AAS will enhance both aggressive behavior (as demonstrated previously [39,46]) and aggressive motivation. Expression of agonistic behavior involves dopamine (DA) release in the hypothalamus [47]. Winning a fight is also accompanied by DA release from midbrain neurons of the ventral tegmental area (VTA) that project to the nucleus accumbens (Acb) [43,44,46,48]. Adjacent to VTA, dopaminergic neurons in substantia nigra (SN) that project to the caudate-putamen (CPu) coordinate motor control [49]. DA also contributes to executive function in the medial prefrontal cortex (PFC) [50]. Accordingly, the present study used male rats as a model to test the hypothesis that chronic exposure to AAS increases motivation for aggression and enhances impulsive behavior, and that these effects are mediated by increased DA activity in Acb, CPu, PFC, and VTA/SN.

2. Materials and methods

2.1. Animals

Adolescent male Long–Evans rats (4 weeks of age, ca. 75 g BW at the start of the study, Charles River Laboratories, MA) were individually housed under a reversed 12L:12D photoperiod. They remained gonad-intact to approximate AAS use in humans. Behavior was tested under dim red light during the first 4 h of the dark phase when activity peaks.

2.2. AAS treatment

Beginning at 5 weeks, rats received testosterone (7.5 mg/kg; Steraloids, RI) or vehicle [3% ethanol and 13% cyclodextrin (RBI, MA) in water] by daily sc injection 5 days/week (n = 8/group). The 7.5 mg/kg dose approximates a heavy steroid dose in humans, and has been used previously to demonstrate AAS effects on mating and aggression in rats [51,52].

2.3. Aggressive motivation

Methods to test motivation for agonistic behavior are modified from Fish et al. [43]. From 7 weeks of age, males were trained in daily sessions to respond on a nose-poke for the opportunity to fight. An operant conditioning panel containing a nose-poke with stimulus light (Med Associates, VT) was introduced into the home cage 10 min after injection of testosterone or vehicle. A gonad-intact male intruder of similar age and weight was present behind a perforated Plexiglas screen adjacent to the nose-poke, permitting transmission of visual, auditory and olfactory stimuli. Responses on the nose-poke were recorded and reinforced on a fixed-interval (FI) schedule, with introduction of the intruder for 5 min as the reinforcer. Initially, the intruder was introduced 30 s after the start of the session. Subsequently, the FI was increased to 1 min, and by 1-min increments thereafter until a 10 min FI was reached. Intruders were rotated daily, with each test male exposed to the same intruder once every 3 weeks. Using the resident–intruder model ensured that all home-cage rats (testosterone- or vehicle-treated) were dominant to intruders [53].

Testing on the FI10 schedule continued until response rates stabilized (ca. 95 days of age). At this point, aggressive behavior was recorded on videotape during presentation of the intruder male, and was scored by an observer blinded to the treatment groups. Measures of offensive aggression include the number of rolling fights, as well as the latency to the first rolling fight. In addition, we tracked contact with the intruder male in seconds (investigation, threats and dominance displays, aggression), as well as self-grooming and exploration of the cage. The total duration of contact, the number of contact bouts, and the duration of each bout were compared.

2.4. Impulsivity

Rats were subsequently trained and tested for impulsivity, measured as operant responding for food by delay-discounting according to Winstanley et al. [54]. Operant chambers were equipped with a house-light and 2 retractable levers with stimulus lights flanking a food trough connected to a pellet dispenser. Initially, rats were trained to respond on both levers for 45-mg food pellets (Bio-Serv Inc., Frenchtown, NJ). Thereafter, they were tested daily in a series of 4 blocks of 12 trials each. Each block began with 1 forced trial on each lever with stimulus light illuminated, presented in a random order. This was followed by 10 choice trials (both levers extended with lights illuminated). During a 70 s trial, the rat must respond within 10 s after the levers are extended. After receiving reinforcement (or after lever retraction in unreinforced trials), each trial was followed by a time-out in the dark with levers retracted. In the first block of trials, one lever delivered 1 pellet; the 2nd lever delivered 4 pellets. In subsequent blocks, an increasing delay (15, 30, or 45 s) was imposed between a response on the 2nd lever and pellet delivery. When the rat made a response on the lever delivering the large reward, the stimulus light over that lever remained illuminated during the delay. The location of the lever for the large reward (to the left or right of the food trough) was balanced among rats to control for side preferences. Preference for the smaller immediate reward over the larger delayed reward is thought to reflect impulsive behavior [55]. Testing lasted 15 days (until rats were ca. 140 days of age); average daily responses for the last 5 days were compared in testosterone- and vehicle-treated rats. Afterwards, 24-h food intake was measured in both groups of rats to determine if testosterone treatment altered food consumption.

