Published in final edited form as:

Horm Behav. 2015 March ; 69: 132–138. doi:10.1016/j.yhbeh.2015.01.009.

Anabolic/Androgenic Steroid Administration During Adolescence and Adulthood Differentially Modulates Aggression and Anxiety

Thomas R. Morrison, Lesley A. Ricci, and Richard H. Melloni Jr.

Behavioral Neuroscience Program, Department of Psychology, 125 Nightingale Hall,
Northeastern University, 360 Huntington Avenue, Boston, MA 02155

Abstract

Anabolic/androgenic steroid (AAS) use remains high in both teens and adults in the U.S. and worldwide despite studies showing that AAS use is associated with a higher incidence of aggression and anxiety. Recently we showed that chronic exposure to AAS through adolescence increases aggression and decreases anxious behaviors, while during AAS-withdrawal aggression is lowered to species-normative levels and anxiety increases. AAS exposure is known to differentially alter behaviors and their underlying neural substrates between adults and adolescents and thus the current study investigated whether exposure to AAS during *adulthood* affects the relationship between aggression and anxiety in manner similar to that previously observed in adolescents. Male hamsters were administered a moderate dose of AAS (5.0mg/kg/day $\times$ 30days) during adolescence (P27–56) or young adulthood (P65–P94) and then tested for aggression and anxiety during AAS exposure (i.e., on P57 or P95) and during AAS withdrawal (i.e., 30 days later on P77 or P115). Adolescent exposure to AAS increased aggressive responding during the AAS exposure period and anxiety-like responding during AAS withdrawal. Neither behavior was similarly influenced by adult exposure to AAS. Adult AAS exposure produced no difference in aggressive responding during AAS exposure (P95) or AAS withdrawal (P115); however, while AAS exposure during adulthood produced no difference in anxiety-like responding *during* AAS exposure, adult hamsters administered AAS were less anxious than vehicle control animals following AAS withdrawal. Together these data suggest that the aggression and anxiety provoking influence of AAS are likely a developmental phenomenon and that adult exposure to AAS may be anxiolytic over the long term.

© 2015 Published by Elsevier Inc.

Correspondence to: Richard H. Melloni, Jr., Ph.D., Program in Behavioral Neuroscience, Department of Psychology, 125 Nightingale Hall, Northeastern University, 360 Huntington Avenue, Boston, MA 02155, Tel.No. (617) 373-3043, FAX No. (617) 373-8714, r.melloni@neu.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

INTRODUCTION

Abuse of anabolic/androgenic steroids (AAS) has remained a concern for decades, yet its use has risen in recent years worldwide (Harmer, 2010; NIDACapsules, 2007) despite strong evidence for negative acute and long-term physical, psychological, and behavioral consequences. While the most common behavioral side effect of AAS use is increased aggression in adult (Kouri, Lukas, Pope, & Oliva, 1995; Pope & Katz, 1994; Pope, Kouri, & Hudson, 2000; Su et al., 1993) and youth populations (Beaver, Vaughn, Delisi, & Wright, 2008; Dabbs, Jurkovic, & Frady, 1991; Johnson, Jay, Shoup, & Rickert, 1989; Johnson, 1990; Mattsson, Schalling, Olweus, Löw, & Svensson, 1980; Olweus, Mattsson, Schalling, & Löw, 1980), there is also a high incidence of anxiety-related disorder diagnoses in AAS users (Bahrke, Yesalis, & Wright, 1990; Johnson, 1990; Pagonis, Angelopoulos, Koukoulis, Hadjichristodoulou, & Toli, 2006; Pagonis, Angelopoulos, Koukoulis, & Hadjichristodoulou, 2006; Pope & Katz, 1994), particularly during withdrawal from AAS use (Bahrke et al., 1990; Brower, 2002; Corrigan, 1996; Lindqvist et al., 2007; Malone, Dimeff, Lombardo, & Sample, 1995; Malone & Dimeff, 1992; Perry, Andersen, & Yates, 1990). Clinical data reflect this incidence showing marked increases in both aggression *and* anxiety in AAS users (Hall, Hall, & Chapman, 2005; Pagonis, Angelopoulos, Koukoulis, & Hadjichristodoulou, 2006; Pope et al., 2000; Su et al., 1993); suggesting that AAS exposure may promote the development of both negative behavioral phenotypes simultaneously. While a number of preclinical studies have investigated the link between AAS use and the expression of aggression (Farrell & McGinnis, 2004; Lumia, Thorner, & McGinnis, 1994; McGinnis, Lumia, Breuer, & Possidente, 2002; McGinnis, Lumia, & Possidente, 2002; Melloni & Ricci, 2010) less is known regarding the relationship between AAS exposure and anxiety. AAS exposure produces variable effects on anxiety-like responding in animal models (Agis-Balboa, Pibiri, Nelson, & Pinna, 2009; Aikey, Nyby, Anmuth, & James, 2002; Bitran, Kellogg, & Hilvers, 1993; Fernández-Guasti & Martínez-Mota, 2005; Ricci, Morrison, & Melloni, 2012; Rocha, Calil, Ferreira, Moura, & Marcondes, 2007), despite consistent evidence for an anxiolytic effect of testosterone (Bing et al., 1998; Frye, Edinger, & Sumida, 2008; Toufexis, Davis, Hammond, & Davis, 2005; Zuloaga, Morris, Jordan, & Breedlove, 2008). Though evidence between androgen insensitive mice and rats suggests that this inconsistency may involve species differences (Zuloaga et al., 2008; Zuloaga, Poort, Jordan, & Breedlove, 2011), it is also plausible that inconsistent findings can be explained by the age of AAS administration since no preclinical study has investigated the effects of AAS administration on the emergence of these two behaviors during AAS exposure and withdrawal in both adolescent *and* adult populations – especially as it pertains to experimental, novice use.

