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Anabolic—androgenic steroids and decision making: Probability and effort discounting in male rats

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Abstract Anabolic—androgenic steroid (AAS) abuse is implicated in maladaptive behaviors such as increased aggression and risk taking. Impaired judgment due to changes in the mesocorticolimbic dopamine system may contribute to these behavioral changes. While AAS are known to influence dopamine function in mesocorticolimbic circuitry, the effects on decision making are unknown. This was the focus of the present study. Adolescent male Long-Evans rats were treated chronically with high-dose testosterone (7.5 mg/kg) or vehicle (13% cyclodextrin in water), and tested for cost/benefit decision making in two discounting paradigms. Rats chose between a small reward (1 sugar pellet) and a large discounted reward (3 or 4 pellets). Probability discounting (PD) measures sensitivity to reward uncertainty by decreasing the probability (100, 75, 50, 25, 0%) of receiving the large reward in successive blocks of each daily session. Effort discounting (ED) measures sensitivity to a work cost by increasing the lever presses required to earn the large reward (1, 2, 5, 10, 15 presses). In PD, testosterone-treated rats selected the large/uncertain reward significantly less than vehicle-treated controls. However, during ED, testosterone-treated rats selected the large/high effort reward significantly more than controls. These studies show that testosterone has divergent effects on different aspects of decision making. Specifically, testosterone increases aversion to uncertainty but decreases sensitivity to the output of effort for reward. These results have implications for understanding maladaptive behavioral changes in human AAS users.

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1. Introduction

Anabolic—androgenic steroids (AAS) are drugs of abuse used by athletes to increase muscle mass and enhance athletic performance. While media attention focuses on steroid use among elite athletes, the use of AAS is far more widespread. As many as 4 million Americans have used AAS (Pope et al., 2013). AAS are in high schools, fitness centers, and ''rejuvenation'' clinics. A typical AAS user is a young man in his late teens or early 20s (Pope et al., 2014). Among U.S. high school students, 4—6% of boys have used AAS (Johnston et al., 2013), comparable to the rates of crack cocaine or heroin use. It is estimated that AAS use among men in their 20s is even higher (Pope et al., 2013).

Emerging evidence highlights a range of adverse health effects from chronic AAS abuse, including cardiovascular, hepatic, reproductive and psychiatric dysfunction (Pope et al., 2014). Indeed, as many one third of AAS users meet DSM criteria for psychoactive substance dependence (Pope et al., 2013). Furthermore, AAS users have higher mortality rates than the general population, often due to suicide or homicide (Thiblin et al., 2000). In this regard, AAS use is associated both with depression and anxiety (Perry et al., 1990), as well as increased aggression, commonly known as '''roid rage'' (Hall et al., 2005). Thus, a key danger of AAS abuse reflects the likelihood that users will engage in behaviors that pose risks to themselves and to those around them. In a study of American high-school students, AAS use was associated with risky sex, drinking and driving, carrying a weapon, and not wearing a helmet or seat belt (Middleman et al., 1995). Psychological evaluations of human users have also implicated AAS in impaired decision making stemming from feelings of invincibility (Pope and Katz, 1990). To evaluate decision-making ability under the influence of AAS, the present study tested cost/benefit tasks of probability and effort in male rats treated chronically with high-dose testosterone beginning in adolescence. Cost/benefit decision making depends on prefrontal cortical (PFC)-striatal circuitry (Floresco et al., 2008a), that develops during adolescence (Blakemore and Robbins, 2012). AAS perturb dopamine (DA) function in this system (Kindlundh et al., 2001; Kurling-Kailanto et al., 2010; Wood et al., 2013), and have the strongest behavioral effects when introduced in adolescence (Salas-Ramirez et al., 2008). Therefore, chronic high-dose testosterone exposure beginning in adolescence has potential to alter decision making behavior.

To test decision making, discounting paradigms require subjects to choose between two rewards: a small ''safe'' reward, and a large reward that is ''discounted'' or made less desirable by pairing with a cost such as delay, effort, uncertainty, or punishment. In a test of punishment discounting, we have demonstrated that testosterone-treated rats are more likely than controls to choose a large reward paired with a footshock over a small reward with no shock (Cooper et al., 2014). Similarly, testosterone-treated rats are more willing to wait for a large/delayed reward compared to vehicle-treated controls (Wood et al., 2013). The present study investigated the effects of chronic high-dose testosterone on response to uncertainty (probability discounting; PD) and physical effort (effort discounting; ED). In PD, rats chose between a small/certain reward and a large/uncertain reward delivered with decreasing probability. Endogenous testosterone levels in humans correlate with increased risk taking under uncertainty in both the Iowa Gambling Task (Stanton et al., 2011) and the stock market (Coates and Herbert, 2008). Therefore, we hypothesized that AAS would increase risk taking during PD, by increasing selection of the large/uncertain food reward. ED tests a subject's willingness to exert physical effort to obtain reward. In ED, rats choose between a small/low effort reward and a large/high effort reward. This ED paradigm is relevant to human AAS users, as body builders and athletes expend tremendous physical effort in pursuit of their aesthetic and athletic goals. Thus, we expected that testosterone-treated rats would be willing to work harder to obtain food reward, reflecting decreased sensitivity to effort.

2. Methods

2.1. Animals

Male Long-Evans rats (5 weeks of age at the start, Charles River Laboratories, MA) were pair-housed under a reversed 14L:10D photoperiod. 42 rats were treated with testosterone or vehicle, and were trained and tested for PD (vehicle: $n = 12$; testosterone: $n = 11$) or ED (vehicle: $n = 10$; testosterone: $n = 9$). All behavior was tested during the first 4 h of the dark phase. To approximate AAS use by humans, rats remained gonad-intact. As in our previous studies (Cooper et al., 2014), rats were food-restricted to maintain a slow rate of growth (3—4 g/day) and facilitate operant responding. Body weights in testosterone- and vehicle-treated rats did not differ at the start of the study (vehicle: 139.2 ± 1.6 g, testosterone: 138.5 ± 1.4 g) or throughout behavioral training and testing. 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; National Research Council (US), 2011).

2.2. AAS treatment

Beginning at least 2 weeks prior to behavioral training, rats received daily sc injections of testosterone (7.5 mg/kg; Steraloids, RI) or aqueous vehicle [3% ethanol and 13% cyclodextrin (RBI, MA)] 5 d/week. Testosterone is the prototypical AAS, and is the most common performance-enhancing substance (55.5%) detected in urine tests by World Anti-Doping Agency-accredited laboratories (WADA, 2012). The 7.5 mg/kg dose is equivalent to the doses used by humans to enhance performance, and has previously been used to test the effects of AAS on decision making and cognition in rats (Cooper et al., 2014; Wood et al., 2013; Wallin and Wood, 2015). Daily injections were administered early in the dark phase, immediately prior to behavioral training and testing. Importantly, although testosterone treatment was initiated during adolescence at 5 weeks of age (Spear, 2000), behavioral testing was not complete until rats had reached young adulthood, at least 14 weeks of age.