2.5. Tyrosine hydroxylase immunoreactivity

At 20 weeks of age, brains were collected 24 h after the final injection of testosterone or vehicle for measurement of TH protein by Western immunoblot. TH is the rate-limiting enzyme in DA synthesis, and DA is a key neurotransmitter for reward. Rats were sacrificed by decapitation. Brains were quickly removed and regions of interest identified using a standard rat brain atlas [56]. Medial prefrontal cortex (PFC), nucleus accumbens (Acb), caudate-putamen (CPu), and ventral tegmental area/substantia nigra (VTA/SN) were rapidly dissected, immediately frozen on dry ice and stored at −80 °C.

TH was measured according to methods of Jakowec et al. [57]. Briefly, tissue samples were homogenized in buffer (25 mM Tris–HCl, pH 7.4;

150 mM NaCl; 1 mM EDTA; 100 μM phenylmethylsulfonyl fluoride). Relative expression of proteins for TH (58 kDa) and beta-tubulin (50 kDa, as loading control) were analyzed by Western immunoblot [58] using commercially-available primary antibodies (TH: mouse monoclonal, Millipore, Temecula, CA; beta-tubulin: rabbit polyclonal, LI-COR Biosciences, Lincoln, NB). Protein bands were visualized by affinity purified goat anti-rabbit or anti-mouse secondary antibodies conjugated to $IRDye_{680}$ or $IRDye_{800}$ (Rockland, Gilbertsville, PA). Fluorescent signal was detected by scanning the membrane in a LI-COR Odyssey near infrared imaging platform and quantified using Odyssey 3.0 software (LI-COR Biotechnology, Lincoln, NE). The ratio of TH to beta-tubulin in testosterone-treated rats is shown as relative expression levels compared with the vehicle group (set to 100%).

Aggressive behavior and TH in testosterone- and vehicle-treated males were compared by Student's *t*-test. Operant responses in the delay-discounting procedure were compared by repeated measures analysis of variance (RM-ANOVA). For all statistical tests, significance was set at $p<0.05$.

3. Results

3.1. Aggressive motivation

Fig. 1 shows operant responding for access to an intruder, and aggressive behavior when the intruder was introduced into the test rat's home cage. As the FI increased during initial training (Fig. 1A), vehicle- and testosterone-treated rats increased the number of nose-pokes for access to the intruder. Once operant responding stabilized after 8 days of testing at FI10, there was no difference in response rates between vehicle- (32.4 ± 7.0 nose-pokes/10 min) and testosterone-treated rats (28.4 ± 1.6, $p>0.05$). Overall operant responding for an aggressive encounter was similar to that reported previously for mice [43].

Nonetheless, compared with vehicle-treated rats, testosterone-treated rats were more aggressive towards intruders. This replicates previous findings that chronic high-dose androgens increase aggression in males [38–42]. During 5 min with the intruder, testosterone-treated males made more attacks (6.3 ± 1.3) with a shorter latency (73.6 ± 22.7 s) compared to vehicle-treated males (2.4 ± 0.8 and 157.0 ± 33.1 s, $p<0.05$). However, there was no correlation in individual animals between aggressive behavior and aggressive motivation measured by operant behavior.