For over a decade we have used pubertal male Syrian hamsters (*Mesocricetus auratus*) as an adolescent animal model to investigate the effects of adolescent AAS exposure on the behavioral neurobiology of two of the most common side effects of AAS exposure, i.e., offensive aggression (DeLeon, Grimes, & Melloni, 2002; Harrison, Connor, Nowak, Nash, & Melloni, 2000; Melloni & Ricci, 2010) and anxiety (Ricci et al., 2012, 2013). Behavioral data from these studies show that adolescent hamsters repeatedly exposed to moderate doses of AAS (5.0 mg/kg/day) display significant increases in aggression during the adolescent

AAS exposure period followed by significant increases in anxiety during withdrawal. Linear regression analysis revealed that the difference in aggressive responding between the AAS exposure and withdrawal periods was a significant predictor of changes in anxiety-like behavior between these two periods, indicating that moderate adolescent AAS exposure has potent aggression- and anxiety- eliciting effects, and that these behavioral changes occur alongside a predictive relationship that exists between these two behaviors over time (Ricci et al., 2013). While these alterations in aggressive and anxiety-like responding exist for adolescents exposed to AAS, it is unknown whether adults exposed to moderate doses of AAS experience similar behavioral side effects in parallel. To determine whether adult exposure to moderate dose AAS alters aggression and anxiety in a manner similar to adolescent exposure, the current study compares the effect(s) of moderate dose AAS administration between adolescents and adults on the expression of aggression during AAS exposure and anxiety during withdrawal.

METHODS

Animals

Intact male Syrian hamsters (*Mesocricetus auratus*) postnatal day 21 (P21; pubertal hamsters) or postnatal day 59 (P59; young adult hamsters) were obtained from Charles River Laboratories (Wilmington, MA), individually housed in polycarbonate cages, and maintained at ambient room temperature (22–24°C with 55% relative humidity) on a reverse light/dark cycle (14L:10D; lights off at 7:00). Food and water were provided *ad libitum*. For aggression testing, stimulus (intruder) males of equal size and weight to the experimental animals were obtained from Charles River one week prior to the behavioral test, group housed at 5 animals/cage in large polycarbonate cages, and maintained as above to acclimate to the animal facility. All intruders were evaluated and prescreened for low aggression (i.e., disengage and evade) and submission (i.e., tail-up freeze, flee, and fly-away) one day prior to the aggression test to control for behavioral differences between stimulus animals, as previously described in a number of our studies (Ferris et al., 1997; Grimes & Melloni, 2002; Ricci, Schwartz, & Melloni, 2009). Intruders displaying significantly low aggression and/or submissive postures were excluded from use in the behavioral assay. All experimental treatments and behavioral tests described below were administered during the first four hours of the dark cycle under dim-red illumination to control for circadian influences. All studies using live animals were approved by the Northeastern University Institutional Animal Care and Use Committee (NU-IACUC), and all methods used were consistent with guidelines provided by the National Institute of Health for the scientific treatment of animals.

Anabolic/Androgenic Steroid Treatment

Postnatal day 27 (P27; pubertal) and postnatal day 65 (P65; adult) hamsters were weighted and received daily subcutaneous (SC) injections (0.1ml – 0.2ml) for 30 consecutive days (P27 – P56, pubertal; P65 – P94, adult) of a mixture (or “stack”) of 3 commonly used AAS (Hall et al., 2005) in doses consistent with repeated, moderate use in humans as described (see Melloni & Ricci, 2010 for a review). The AAS cocktail was composed of 2 mg/kg testosterone cypionate, 2 mg/kg nortestosterone and 1 mg/kg dihydrotestosterone

undecylate (Steraloids, Newport, RI) dissolved in sesame oil (SO). As a control, a separate set of P27 and P65 male hamsters received daily SC injections (0.1ml – 0.2ml) for 30 consecutive days (P27 – P56 or P65 – P94) of SO (vehicle control).

Experimental Design

The day following the last AAS injection (P57 or P95), AAS-treated animals (P57, n=7; P95, n=10) and SO-treated controls (P57, n=7; P95, n=10) were randomly assigned to one of two counterbalanced groups and tested for anxiety-like responding using the Elevated Plus Maze (EPM) test and aggressive behavior using the Resident/Intruder (RI) test. At the completion of behavioral testing on P57 or P95, animals were placed back into their home cage and withdrawn from AAS (or SO) for 21 days (i.e., until P77 or P115) and then tested again for anxiety and aggression.

Behavior Testing

Aggression—Hamsters were tested for offensive aggression using the resident-intruder (RI) paradigm, a well-characterized and ethologically valid model of offensive aggression in Syrian hamsters (Floody & Pfaff, 1977; Lerwill & Makings, 1971). For this measure, a novel intruder of similar size and weight was introduced into the home cage of the experimental animal (resident) and the resident was scored for specific and targeted aggressive responses observed as lateral, flank-directed attacks as previously described (Grimes, Ricci, & Melloni, 2003; Ricci, Rasakham, Grimes, & Melloni, 2006). An attack was scored each time the resident animal would pursue and then either [1] lunge toward and/or [2] confine the intruder by upright and sideways threat; each generally followed by a direct attempt to bite the intruder's dorsal rump and/or flank target area(s). The latency to attack was defined as the period of time between the beginning of the behavioral test and the first attack the residents made toward an intruder. In the case of no attacks, latencies to attack were assigned the maximum latency (i.e., 600s). Each aggression test lasted for 10 minutes and was videotaped and scored manually by two observers unaware of the hamsters' experimental treatment. Inter-rater reliability was set at 95%. No intruder was used for more than one behavioral test, and all subjects were tested during the first 4 hours of the dark cycle under dim red illumination to control for circadian influences on behavioral responding.

