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Cognitive deficits in long-term anabolic-androgenic steroid users

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ABSTRACT

Background: Millions of individuals worldwide have used anabolic-androgenic steroids (AAS) to gain muscle or improve athletic performance. Recently, in vitro investigations have suggested that supraphysiologic AAS doses cause apoptosis of neuronal cells. These findings raise the possibility, apparently still untested, that humans using high-dose AAS might eventually develop cognitive deficits.
Methods: We administered five cognitive tests from the computerized CANTAB battery (Pattern Recognition Memory, Verbal Recognition Memory, Paired Associates Learning, Choice Reaction Time, and Rapid Visual Information Processing) to 31 male AAS users and 13 non-AAS-using weightlifters age 29–55, recruited and studied in May 2012 in Middlesbrough, UK. Testers were blinded to participants' AAS status and other historical data.
Results: Long-term AAS users showed no significant differences from nonusers on measures of response speed, sustained attention, and verbal memory. On visuospatial memory, however, AAS users performed significantly more poorly than nonusers, and within the user group, visuospatial performance showed a significant negative correlation with total lifetime AAS dose. These were large effects: on Pattern Recognition Memory, long-term AAS users underperformed nonusers by almost one standard deviation, based on normative population scores (adjusted mean difference in z-scores = 0.89; $p = 0.036$), and performance on this test declined markedly with increasing lifetime AAS dose (adjusted change in z-score = −0.13 per 100 g of lifetime AAS dose; $p = 0.002$). These results remained stable in sensitivity analyses addressing potential confounding factors.
Conclusions: These preliminary findings raise the ominous possibility that long-term high-dose AAS exposure may cause cognitive deficits, notably in visuospatial memory.

1. Introduction

The anabolic-androgenic steroids (AAS) are a group of hormones, comprising testosterone and its synthetic relatives, which permit users to greatly increase their muscle mass and improve athletic performance (Kanayama et al., 2010; Sjoqvist et al., 2008). Prior to the 1980s, AAS use was largely restricted to elite athletes, but in recent decades these drugs have spread to the general population, and have now emerged as a major new form of substance abuse throughout the Western world (Kanayama et al., 2008). Importantly, recent studies suggest that as many as 30% of AAS abusers may develop an AAS dependence syndrome, characterized by prolonged use of these drugs, sometimes for many years, at doses 10–100 times the normal endogenous male output of testosterone (Kanayama et al., 2009a). The eventual public health consequences of such high-dose AAS exposure are still largely unknown, because most AAS users in the general population did not begin using these drugs until after 1980. Thus the oldest of these users – those who started AAS as youths in the 1980s – are only now reaching middle age and entering the age of risk for adverse effects of long-term use (Kanayama et al., 2008).

Pending larger clinical studies of this first wave of aging AAS users, one can look to laboratory data for evidence as to where AAS toxicity might manifest itself in humans. Among these data are findings that supraphysiologic concentrations of testosterone and other AAS can induce apoptosis in many types of mammalian cells, including myocardial (Fanton et al., 2009; Riezzo et al., 2011; Zaugg et al., 2001), skeletal muscle (Abu-Shakra et al., 1997), endothelial (D'Ascenzo et al., 2007), and neuronal cells (Estrada et al., 2006). Of particular concern among these studies is one report demonstrating apoptosis of human neuroblastoma cells in vitro after only 6–12 h of exposure to testosterone concentrations as low as 1 μM (Estrada et al., 2006). This study demonstrated decreased cell viability cause by testosterone-induced activation of the apoptotic program, as evidenced by increased numbers of annexin

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V-positive cells, DNA fragmentation, and caspase activation. These changes were likely initiated by a marked and sustained increase in intracellular calcium, which in turn appeared to be mediated by testosterone's effects on inositol 1,4,5-triphosphate-sensitive calcium release channels. Since testosterone concentrations of 1 μM and above are within the range plausibly attainable by human AAS abusers, the investigators speculated that long-term AAS abuse might lead to irreversible cognitive deficits.

More recently, two other groups have also demonstrated neurotoxic effects in mammalian neuronal cells exposed to AAS concentrations within the probable human-abuse range (Caraci et al., 2011; Cunningham et al., 2009). One of these groups (Caraci et al., 2011) additionally demonstrated that nandrolone and methandrostenolone, two widely abused AAS, appeared to potentiate the apoptotic stimulus provided by beta-amyloid, the likely principal culprit in Alzheimer's disease. These investigators also speculated that AAS abuse might facilitate the onset or progression of neurodegenerative diseases.

Although AAS can certainly precipitate acute psychiatric effects in some individuals (Hall et al., 2005; Kanayama et al., 2010), we are not aware of any reports of AAS-induced neurodegenerative diseases in humans. If supraphysiologic AAS exposure can cause such diseases, why would this not already have been witnessed? In response, it must be remembered that most of the world's illicit AAS users are still under age 50, as just explained. Therefore, these men might have incurred neurotoxic effects, but still be too young to exhibit gross cognitive or motor deficits. Admittedly, there are some men over age 50 who used AAS when competing in elite athletics or bodybuilding before the 1980s. However, the AAS doses used in that era were typically lower than those used today (Duchaine, 1981), and thus perhaps less likely to induce neurotoxicity. Therefore, it remains plausible that human AAS-induced neurotoxicity could be a genuine phenomenon that has simply not yet emerged into view.