Although testosterone-treated males showed more agonistic behavior, they spent significantly less time in contact with the intruder male (46.8 ± 5.3% of 5-min test, vs 65.0 ± 6.3% for vehicle-treated males, $p<0.05$), and more time self-grooming (3.8 ± 0.7% vs 1.4 ± 0.5%, $p<0.05$). The number of contact bouts did not differ between testosterone-treated (19.7 ± 1.4 bouts/5 min) and vehicle-treated males (18.0 ± 1.5 bouts/5 min, $p>0.05$). However, for testosterone-treated males, the average duration of each bout was shorter (7.1 ± 0.8 s vs 11.6 ± 1.7 s for vehicle controls, $p<0.05$).

3.2. Impulsivity

Fig. 2 presents body weight, food intake, and operant responses measured during testing with the delay-discounting procedure. Body weights and food intake (either during daily testing or over 24 h) did not differ between testosterone- and vehicle-treated rats. Rats received 17.6 ± 1.1% of their total daily food intake (33.3 ± 1.9 g) during the 56-min test for impulsivity. Similarly, the number of unreinforced trials (in which the rat made no response on either lever within 10 s) was not different between the two groups. In each daily test, only 9.8 ± 3.8% (vehicle) and 6.0 ± 1.5% (testosterone) of 40 trials were unreinforced.

Fig. 3 illustrates the likelihood of selecting the large reward with an increasing delay (0, 15, 30 or 45 s). When no delay was imposed,

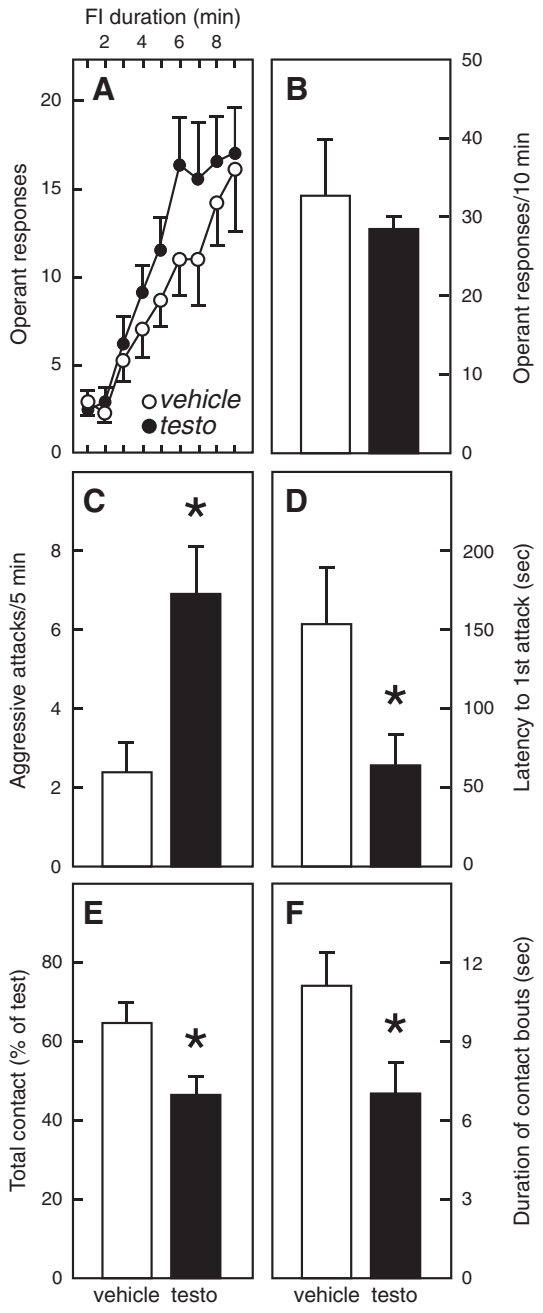

Fig. 1. Top: Operant responses (mean ± SEM) under a fixed-interval (FI) schedule for access to an unfamiliar intruder in a resident–intruder test of aggression in Long–Evans male rats treated chronically with testosterone (*closed symbols*) or vehicle (*open symbols*). Operant behavior during initial training (A), and at the end of the study (B). Middle: Aggressive behavior towards the intruder, measured as the number of attacks (C) and latency to the first attack (D). Bottom: Contact with the intruder, measured as total contact (E) and duration of individual contact bouts (F). *Asterisks* indicate significant differences between treatment groups.