Anxiety—Hamsters were tested for anxiety-related behavior using the elevated plus maze (EPM) test as in our previous studies (Ricci et al., 2012, 2013) and elsewhere (Gannon et al., 2011; Prendergast & Nelson, 2005). The EPM has been used extensively in rodents as a reliable test of anxiety-like responding, with particular use as a sensitive behavioral test to screen for anxiolytic drug effects (Gannon et al., 2011; Pellow, Chopin, File, & Briley, 1985; Pellow & File, 1986). The apparatus consisted of two open arms and two closed arms (30 × 5 cm) elevated to a height of 38.5 cm and intersecting in a central platform (5 × 5 cm). The closed arms had black Plexiglas walls (15 cm high) covered with a black Plexiglas lid on the roof. The apparatus was arranged such that the open arms were opposite to each other. Animals were individually placed in the center of the apparatus facing one of the closed arms. The duration of time (sec) spent beyond a complete body length in the open arms was calculated for each animal over a 5-minute period. An increase in the duration of

time spent in the open arms of the EPM was used as an index of anxiolytic behavior (Lister, 1987; Pellow et al., 1985). Each anxiety test was videotaped and coded by two observers unaware of experimental treatment. Animals were tested during the first four hours of the dark cycle under dim-red illumination to control for circadian influences in behavioral responding.

Statistical Analyses

Behavioral results from aggression (i.e., attacks and latency to attack) and anxiety (i.e., number of entries and duration of time spent within the open arms of the EPM) during AAS exposure (P57 and P95) and AAS withdrawal (P77 and P115) measures were compared between AAS and SO treatment groups using paired Student's *t*-test (two-tailed). The α level for all statistical analyses was set at 0.05.

RESULTS

Adolescent AAS Exposure and Withdrawal

Figure 1a (Left) shows that during adolescent exposure (P57), AAS-treated animals were significantly more aggressive than SO-treated control animals. Adolescent AAS-treated animals directed significantly more rump/belly attacks ($t(12)=4.15$, $p<0.01$) and were faster to attack ($t(12)=3.92$, $p<0.01$) intruders than SO-treated control animals. In fact, AAS animals exhibited a greater than tenfold increase in number of rump/belly attacks and were four times faster to attack intruders compared to SO-treated controls. Conversely, during the adolescent AAS exposure period (i.e., on P57), animals showed no change in anxiety-like responding compared to SO-treated controls (Figure 1a, Right). During this time, there were no differences in the number of entries into- ($t(12)=0.51$, $p>0.1$) and the duration of time within- ($t(12)=1.35$, $p>0.1$) the open arms of the EPM between AAS- and SO-treated animals.

Consistent with our previous data (Carrillo, Ricci, & Melloni, 2011; Grimes & Melloni, 2006; Ricci et al., 2012), the aggression-stimulating effects of adolescent AAS exposure were no longer present at 3 weeks of AAS withdrawal (i.e., on P77), i.e., AAS-treated animals displayed a non-aggressive phenotype identical to SO-treated control animals (Figure 1b, Left). During withdrawal from AAS (P77), adolescent animals were no longer aggressive as evidenced by nearly identical numbers of rump/belly attacks (i.e., 2.14 ± 0.9 attacks) and an attack latency period (i.e., 409.3 ± 78 seconds) similar to SO-treated controls (i.e., 1.14 ± 0.5 attacks and 444 ± 73 seconds). Neither of these behavioral differences were statistically significant (attacks; $t(12)=0.94$, latency to attack; $t(12)=0.32$, $p>0.1$ each). In contrast, adolescent AAS-treated animals had significantly fewer open arm entries ($t(12)=3.75$, $p<0.01$) and spent significantly less time in the open arms ($t(12)=5.17$, $p<0.001$) than SO-treated control animals during withdrawal (Figure 1b, Right). In fact, AAS animals exhibited threefold fewer entries into-, and spent nearly half the time (>42% of time) within- the open arms of the EPM compared to SO-treated control animals.

Adult AAS Exposure and Withdrawal

Figure 2a and 2b show the effects of AAS exposure and withdrawal (respectively) on aggression and anxiety measures in adult animals. During exposure, both AAS- and SO-treated animals directed a high number of rump/belly attacks onto- (i.e., 27.6 ± 4.4 vs. 27.8 ± 3 attacks, respectively) and were quick to attack intruders (i.e., 85.3 ± 12 vs. 92.6 ± 11 seconds, respectively). Neither of these behavioral measures were statistically significantly different between SO and AAS animals (attacks; $t(18)=0.11$; latency to attack; $t(18)=0.4$, $p>0.1$ each). Similar to adolescent animals, adult AAS exposure had no significant effect on anxiety-like responding during the exposure period (i.e., on P95), i.e., AAS-treated animals showed no change in anxiety-like responding compared to SO-treated controls (Figure 2a, Right). During this time, there were no differences in the number of entries into- ($t(18)=0.41$, $p>0.1$) and the duration of time within- ($t(18)=0.05$, $p>0.1$) the open arms of the EPM between AAS- and SO- treated animals.

During withdrawal from AAS (i.e., on P115), adults displayed an aggressive phenotype that was identical to SO-treated control animals (Figure 2b, Left). AAS-treated adults had similar numbers of rump/belly attacks (i.e., 29.4 ± 4 vs. 23.6 ± 4 , respectively) and similar attack latency times (i.e., 90.3 ± 13 vs. 81.4 ± 12 seconds, respectively) to that of SO-treated controls during the withdrawal period. Neither of these behavioral differences were statistically significant (attacks; $t(18)=0.98$, latency to attack; $t(18)=0.53$, $p>0.1$ each). Conversely, during withdrawal from AAS administration (i.e., on P115), adult animals displayed a lower level of anxiety-like responding compared to SO-treated controls by showing a higher frequency of open-arm entries ($t(18)=2.6$, $p<0.05$) and spending significantly more time within the open arms of the EPM ($t(18)=3.63$, $p<0.01$). In fact, adult AAS animals exhibited twice the number of entries into- and spent nearly seven times the amount of time within- the open arms of the EPM compared to SO-treated control animals.

