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Anabolic androgenic steroid affects social aggression and fear-related behaviors in male pair-housed rats

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Abstract

This study examines the effect of chronic administration of the anabolic androgenic steroid nandrolone decanoate (ND) on dominant and subordinate male rats in a pair-housed condition. Pair-housed rats were assessed for dominance status based on their behavior and alterations in body weights. Throughout the study the rats were allowed limited social interactions on a daily basis. At all other times, a Plexiglas divider kept the rats separated, allowing olfactory and visual contact between the cage mates while preventing significant physical contact. One week into the study all subjects were subcutaneously implanted with a pellet that continuously infused either ND (15 mg/kg/day) or placebo for 21 days. Following the pellet implant, behavioral tests including reassessment for dominance status, and a conditioned fear test were conducted over a period of approximately 2 months to investigate possible long-term changes. The main finding is that during the allowed social interactions, the dominant ND-pretreated rats spent more time on highly aggressive behaviors than the dominant placebo-treated rats. In addition, the probability for highly aggressive behaviors was maintained for the ND-treated rats throughout the study, whereas it was decreased for the placebo-treated rats. The ND-treated subordinate rats showed less fear in a potential threatening situation compared to placebo-treated controls. These findings support the relatively long-term behavioral changes that have been seen in humans after abuse of ND and other anabolic androgenic steroid compounds.

Keywords: Anabolic androgenic steroids; Nandrolone decanoate; Social aggression; Fear-related behavior; Pair-housed rats

Introduction

The use of anabolic androgenic steroids (AAS) is no longer limited to athletes and body builders. Studies conducted in several countries during the last decade have shown that adolescents and adults with no primarily interest in sports, but interested in weight gain and improvement of their physical appearance have started to abuse AAS (Kindlundh et al., 1998; Tanner et al., 1995; Yesalis et al., 1997). The common link between them is that they want to look, perform, and feel better, at almost any cost (for a review, see Bahrke et al., 2000). Furthermore, some adolescents claim to use AAS to become intoxicated and braver (Kindlundh et al., 1998).

The psychiatric side effects of AAS range from depression to psychosis depending on the individual taking the steroids, the stage and pattern of drug intake, dose, and the specific AAS compound that is used. For example, increased energy and libido, as well as delusions and manic episodes, are often associated with AAS (for a recent review, see Clark and Henderson, 2003). Nevertheless, aggression, particularly in response to provocation, is one of the most commonly reported psychiatric side effects after use of AAS (for a review, see Bahrke et al.,

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2000). Verbal aggression and violence against their significant other is commonly reported among AAS users (Choi and Pope, 1994; Conacher and Workman, 1989; Porcerelli and Sandler, 1998; Thiblin et al., 2000). Violent behavior in an AAS user is often induced by minimal provocation and has great intensity and long duration. These characteristically and sudden outbursts of aggression after AAS abuse are known as "roid rage" (Choi and Pope, 1994; Conacher and Workman, 1989). Also, AAS are used to increase aggressiveness and or self-confidence by various criminal groups (Thiblin et al., 1997). Disinhibitory behavior has also been reported among individuals abusing AAS (Brower et al., 1991; Galligani et al., 1996; Parrott et al., 1994; Perry et al., 1990; Pope and Katz, 1994; Porcerelli and Sandler, 1995, 1998; Su et al., 1993; Yates et al., 1990). Whether AAS abuse induces this type of behavior, or if individuals with disinhibitory behavior are more prone to abuse AAS as a result of their disorder is still unclear and the question is controversial. It has been suggested that antisocial personality disorder triggers AAS use and common personality characteristics for both alcoholics and AAS users have been found (Yates et al., 1990). However, disinhibitory behavior has been found among AAS users without prior history of drug abuse or psychiatric disorders, suggesting that use of AAS induces these kinds of behaviors (Conacher and Workman, 1989; Galligani et al., 1996; Pope and Katz, 1994; Porcerelli and Sandler, 1995; Su et al., 1993).

Whether AAS induce long-term behavioral changes in humans is currently poorly understood and findings are inconclusive. Increased verbal aggression was found in men that had been abstinent from AAS for at least 6 months (Galligani et al., 1996). To the contrary, minor or no alterations in aggressive behavior were found among AAS users who had been abstinent for at least a year (Malone et al., 1995; Yates et al., 1992). Recent animal studies suggest that AAS may induce long-lasting but possibly not persistent behavioral changes with regards to aggression (McGinnis et al., 2002a; Steensland et al., 2005) and dominance (Lindqvist and Fahlke, 2005).

The aggression-enhancing properties of AAS have been confirmed in several studies in rodents (Clark et al., 1996; DeLeon et al., 2002; Harrison et al., 2000; Johansson et al., 2000a; Long et al., 1996; Lumia et al., 1994; McGinnis et al., 2002a,b; Melloni et al., 1997; Steensland et al., 2005). Many of the rodent studies of AAS effects on aggression have focused on inter-male aggression, a form of aggressive behavior that is dependent of the presence of androgens (Christie and Barfield, 1979). The most common behavior model of inter male social aggression is the resident–intruder paradigm which involves determination of the quality and quantity of aggressive attacks from an animal in its home cage towards a novel male. In the present study we used a pair-housed social interaction/aggression paradigm. This pair-housed paradigm was modified from the previously described triad-housing paradigm where three subjects live together (Pohorecky et al., 1999). Dominance relationships between rodents form rapidly (Lore and Stipo-Flaherty, 1984) and this hierarchy remains stable over time (Blanchard et al., 1988; Brain and Benton, 1979). Throughout the present study the rats were allowed to interact for a certain period of time each day, at all other times a Plexiglas divider kept the rats separated.

The aim of the present study was to investigate how nandrolone decanoate (ND) affects social interactions (with focus on aggression and fear-related behaviors) of pair-housed rats. The rats were studied during the ND treatment and for an additional 6 weeks after the end of the ND treatment to investigate possible long-term behavioral changes.

Materials and methods

Subjects and environment

The subjects were 55 male Long–Evans rats (Harlan Sprague–Dawley, Indianapolis, IN) weighing approximately 250 g at the beginning of the study. Initially, the rats were individually housed in hanging stainless steel wire cages and allowed to adapt to the novel laboratory environment for 14 days before the experiment started. Purina chow and water were available ad libitum throughout the study. The vivarium temperature was maintained at 23 ± 1°C, with controlled humidity and a 12/12 reverse light/dark cycle (lights off at 11:30 am). All rats were habituated to handling by the experimenters before any behavioral testing. On day one of the study, 40 of the 55 subjects were assigned to specific pair-housed cages (see details in the next section). The remaining 15 were kept individually housed and are referred to as housing controls. All cages were made of Plexiglas walls and lids with a wire mesh floor (pair-housed: 26 × 82 × 30 cm; individual: 25 × 25 × 30 cm). The pair-housed cages could be separated into two equal halves by insertion of a transparent Plexiglas divider with a 6-cm-high strip of 1 cm^2 wire mesh along the bottom edge, allowing visual and olfactory contact between the cage mates but preventing significant physical contact. Each rat had free access to its own food and water supply except during periods of social interaction (see description in next section) when food and water was removed. Housing controls were kept in a separate colony room (under the same environmental conditions) to prevent influence of pheromones released during interactions between the pair-housed rats. All tests were conducted during the dark phase of the light/dark cycle. All procedures were in accord with NIH guidelines and were reviewed and approved by the Institutional Animal Care and Use Committees of Rutgers University. The animal facilities have been certified by AALAC.