both testosterone- and vehicle-treated rats strongly favored the large reward (92.0 ± 3.4% and 92.3 ± 1.8% of 10 trials, respectively). As the delay to receive the 4-pellet reinforcement increased, selection of the large reward diminished. With a 45-s delay, vehicle-treated rats selected the large reward in only 24.6 ± 5.1% of trials, while testosterone-treated rats chose the large reward in 44.9 ± 7.2%. By RM-ANOVA, there was a significant effect of treatment [$F_{(1,14)}=6.50$, $p<0.05$] and delay [$F_{(1,14)}=126.72$, $p<0.05$], as well as a treatment × delay interaction [$F_{(1,14)}=7.51$, $p<0.05$]. As for aggressive behavior, there was no correlation in individual animals between

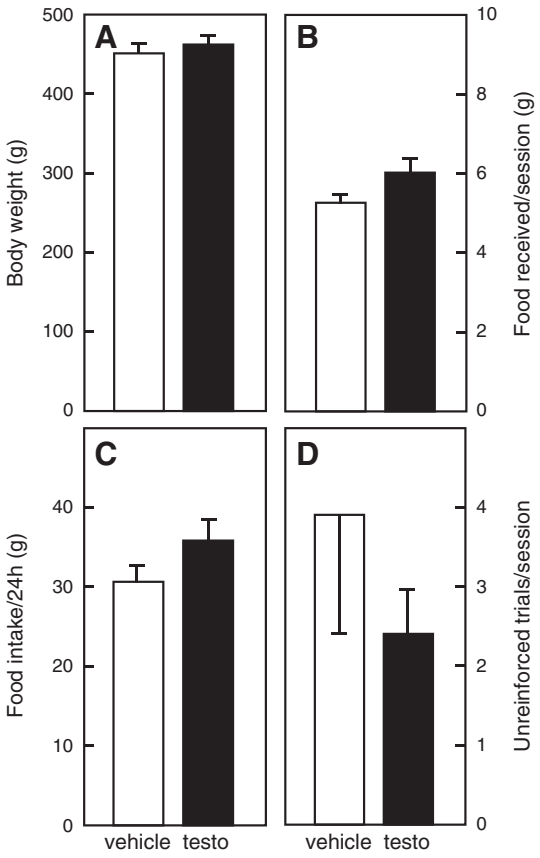

Fig. 2. Physiologic and behavioral measures during a test of delay-discounting for food to assess impulsive behavior. Compared with vehicle-treated rats (*open bars*), there was no effect of testosterone (*closed bars*) on body weight (A), food received during the delay-discounting test (B), 24-hour food intake (C), or the percent of unreinforced trials (D).

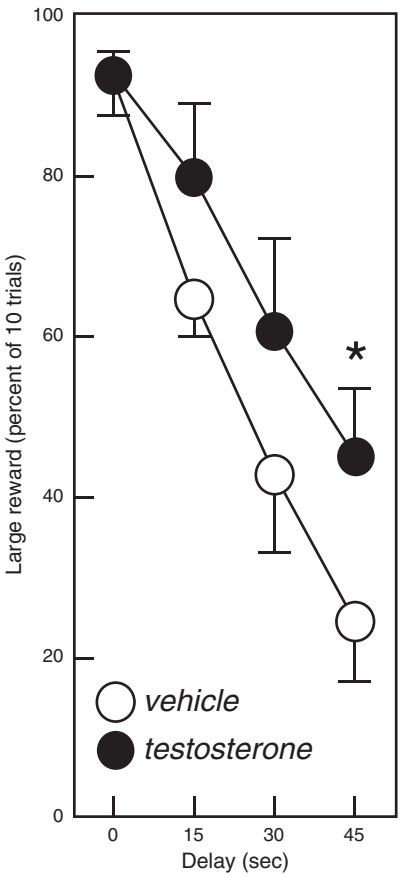

Fig. 3. Preference for a large food reward across an increasing time delay under a delay-discounting test in Long–Evans male rats. Compared with vehicle-treatment (*open circles*) testosterone treatment (*closed circles*) increased preference for the larger reward at longer delay intervals. *Asterisks* indicate significant differences between treatment groups.

aggression (number of fights) and impulsive behavior (selection of large reward at 45 s delay).