DISCUSSION

Here we present the first set of preclinical studies that investigate the effect of adolescent vs. adult AAS exposure on the relationship between aggression *and* anxiety during AAS exposure *and* withdrawal. In these studies pubertal and adult male hamsters were repeatedly administered a mixture of AAS that mimics a 'heavy use' regimen in humans (Pope & Katz, 1988, 1994), although recent surveys indicate that these doses (i.e., 5mg/kg/day, which corresponds to $\sim 20\times$ the therapeutic dose of testosterone) are more moderate by today's standards where recommendations and examples can exceed this amount up to fivefold; ranging between $35\text{--}100\times$ the therapeutic dose of testosterone (i.e., upwards toward 3000mg/week) (see <http://www.Steroidtips.com> and www.steroid.com/steroid_cycles.php for examples). The behavioral data confirm our previous findings that show that moderate dose AAS exposure significantly increases aggressive responding in adolescents during AAS exposure but not during AAS withdrawal, while increasing anxiety-like responding in adolescents during AAS withdrawal but not AAS exposure (Ricci et al., 2012, 2013). By comparison, unlike that observed following adolescent exposure, repeated administration of AAS to adult animals did not affect offensive aggressive behaviors during AAS exposure or AAS withdrawal, but had an anxiolytic effect during AAS withdrawal.

The severity of AAS abuse has been shown to correlate with adverse behavioral effects in humans, with higher doses and longer use times correlating with both aggression and anxiety (Pagonis, Angelopoulos, Koukoulis, Hadjichristodoulou, et al., 2006; Pagonis, Angelopoulos, Koukoulis, & Hadjichristodoulou, 2006; Payne, 1974a; Pope & Katz, 1987, 1988, 1994; Su et al., 1993). For instance, in adults the prolonged use of high dose AAS (i.e., upwards of 100× the therapeutic dose of testosterone – typically equivalent to near 3000 mg/week) has been correlated with increased aggressive behavior (Isacsson & Bergman, 1993; Kouri et al., 1995; Kreuz & Rose, 1972; Pope & Katz, 1988, 1994; Pope et al., 2000; Strauss, Wright, & Finerman, 1983; Strauss, 1987; Su et al., 1993). Similarly, in adolescent teenagers, aggression correlates with testosterone level (Archer, 1991; Johnson et al., 1989; Johnson, 1990; Mattsson et al., 1980; Scerbo & Kolko, 1994; Schaal, Tremblay, Soussignan, & Susman, 1996) where high levels of testosterone as well as AAS use are associated with provoked aggression and violence in adolescent males (Beaver et al., 2008; Dabbs, Frady, Carr, & Besch, 1987; Dabbs et al., 1991; Mattsson et al., 1980; Olweus et al., 1980; Olweus, 1987; Scerbo & Kolko, 1994; Schalling, 1987). Interestingly, there are also reports of increased aggression in adolescents administered lower (e.g., physiologic) levels of AAS (Finkelstein et al., 1997), suggesting that adolescent users may have a greater sensitivity to the aggression-provoking effects of testosterone. Like aggression, an increased incidence of anxiety-related disorders is correlated with prolonged, high dose AAS use (Bahrke et al., 1990; Daly et al., 2003; Johnson, 1990; Pagonis, Angelopoulos, Koukoulis, Hadjichristodoulou, et al., 2006; Pagonis, Angelopoulos, Koukoulis, & Hadjichristodoulou, 2006; Pope & Katz, 1988, 1994), particularly during withdrawal (Bahrke et al., 1990; Brower, 2002; Corrigan, 1996; Lindqvist et al., 2007; Malone et al., 1995; Malone & Dimeff, 1992; Perry et al., 1990), although it is unclear whether the level of maturity during the exposure or withdrawal periods contributes to the development and expression of this behavioral phenotype or whether young users have a greater sensitivity to the anxiety-provoking effects of testosterone.

In laboratory studies using adolescent and adult male rats and hamsters, chronic AAS exposure has consistently been shown to produce elevated levels of aggression during the AAS exposure period (Farrell & McGinnis, 2004; Lumia et al., 1994; McGinnis, Lumia, Breuer, et al., 2002; McGinnis, Lumia, & Possidente, 2002; Melloni & Ricci, 2010). This elevated level of aggression has been shown to be both maintained (Farrell & McGinnis, 2004) or reduced (Grimes & Melloni, 2006; Grimes, Ricci, & Melloni, 2006) during AAS withdrawal. The findings here and in our previous reports that show that adolescent AAS exposure significantly increases aggressive responding during AAS exposure, but not during AAS withdrawal, are to some extent similar to data from several of these studies (Farrell & McGinnis, 2004; McGinnis, Lumia, Breuer, et al., 2002; McGinnis, Lumia, & Possidente, 2002). In these studies, intact adolescent and adult rats were treated with AAS for greater than 9 weeks and then tested for aggressive behavior at the end of the AAS exposure period and/or following short-term (i.e., 3–5 weeks) or long-term (i.e., 9–12 and/or 15–17 weeks) AAS withdrawal (Farrell & McGinnis, 2004; McGinnis, Lumia, Breuer *et al.*, 2002; McGinnis, Lumia, & Possidente, 2002). In these studies, immediate and lasting increases in aggressive behavior were observed after the cessation of AAS treatment. Contrary to our findings, in adolescent AAS-treated animals, heightened aggression has been observed

during AAS withdrawal (although only in animals physically provoked to fight) (Farrell & McGinnis, 2004). No effect of adolescent AAS exposure was observed on aggression during withdrawal in animals without prior provocation, suggesting that an external physical stimulus is necessary to activate the aggressive response during AAS withdrawal in rats. Further, unlike rats, moderate dose AAS administration during adulthood (i.e., 5mg/kg/day $\times$ 30 days) did not affect aggression during the exposure or withdrawal period in hamsters.