Laboratory test data from an ongoing study at our center raise further concern about the vulnerability of AAS abusers. In 11 sequential men currently injecting testosterone, we found a mean (SD) serum testosterone level of 6401 (5448) ng/dL, with one man reaching 20,300 ng/dL (normal range in our laboratory 175–781 ng/dL). Importantly, these levels substantially *underestimated* the men's total burden of AAS, since most were taking other AAS simultaneously with testosterone at the time of evaluation. These observations demonstrate that human abusers can achieve total serum AAS levels at least 50 times average physiologic levels. Given that the above in vitro studies found some neuronal apoptotic effects of AAS at even 10–20 times physiologic concentrations, after only 6–48 h of exposure, the possibility of clinically significant neurotoxicity in long-term human AAS abusers cannot be dismissed.

In a pilot study to explore this possibility, we administered a battery of cognitive tests to male AAS users and to comparison weightlifters reporting no AAS use.

2. Methods

2.1. Study participants

We recruited male weightlifters age 29–55 in Middlesbrough, England, a city with a high prevalence of AAS users where we have previously conducted research (Pope et al., 2010). Participants were recruited by one of the investigators (JK) from among clients of Lifeline Middlesbrough, a charitable organization providing needle exchange facilities and counseling for drug users, and by advertising in local gymnasia for experienced weightlifters, using methods previously described (Kanayama et al., 2009b, 2003; Pope et al., 2012, 2010). We chose a minimum age of 29 in order to favor individuals with long-term AAS use, and hence presumably at greater risk for AAS-induced cognitive effects if they existed. We imposed no other formal inclusion or exclusion criteria, but for the purposes of this pilot investigation, the recruiter attempted to enrich the sample with men likely to fall at opposite ends of the distribution of AAS exposure (i.e., men with very long-term AAS use and men with no AAS use at all). Participants were compensated £50 (approximately $80 US). All participants were recruited and evaluated within the month of May 2012.

2.2. Study evaluation

Upon arriving for evaluation, all participants signed written informed consent for the study, which was approved by the McLean Hospital Institutional Review Board. Participants then received (1) an interview administered by one of the investigators (JK) and (2) a computerized battery of cognitive tests administered by two of the other investigators (GK and HGP). The interviewer and the testers remained blinded to each others' findings until both evaluations were completed. Thereafter, blindness was broken, and the interview results were reviewed with the participant by the senior investigator (HGP) to clarify any questions about history of AAS and other substance use, as well as medical or psychiatric conditions that might have influenced cognitive performance.

2.2.1. Interview evaluation. The interviewer administered a semi-structured instrument to each participant, similar to that used in our prior studies (Kanayama et al., 2003; Pope et al., 2012, 2010), covering (1) demographic data; (2) weightlifting history; (3) history of treatment for medical or psychiatric disorders; (4) history of tobacco, alcohol, and classical illicit substance use; (5) history of AAS use; and (6) use of any other performance- or image-enhancing drugs such as human growth hormone, clenbuterol, and insulin (Baker et al., 2006; Skarberg et al., 2009). In men reporting AAS use, the interviewer determined as accurately as possible their (a) age at onset of AAS use; (b) maximum weekly dose of AAS, expressed as mg of testosterone equivalent, calculated as we (Kanayama et al., 2009b, 2003; Pope and Katz, 1994) and others (Pope and Katz, 2003) have done in past studies; (c) lifetime average weekly dose of AAS; (d) total lifetime weeks of AAS exposure; and (e) time of most recent AAS use.

2.2.2. Cognitive evaluation. The cognitive testers first administered the New Adult Reading Test (NART) to estimate verbal IQ (Crawford et al., 2001; Willshire et al., 1991), followed by five tests from the CANTAB battery (Cambridge Cognition, Cambridge, UK), a widely used collection of computerized cognitive tests (Robbins et al., 1998, 1994). When administering this battery, the testers first oriented participants to use of the touchscreen computer, and then provided brief verbal instructions for each successive test, using verbatim scripts from the CANTAB test administration manual. The five selected tests, lasting a total of approximately 40 min, began with Pattern Recognition Memory, which assessed visual memory by serially presenting 12 visual patterns, followed by a recognition phase where participants were shown two patterns and asked to touch the one that they had previously seen. The recognition phase was administered both immediately and again after a 30-min delay. Second, Verbal Recognition Memory assessed verbal memory by serially presenting 18 words, followed immediately by (a) a free-recall phase, where participants were asked to recall as many words as possible without cues, and then (b) a recognition phase, where participants were shown two words and asked to touch the word that they had previously seen. The recognition phase was administered both immediately and after a 20-min delay. Third, Paired Associates Learning assessed both visuospatial memory and

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