3.3. Brain levels of TH

As shown in Fig. 4, testosterone treatment had no significant effect on TH levels measured by Western immunoblot analysis in Acb (106.2 ± 13.6%), PFC (97.6 ± 6.1%) or VTA/SN (105.1 ± 7.4%) as a percent of control values. However, TH was significantly lower in CPu of testosterone-treated rats (76.9 ± 3.1%, $p < 0.05$) compared with vehicle controls.

4. Discussion

Results of the present study support previous studies from different species (reviewed in [59]) that chronic high-dose androgens enhance aggression. Our study investigated potential underlying causes of this increase in agonistic behavior. Specifically, we hypothesized that testosterone stimulated either aggressive motivation and/or impulsive behavior. Instead, there was no effect of testosterone on operant responses to gain access to an intruder under an FI schedule of reinforcement. This suggests that the motivation to engage in aggression was unaffected by testosterone. Since aggressive behavior was significantly enhanced in testosterone-treated rats, our results further indicate that testosterone's effects on appetitive and consummatory aspects of agonistic behavior are not necessarily linked. In a subsequent test of impulsivity with the delay-discounting test for food, rats treated with testosterone were more likely than vehicle controls to select the lever associated with a larger delayed reward compared with the lever delivering a smaller immediate reward. Preference for the large reward was not due to increased food intake resulting from anabolic effects of testosterone, since both groups had similar body weights and consumed similar amounts of food. Rather than increasing impulsive behavior, our data suggest that testosterone reduces impulsive choice. Measurement of TH in brain regions associated with reward (Acb, VTA/SN) and executive function (PFC) support the foregoing behavioral observations. Testosterone had no effect on TH levels in Acb, PFC, or VTA/SN. However, TH protein levels were reduced in CPu, which could contribute to behavioral disinhibition.

As a model for AAS abuse, the present study exposed male rats to chronic high-dose testosterone beginning in adolescence. High-dose testosterone in male adolescents offers parallels with patterns of human use, and has a precedent in animal studies. While media attention focuses on steroid use among elite athletes, it appears that an adolescent male taking high doses of testosterone reflects a "typical" pattern of human AAS use. The majority of users are men. Among American high school students, 4–6% of men have used AAS vs 1–2% of women [60]. Although we have shown that female hamsters voluntarily self-administer testosterone at rates comparable to males [24], males are still a more relevant model for human users. As with other illicit drugs, AAS abuse is a problem of adolescence. Steroid use peaks at 18 years of age [61], coincident with the peak in endogenous testosterone production. Similarly, in animal studies testing AAS effects on mating and aggression, the majority have been conducted in adolescent males [38–42,62]. Due to the extended requirements for training and test in the present study, aggressive motivation and impulsivity were tested in adulthood.