Alongside AAS studies, it is interesting to note that testosterone levels correlate positively with dominant behaviors through development, both of which stabilize during early adulthood (Vomachka and Greenwald, 1979; Whitsett, 1975; Menard et al., 2003). In contrast, aggression levels are the same in the absence or presence of exogenous testosterone in castrated adult hamsters (Romeo, Schulz, Nelson, Menard, & Sisk, 2003), and similarly, the present findings show that AAS exposure and withdrawal produced no observable changes in offensive aggressive responding in adults when compared with their vehicle-treated counterparts. Although these findings contrast some early evidence that testosterone enhances aggressive behavior in adult rodents (e.g., Grelk, Papson, Cole, & Rowe, 1974; Payne & Swanson, 1972; Payne, 1974b), differences between our findings and these results are likely due to a range of methodological inconsistencies such as treatment regimen (i.e., acute vs. chronic administration), age of treatment, testing conditions, and behavioral observations (i.e., dominance, offensive, defensive or submissive) (see Albers, Huhman, & Meisel, 2002 for review). Relatedly, across species, studies that examined the effects of AAS-withdrawal in adult rats have reported that aggression increased following short-term withdrawal, but only in animals administered moderate doses of AAS for a considerably extended period of time (5mg/kg/day $\times$ 12 weeks) (McGinnis, Lumia, Breuer *et al.*, 2002; McGinnis, Lumia, & Possidente, 2002), i.e., three times longer than that administered in the current set of studies. Taken together, data generated from other researchers as well as those presented in this report indicate that AAS may have differential lasting effects on aggressive behavior that depend upon age of exposure, length of treatment, and dose of AAS.

Compared to aggression, there are little data from too few preclinical studies that adequately describe how AAS exposure and/or withdrawal affect anxiety across different stages of maturation. Two such studies related to these topics found that 17 α -methyltestosterone did not alter anxiety-related behaviors after chronic administration in adults (Rojas-Ortiz, Rundle-González, Rivera-Ramos, & Jorge, 2006) or acute administration in adolescents (Ramos-Pratts, Rosa-González, Pérez-Acevedo, Cintrón-López, & Barreto-Estrada, 2013). In contrast, recent data from our laboratory show that hamsters chronically exposed to a mixture of AAS throughout adolescence have reduced levels of anxiety during AAS exposure and then heightened levels of anxious responding after a withdrawal period (Ricci et al., 2012, 2013). These data are consistent with studies showing rats chronically treated with nandrolone or testosterone propionate during adolescence exhibit increased levels of anxiety after a withdrawal (or washout) period from AAS (Olivares et al., 2014; Rainer et al., 2014). Behavioral reports using adult rodents indicate that acute exposure to AAS decreases anxiety (Aikey et al., 2002; Bitran et al., 1993; Melchior & Ritzmann, 1994), while chronic exposure has been shown to either enhance anxious responding (Ambar & Chiavegatto, 2009; Rocha et al., 2007) or have no effect (Rojas-Ortiz et al., 2006; Zotti et

al., 2014). While several of these chronic studies fall in line with our current results showing that adult exposure to AAS does not alter anxious behavior, the differences between our results and other chronic studies may be due in large part to drug regimen and/or the behavioral data analyses used. For example, as an index of anxious behavior, Ambar et al. measured the time each animal spent in the open arms *combined with* time spent in the neutral area at the center of the elevated plus maze (EPM), while our measures only included the time animals spent in the open arms. In fact, similar to our results, Ambar et al. did not find any difference in open arm entries, an important measure of anxious behavior when using the EPM apparatus (Pellow et al., 1985). Rocha et al. used scoring criteria similar to our study, however they also used a different treatment regimen along with a single AAS (i.e., nandrolone) as apposed to a mixture of AAS used in our study. Specifically, Rocha et al. administered AAS twice per week limiting the circulating dose of nandrolone. This difference in regimen is also notable since similar studies using larger doses and daily injections of nandrolone showed increased numbers of entries- and time spent in the open arms of the EPM (Kouvelas et al., 2008), suggesting the dose-response of nandrolone for anxious behavior resembles an inverse sigmoidal curve which may or may not be similar to the effects of other AAS or AAS mixtures.

In summary, these studies provide data that indicate that moderate dose AAS exposure during adolescence and adulthood differentially modulates aggression and anxiety in hamsters. Specifically, these data show that moderate dose adolescent AAS exposure significantly increases aggressive responding during the adolescent AAS exposure period but not during AAS withdrawal while increasing anxiety-like responding during AAS withdrawal but not during the adolescent AAS exposure period. By comparison, unlike adolescent exposure, repeated adult exposure to moderate dose AAS does not influence offensive aggression during AAS exposure or AAS withdrawal, but appears to have a slight anxiolytic effect following cessation of administration. Together, these data suggest that the aggression and anxiety provoking influence of moderate doses of AAS are most likely to appear when the exposure period to AAS is early (e.g., during adolescence) thus representing a developmental phenomenon. This notion, in addition to our previous findings showing that the magnitude of adolescent AAS-facilitated aggressive responding has the ability to predict anxiety-like withdrawal (Ricci et al., 2012, 2013), further supports the notion of a common neuroanatomical locus modulating both aggression and anxiety. It is likely that the neurochemical signals (e.g., serotonin and GABA) that modulate aggression and anxiety are sensitive to neuroplastic changes during developmental exposure to AAS, and lose sensitivity beyond this critical period at a time when these systems have established functional maturity within brain regions that control the expression of aggression and anxiety.

