Psychoneuroendocrinology (2014) 40, 201–212

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/psyneuen

Testosterone enhances risk tolerance without altering motor impulsivity in male rats

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Received 25 July 2013; received in revised form 21 November 2013; accepted 21 November 2013

KEYWORDS
Anabolic agents;
Risk;
Reward;
Punishment;
Response inhibition;
Go/no-go

Summary Anabolic–androgenic steroids (AAS) increase impulsive and uncontrolled aggressive ('roid rage) in humans and enhance agonistic behavior in animals. However, the underlying mechanisms for AAS-induced aggression remain unclear. Potential contributing elements include an increase risk-taking and/or motor impulsivity due to AAS. This study addressed the effects of chronic high-dose testosterone on risk tolerance using a risky decision-making task (RDT) and motor impulsivity with a go/no-go task in operant chambers. Male Long–Evans rats were treated for at least 4 weeks with testosterone (7.5 mg/kg) or vehicle beginning in late adolescence. Testosterone was used because it is popular among human AAS users. In RDT testing, one lever was paired with delivery of a small "safe" food reward, while the other was paired with a large "risky" reward associated with an increasing risk of footshock (0%, 25%, 50%, 75%, 100%) in successive test blocks. Three shock intensities were used: 1.0, 1.2, and 1.4 mA/kg. As shock intensity and risk of shock increased, preference for the lever signifying a large reward significantly declined for both vehicle- and testosterone-treated rats ($p < 0.05$). There was also a significant effect of drug ($p < 0.05$), where testosterone-treated rats showed greater preference for the large reward, compared to vehicle-treated controls. Increased preference for the large reward, despite risk of footshock, is consistent with increased risk tolerance. In go/no-go testing, rats were trained to press a single lever if the go cue was presented (stimulus light) or to refrain from pressing during the no-go cue (tone). There was no effect of testosterone on pre-cue responses, or performance in go and no-go trials. These results suggest that AAS may increase risk-tolerance without altering motor impulsivity.

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0306-4530/$ – see front matter
http://dx.doi.org/10.1016/j.psyneuen.2013.11.017

1. Introduction

Anabolic–androgenic steroids (AAS) are derivatives of testosterone used by athletes at all levels, from casual to elite competitors, to increase muscle-mass and improve performance. Recently, there is concern about negative psychological side-effects of AAS abuse (Kanayama et al., 2009). In particular, AAS can increase aggression in humans and animals, with manic-like episodes of anger ('roid rage) (Schulte et al., 1993; Breuer et al., 2001; Midgley et al., 2001; Farrell and McGinnis, 2003; Pagonis et al., 2006). However, underlying mechanisms for AAS-induced aggression remain unclear. In humans, aggression has been classified as hostile (impulsive, with intent to injure) or instrumental (premeditated, with intent for personal benefit; Ramirez and Andreu, 2006). In AAS users, 'roid rage encompasses irritability, impaired judgment, and feelings of invincibility (Katz and Pope, 1990). This is consistent with hostile, impulsive aggression. Conversely, endogenous testosterone in humans correlates with power motivation and risk-taking in economic and social domains (reviewed in Wood and Stanton, 2012), which would reflect instrumental aggression. Furthermore, to understand how AAS may promote hostile and instrumental aggression, it is difficult to rule out the possibility that AAS users might have a predisposition toward impulsivity and risk-taking. Therefore, the present study investigated the effects of AAS on impulsive behavior and risk assessment in a rodent model. In particular, because impulsive behavior is multifaceted (Winstanley, 2011), we have focused here on motor impulsivity and risk-taking in response to punishment. Male rats were exposed chronically to high-dose testosterone as young adults and behavior was evaluated by established methods using operant responding for food to measure risk tolerance (Simon et al., 2009; Simon and Setlow, 2012) and motor impulsivity (Fardell et al., 2010; Moschak and Mitchell, 2012).