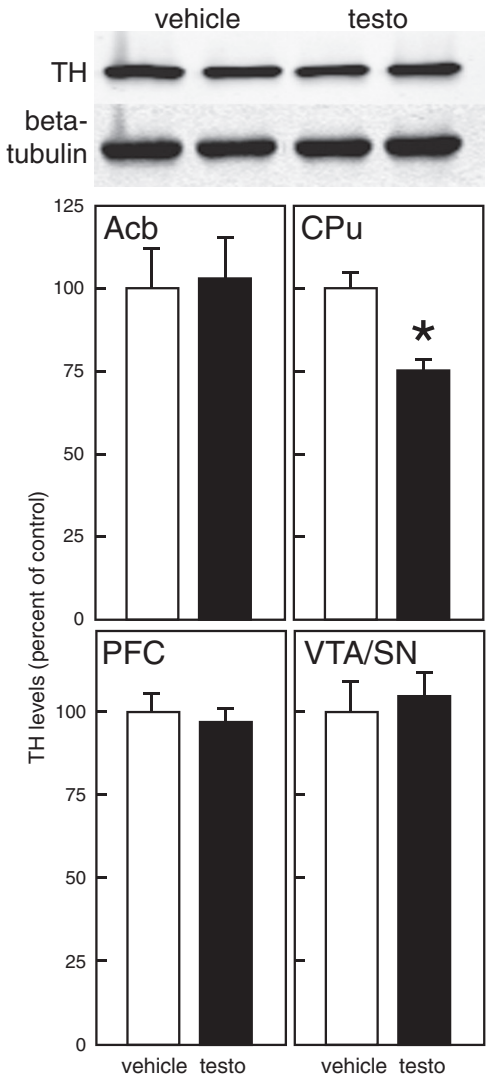

Fig. 4. Top: Western blot assays of tyrosine hydroxylase (TH) and beta-tubulin in caudate-putamen from representative Long–Evans male rats (n = 2 each) treated chronically with vehicle (left) or testosterone (right). Bottom: Levels of TH in microdissected brain regions from testosterone- (*closed bars*) or vehicle-treated rats (*open bars*). ACB: nucleus accumbens, CPu: caudate-putamen, PFC: medial prefrontal cortex, VTA/SN: ventral tegmental area/substantia nigra. *Asterisks* indicate significant differences between treatment groups.

However, rats were exposed to high-dose testosterone continuously since adolescence.

For AAS treatment, rats in the present study received testosterone. Testosterone is the prototypical AAS, both for its popularity and for its chemical structure. All AAS are derived from testosterone. Furthermore, testosterone remains the most popular choice for human users, typically in the form of long-acting esters such as testosterone propionate. In 2006, testosterone was the most-common banned substance detected in urine tests at World Anti-Doping Agency-accredited laboratories, representing 26% of all "adverse analytical findings"; nandrolone was 4th at 5.5% [63]. Similarly, testosterone accounted for 34% of AAS-positive urine tests at the 2000 Sydney Olympic Games; nandrolone was detected in 32% [64]. Testosterone esters are popular among elite athletes because of the difficulties in identifying exogenous sources vs naturally-occurring endogenous production. They are popular among more casual users because of their low price and ready availability.

In the present study, it was reasonable to expect a synergistic effect of aggression and testosterone because winning a fight and androgens are each reinforcing [43–45,59]. Instead, our hypothesis was not supported: testosterone increased expression of agonistic behavior without altering the motivation to engage in aggression. Similar findings have been observed with alcohol, allopregnanolone and the benzodiazepine midazolam in mice [43,65,66]. It has been suggested that these $GABA_A$ agonists increase fighting by compromising the termination of an aggressive bout. In the present study, this explanation does not account for the reduced latency to initiate fighting.

Naturally, there are caveats. Previous studies have shown that endogenous androgen production increases in expectation of competition (the challenge hypothesis [67]), and as a result of success in competition (the winner effect [68]). Accordingly, it is likely that endogenous androgens increased in both vehicle- and testosterone-treated rats due to agonistic encounters with the intruders. Even so, the increase in endogenous androgens is both limited and transient compared with the daily supraphysiologic injections of testosterone used here. Secondly, our study focused on males favored to win in agonistic encounters: residents fighting unfamiliar intruders. What is the relationship between androgens, motivation, and losing fights? In other words, does chronic androgen exposure enhance motivation to engage in agonistic behavior, even when losing is inevitable? A recent report suggests that adolescent AAS treatment selectively eliminates submissive behaviors [62]. Future studies could explore the effects of testosterone on intruder males. However, this is somewhat more challenging because intruder males treated with testosterone may win fights, thereby complicating data interpretation. Finally, testosterone may alter a variety of responses aside from motivation that modify social behavior. Users describe feelings of power and invincibility. This suggests that AAS may alter assessment of risk. This could be investigated using tests of conditioned fear and response to novel object in rats treated with high-dose testosterone.