ACKNOWLEDGMENTS

The authors would also like to thank Jillian Joyce and Courtney Davis for their technical support in the completion of the experimental procedures. This study was supported by research grant (R01) DA10547 from NIH to R.H.M. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH.

REFERENCES

- Agis-Balboa RC, Pibiri F, Nelson M, Pinna G. Enhanced fear responses in mice treated with anabolic androgenic steroids. *Neuroreport*. 2009; 20(6):617–621. [PubMed: 19287318]
- Aikey JL, Nyby JG, Anmuth DM, James PJ. Testosterone Rapidly Reduces Anxiety in Male House Mice (*Mus musculus*). *Hormones and Behavior*. 2002; 42(4):448–460. [PubMed: 12488111]
- Albers, HE.; Huhman, KL.; Meisel, RL. Hormonal Basis of Social Conflict and Communication. In: Pfaff, DW.; Arnold, AP.; Etgen, AM.; Fahrbach, SE.; Rubin, RT., editors. *Hormones, Brain, and Behavior*. San Diego: Academic Press; 2002. p. 393-434.
- Ambar G, Chiavegatto S. Anabolic-androgenic steroid treatment induces behavioral disinhibition and downregulation of serotonin receptor messenger RNA in the prefrontal cortex and amygdala of male mice. *Genes, Brain, and Behavior*. 2009; 8(2):161–173.
- Anabolic steroid cycles and stacks. 2014 from http://www.steroid.com/steroid_cycles.php.
- Archer J. The Influence of testosterone on human aggression. *British Journal of Psychology*. 1991; 82:1–28. [PubMed: 2029601]
- Bahrke MS, Yesalis CE, Wright JE. Psychological and behavioural effects of endogenous testosterone levels and anabolic-androgenic steroids among males. *Sports Medicine*. 1990; 10(5):303–337. [PubMed: 2263798]
- Beaver KM, Vaughn MG, Delisi M, Wright JP. Anabolic-androgenic steroid use and involvement in violent behavior in a nationally representative sample of young adult males in the United States. *American Journal of Public Health*. 2008; 98(12):2185–2187. [PubMed: 18923108]
- Bing O, Heilig M, Kakoulidis P, Sundblad C, Wiklund L, Eriksson E. High doses of testosterone increase anticonflict behaviour in rat. *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology*. 1998; 8(4):321–323. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9928924>. [PubMed: 9928924]
- Bitran D, Kellogg CK, Hilvers RJ. Treatment with an Anabolic-Androgenic Steroid Affects Anxiety-Related Behavior and Alters the Sensitivity of Cortical GABAA Receptors in the Rat. *Hormones and Behavior*. 1993; 27:568–583. [PubMed: 8294123]
- Brower KJ. Anabolic steroid abuse and dependence. *Current Psychiatry Reports*. 2002; 4(5):377–387. [PubMed: 12230967]
- Carrillo M, Ricci LA, Melloni RH. Developmental and withdrawal effects of adolescent AAS exposure on the glutamatergic system in hamsters. *Behavioral Neuroscience*. 2011; 125(3):452–464. [PubMed: 21500881]
- Corrigan B. Anabolic steroids and the mind. *The Medical Journal of Australia*. 1996; 165(4):222–226. Retrieved from <http://europepmc.org/abstract/MED/8773655>. [PubMed: 8773655]
- Dabbs JM, Frady RL, Carr TS, Besch NF. Saliva testosterone and criminal violence in young adult prison inmates. *Psychosomatic Medicine*. 1987; 49(2):174–182. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/3575604>. [PubMed: 3575604]
- Dabbs JM, Jurkovic GJ, Frady RL. Salivary testosterone and cortisol among late adolescent male offenders. *Journal of Abnormal Child Psychology*. 1991; 19(4):469–478. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/1757712>. [PubMed: 1757712]
- Daly RC, Su TP, Schmidt PJ, Pagliaro M, Pickar D, Rubinow DR. Neuroendocrine and behavioral effects of high-dose anabolic steroid administration in male normal volunteers. *Psychoneuroendocrinology*. 2003; 28(3):317–331. [PubMed: 12573299]
- DeLeon KR, Grimes JM, Melloni RH. Repeated anabolic-androgenic steroid treatment during adolescence increases vasopressin V(1A) receptor binding in Syrian hamsters: correlation with offensive aggression. *Hormones and Behavior*. 2002; 42(2):182–191. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12367571>. [PubMed: 12367571]
- Farrell SF, McGinnis MY. Long-term effects of pubertal anabolic-androgenic steroid exposure on reproductive and aggressive behaviors in male rats. *Hormones and Behavior*. 2004; 46(2):193–203. [PubMed: 15256309]
- Fernández-Guasti A, Martínez-Mota L. Anxiolytic-like actions of testosterone in the burying behavior test: role of androgen and GABA-benzodiazepine receptors. *Psychoneuroendocrinology*. 2005; 30(8):762–770. [PubMed: 15919582]