High-dose testosterone treatment in young adult male rats offers parallels with human use, and has a precedent in animal studies. While media attention focuses on 'designer' steroids used by elite athletes, it appears that a young adult male taking exogenous testosterone reflects a more typical AAS user. The majority of users are men: among American high school students, 4–6% of men have used AAS vs 1–2% of women (Bahrke and Yesalis, 2004). AAS abuse frequently begins in the early 20s (Pope et al., 2013), coincident with the peak in endogenous testosterone production. Many animal studies of AAS on mating and aggression have used adolescent males (Farrell and McGinnis, 2004; McGinnis, 2004; Cunningham and McGinnis, 2006).

Testosterone is used here because it is the prototypical AAS, both for its popularity and for its chemical structure. All AAS are derived from testosterone. Furthermore, testosterone remains a frequent choice for human users, typically in the long-acting forms such as testosterone propionate (Summers, 2003). In 2011, testosterone was the most-common 'adverse analytical finding' in urine tests at World Anti-Doping Agency laboratories (WADA, 2012). Testosterone is also popular among rank-and-file users because of its low price and ready availability (Wood and Stanton, 2012). Most AAS users do not limit themselves to a single dose or a single type of steroid (Summers, 2003). Instead, users combine different steroids (''stacking'') in cycles of increasing and decreasing concentrations. AAS stacks also include non-steroidal drugs to counteract side effects (aromatase inhibitors, estrogen receptor antagonists), to enhance fat and water loss (diuretics, thyroid hormones, β2 adrenergic receptor agonists) and to reactivate endogenous steroidogenesis at the end of a cycle (gonadotropins). While testing AAS stacks is clinically relevant, it becomes difficult to evaluate the contributions of any individual element in the stack. To focus and simplify these studies, treatment was limited to one androgen at a single, consistent dose.

Impulsivity incorporates at least three components including impatience, reduced response inhibition (motor impulsivity), and increased risk-taking (Evenden, 1999; Eagle and Baunez, 2010; Winstanley, 2011). Methods in animals using operant responding for food reward have been developed to individually evaluate these behaviors. For impatience, delay-discounting measures preference for a large reward despite delays in delivery. Stop-signal reaction time and go/no-go tasks measure response inhibition: the ability to inhibit a planned action. The rodent gambling task (rGT) and risky decision-making task (RDT) estimate risk-taking, where the risk is either punishment (footshock in RDT) or absence of reward (rGT).

A recent study from our laboratory (Wood et al., 2013) showed that testosterone treatment at pharmacologic doses in male rats decreased impulsive behavior in a delay-discounting task (Winstanley et al., 2006). Compared with controls, testosterone-treated rats showed greater preference for a large delayed reward. While testosterone may not increase impatience, it could affect other aspects of impulsivity. Thus, the present study investigated testosterone's effects on risk-taking with RDT (Simon et al., 2009; Simon and Setlow, 2012) and response inhibition using the go/no-go task (Fardell et al., 2010; Moschak and Mitchell, 2012). Our hypothesis is that chronic high-dose testosterone increases impulsive behavior by increasing risk tolerance and impairing response inhibition.

2. Methods

2.1. Animals

Male Long–Evans rats (Charles River Laboratories, Wilmington, MA) were individually housed under a reversed 14L:10D photoperiod. RDT was tested in 10 vehicle- and 10 testosterone-treated rats. The go/no-go test included a separate group of 8 vehicle-treated rats and 10 rats treated with testosterone. All rats remained gonad-intact to approximate AAS use in humans. Injection, training and testing were conducted 5×/week under dim illumination during the first 4 h of the dark phase. To facilitate operant responding, rats were weighed daily and food availability was adjusted to maintain a slow rate of growth (1–2 g/day). Experimental procedures were approved by USC's Institutional Animal Care and Use Committee and were conducted in accordance with the Guide for the Care and Use of Laboratory Animals, 8th Ed. (National Research Council, National Academies Press, Washington, DC, 2011).