The reduction in impulsivity for testosterone-treated rats in the delay-discounting test for food reward was also unexpected. However, this finding is nonetheless significant because it refutes one of the most persistent myths about 'roid rage. There is a common misconception that steroids cause a loss of control. In the aftermath of Chris Benoit's double murder-suicide in 2007, WWE, Inc. released a press statement reading in part, "The physical findings announced by authorities indicate deliberation, not rage". This implies that AAS-induced aggression is an uncontrolled response, and that AAS could not have been a contributing factor. Instead, testosterone-treated rats in the present study were more willing than vehicle controls to wait for a larger reward than to settle for a small reward without a delay. Furthermore, we found no correlation between aggressive and impulsive behavior in individual rats. This finding stands in contrast with a study in Syrian hamsters in which highly-aggressive males tested in a delay-discounting procedure were more likely than less-aggressive males to select the small, immediate reward [69]. It may be that impulsivity is common among males selected for high expression of offensive aggressive behavior. Our study would suggest that, unlike aggression, impulsive behavior is not necessarily induced by androgen treatment.

Studies in several rodent species have demonstrated an increase in aggression in response to AAS, see [59]. It has been suggested that the home cage-intruder test most often employed in these studies is a model of offensive aggression, similar to reactive aggression in humans [70]. Reactive aggression has elements of impulsivity and emotionality, while proactive aggression is more premeditated [71]. In the present study, operant responding for access to an intruder could reflect elements of proactive aggression, while impulsivity in the delay-discounting test might correlate with reactive aggression. An early social deprivation model in rats which induces high levels of aggression also demonstrates more attacks towards vulnerable body targets (head, throat, belly) [72]. This has been suggested to reflect proactive aggression. The effects of AAS on attack targets remain to be determined. Although our study did not find evidence of impulsivity for food reward, testosterone-treated males did

demonstrate short-duration contact bouts, similar to male hamsters selected for high aggression [69]. This could reflect evidence of reactive aggression.

Previous studies of AAS-induced aggression in rats do not support a loss of control. McGinnis et al. [39] noted that AAS-induced aggression is not indiscriminate and unprovoked, but that treated rats remained sensitive to the context (location, opponent) of the encounter. Testosterone-treated males do not attack females [41]. Even when stimulated by tail pinch, they only attack anestrous females [42]. Similarly, they are more aggressive towards gonad-intact males than castrates, and in a home cage setting vs a neutral arena [73]. Other studies have found no effect of gonadectomy on impulsive behavior in rats [74], or individual correlation of endogenous testosterone with impulsivity in humans [75–77]. It is worth noting that these studies focused on physiologic androgen levels. At pharmacologic doses, mechanisms of androgen action are not necessarily the same.

Measurement of TH in Acb, VTA/SN and PFC supports our behavioral observations. A large body of evidence demonstrates the important role for DA in motivation and executive function, and TH is a well-established marker for DA synthetic capacity [46,48,49]. That testosterone failed to alter TH levels in these brain regions is consistent with the failure to stimulate aggressive motivation or impulsivity. It is important to mention that DA in the anterior hypothalamus is androgen-sensitive, and has been strongly implicated in the expression of agonistic behavior in both rats and hamsters [47]. These effects are mediated via the DA D2 receptor, which is also upregulated by AAS. Hypothalamic TH levels were not measured in the present study, which focused on aggressive motivation, rather than expression of agonistic behavior per se. Finally, the testosterone-induced reduction in TH in CPu bears some consideration. DA in CPu contributes to habit learning and motor patterning, and testosterone may modulate these behaviors. In particular, dysfunction in the caudate nucleus has been implicated in poor response inhibition in children with attention-deficit hyperactivity disorder (see [78]). Accordingly, it is tempting to speculate that, via a reduction in DA in CPu, testosterone may increase fighting through a selective failure to inhibit behavioral responses. This hypothesis remains to be tested.

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