- Ferris CF, Melloni RH, Koppel G, Perry KW, Fuller RW, Delville Y. Vasopressin/serotonin interactions in the anterior hypothalamus control aggressive behavior in golden hamsters. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*. 1997; 17(11): 4331–4340. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9151749>. [PubMed: 9151749]
- Finkelstein JW, Susman EJ, Chinchilli VM, Kunselman SJ, D'Arcangelo MR, Schwab J, Kulin HE. Estrogen or testosterone increases self-reported aggressive behaviors in hypogonadal adolescents. *The Journal of Clinical Endocrinology and Metabolism*. 1997; 82(8):2433–2438. [PubMed: 9253313]
- Floody OR, Pfaff DW. Aggressive behavior in female hamsters: the hormonal basis for fluctuations in female aggressiveness correlated with estrous state. *Journal of Comparative and Physiological Psychology*. 1977; 91(3):443–464. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/559693>. [PubMed: 559693]
- Frye CA, Edinger K, Sumida K. Androgen administration to aged male mice increases anti-anxiety behavior and enhances cognitive performance. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*. 2008; 33(5):1049–1061. [PubMed: 17625503]
- Gannon RL, Lungwitz E, Batista N, Hester I, Huntley C, Peacock A, Millan MJ. The benzodiazepine diazepam demonstrates the usefulness of Syrian hamsters as a model for anxiety testing: evaluation of other classes of anxiolytics in comparison to diazepam. *Behavioural Brain Research*. 2011; 218(1):8–14. [PubMed: 21094664]
- Grelk DF, Papsen BA, Cole JE, Rowe FA. A comparison of the effects of androstenedione, dihydrotestosterone and testosterone propionate on aggression in the castrated male golden hamster. *Hormones and Behavior*. 1974; 366:355–366. [PubMed: 4477152]
- Grimes JM, Melloni RH. Serotonin modulates offensive attack in adolescent anabolic steroid-treated hamsters. *Pharmacology, Biochemistry, and Behavior*. 2002; 73(3):713–721. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12151048>.
- Grimes JM, Melloni RH. Prolonged alterations in the serotonin neural system following the cessation of adolescent anabolic-androgenic steroid exposure in hamsters (*Mesocricetus auratus*). *Behavioral Neuroscience*. 2006; 120(6):1242–1251. [PubMed: 17201468]
- Grimes JM, Ricci LA, Melloni RH. Glutamic acid decarboxylase (GAD65) immunoreactivity in brains of aggressive, adolescent anabolic steroid-treated hamsters. *Hormones and Behavior*. 2003; 44(3): 271–280. [PubMed: 14609549]
- Grimes JM, Ricci LA, Melloni RH. Plasticity in anterior hypothalamic vasopressin correlates with aggression during anabolic-androgenic steroid withdrawal in hamsters. *Behavioral Neuroscience*. 2006; 120(1):115–124. [PubMed: 16492122]
- Hall RCW, Hall RCW, Chapman MJ. Psychiatric complications of anabolic steroid abuse. *Psychosomatics*. 2005; 46(4):285–290. [PubMed: 16000671]
- Harmer PA. Anabolic-androgenic steroid use among young male and female athletes: is the game to blame? *British Journal of Sports Medicine*. 2010; 44(1):26–31. [PubMed: 19919946]
- Harrison RJ, Connor DF, Nowak C, Nash K, Melloni RH. Chronic anabolic-androgenic steroid treatment during adolescence increases anterior hypothalamic vasopressin and aggression in intact hamsters. *Psychoneuroendocrinology*. 2000; 25(4):317–338. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10725610>. [PubMed: 10725610]
- Isacson G, Bergman U. Can anabolic steroids cause personality changes? *Nordisk Medicin*. 1993; 108(6–7):180–181. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8321641>. [PubMed: 8321641]
- Johnson MD. Anabolic steroid use in adolescent athletes. *Pediatric Clinics of North America*. 1990; 37(5):1111–1123. Retrieved from <http://europepmc.org/abstract/med/2216557>. [PubMed: 2216557]
- Johnson MD, Jay MS, Shoup B, Rickert VI. Anabolic Steroid Use by Male Adolescents. *Pediatrics: Official Journal of the American Academy of Pediatrics*. 1989; 83:921–924.
- Kouri EM, Lukas SE, Pope HG, Oliva PS. Increased aggressive responding in male volunteers following the administration of gradually increasing doses of testosterone cypionate. *Drug and*

- Alcohol Dependence. 1995; 40(1):73–79. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8746927>. [PubMed: 8746927]
- Kouvelas D, Pourzitaki C, Papazisis G, Dagklis T, Dimou K, Kraus M. Nandrolone abuse decreases anxiety and impairs memory in rats via central androgenic receptors. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*. 2008; 11(7):925–934. [PubMed: 18405416]
- Kreuz LE, Rose RM. Assessment of aggressive behavior and plasma testosterone in a young criminal population. *Psychosomatic Medicine*. 1972; 34(4):321–332. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/5074958>. [PubMed: 5074958]
- Lerwill CJ, Makings P. The agonistic behavior of the golden hamster. *Animal Behavior*. 1971; 19:714–721.
- Lindqvist, A.; Eriksson, B.; Ehrnborg, C.; Fahlke, C.; Moberg, T.; Rosen, T. AAS abuse in former competitive sport athletes. First Nordic Conference on Abuse of Anabolic Steroids and Anti-doping Work; Uppsala. 2007.
- Lister RG. The use of a plus-maze to measure anxiety in the mouse. *Psychopharmacology*. 1987; 92(2)
- Lumia AR, Thorner KM, McGinnis MY. Effects of chronically high doses of the anabolic androgenic steroid, testosterone, on intermale aggression and sexual behavior in male rats. *Physiology & Behavior*. 1994; 55(2):331–335. [PubMed: 8153174]
- Malone DA, Dimeff RJ. The use of fluoxetine in depression associated with anabolic steroid withdrawal: a case series. *The Journal of Clinical Psychiatry*. 1992; 53(4):130–132. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/1564048>. [PubMed: 1564048]
- Malone DA, Dimeff RJ, Lombardo JA, Sample RH. Psychiatric effects and psychoactive substance use in anabolic-androgenic steroid users. *Clinical Journal of Sport Medicine : Official Journal of the Canadian Academy of Sport Medicine*. 1995; 5(1):25–31. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/7614077>. [PubMed: 7614077]
- Mattsson Å, Schalling D, Olweus D, Löw H, Svensson J. Plasma Testosterone, Aggressive Behavior, and Personality Dimensions in Young Male Delinquents. *Journal of the American Academy of Child Psychiatry*. 1980; 19(3):476–490. [PubMed: 7410752]
- McGinnis MY, Lumia AR, Breuer ME, Possidente BP. Physical provocation potentiates aggression in male rats receiving anabolic androgenic steroids. *Hormones and Behavior*. 2002; 41(1):101–110. [PubMed: 11863388]
- McGinnis MY, Lumia AR, Possidente BP. Effects of withdrawal from anabolic androgenic steroids on aggression in adult male rats. *Physiology & Behavior*. 2002; 75(4):541–549. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12062318>. [PubMed: 12062318]
- Melchior CL, Ritzmann RF. Dehydroepiandrosterone is an anxiolytic in mice on the plus maze. *Pharmacology, Biochemistry, and Behavior*. 1994; 47(3):437–441. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/7911573>.
- Melloni RH, Ricci LA. Adolescent exposure to anabolic/androgenic steroids and the neurobiology of offensive aggression: a hypothalamic neural model based on findings in pubertal Syrian hamsters. *Hormones and Behavior*. 2010; 58(1):177–191. [PubMed: 19914254]
- NIDACapsules. 2007. Retrieved from <http://www.nida.nih.gov/NIDACapsules/NCIndex.html>
- Olivares EL, Silveira ALB, Fonseca FV, Silva-Almeida C, Côrtes RS, Pereira-Junior PP, Reis LC. Administration of an anabolic steroid during the adolescent phase changes the behavior, cardiac autonomic balance and fluid intake in male adult rats. *Physiology & Behavior*. 2014; 126:15–24. [PubMed: 24382485]
- Olweus, D. Testosterone and adrenaline: aggressive antisocial behavior in normal adolescent males. In: Mednick, SA.; Moffitt, TE.; Stack, SA., editors. *The Causes of Crime: New Biological Approaches*. Cambridge: Cambridge University Press; 1987. p. 239–262.
- Olweus D, Mattsson Å, Schalling D, Löw H. Testosterone, aggression, physical, and personality dimensions in normal adolescent males. *Psychosomatic Medicine*. 1980; 42(2):253–269. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/7454920>. [PubMed: 7454920]
- Pagonis TA, Angelopoulos NV, Koukoulis GN, Hadjichristodoulou CS. Psychiatric side effects induced by supraphysiological doses of combinations of anabolic steroids correlate to the severity

- of abuse. *European Psychiatry : The Journal of the Association of European Psychiatrists*. 2006; 21(8):551–562. [PubMed: 16356691]
- Pagonis TA, Angelopoulos NV, Koukoulis GN, Hadjichristodoulou CS, Toli PN. Psychiatric and hostility factors related to use of anabolic steroids in monozygotic twins. *European Psychiatry : The Journal of the Association of European Psychiatrists*. 2006; 21(8):563–569. [PubMed: 16529916]
- Payne AP. A comparison of the effects of androstenedione, dihydrotestosterone and testosterone propionate on aggression in the castrated male golden hamster. *Physiology & Behavior*. 1974a; 13(1):21–26. [PubMed: 4859192]
- Payne AP. A comparison of the effects of androstenedione, dihydrotestosterone and testosterone propionate on aggression in the castrated male golden hamster. *Physiology & Behavior*. 1974b; 13(1):21–26. [PubMed: 4859192]
- Payne AP, Swanson HH. The effect of sex hormones on the agonistic behavior of the male golden hamster (*Mesocricetus auratus* Waterhouse). *Hormones and Behavior*. 1972; 8(4):687–691.
- Pellow S, Chopin P, File SE, Briley M. Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. *Journal of Neuroscience Methods*. 1985; 14(3):149–167. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/2864480>. [PubMed: 2864480]
- Pellow S, File SE. Anxiolytic and anxiogenic drug effects on exploratory activity in an elevated plus-maze: a novel test of anxiety in the rat. *Pharmacology, Biochemistry, and Behavior*. 1986; 24(3): 525–529. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/2871560>.
- Perry PJ, Andersen KH, Yates WR. Illicit anabolic steroid use in athletes: A case series analysis. *The American Journal of Sports Medicine*. 1990; 18(4):422–428. [PubMed: 2403192]
- Pope HG, Katz DL. Bodybuilder's psychosis. *The Lancet*. 1987; 329(8537):863.
- Pope HG, Katz DL. Affective and Psychotic Symptoms Associated With Anabolic Steroid Use. *American Journal of Psychiatry*. 1988; 145:487–490. [PubMed: 3279830]
- Pope HG, Katz DL. Psychiatric and Medical Effects of Anabolic-Androgenic Steroid Use. *Archives of General Psychiatry*. 1994; 51:375–382. [PubMed: 8179461]
- Pope HG, Kouri EM, Hudson JI. Effects of Supraphysiologic Doses of Testosterone on Mood and Aggression in Normal Men. *Archives of General Psychiatry*. 2000; 57:133–140. [PubMed: 10665615]
- Prendergast BJ, Nelson RJ. Affective responses to changes in day length in Siberian hamsters (*Phodopus sungorus*). *Psychoneuroendocrinology*. 2005; 30(5):438–452. [PubMed: 15721056]
- Rainer Q, Speziali S, Rubino T, Dominguez-Lopez S, Bambico FR, Gobbi G, Parolaro D. Chronic nandrolone decanoate exposure during adolescence affects emotional behavior and monoaminergic neurotransmission in adulthood. *Neuropharmacology*. 2014; 83:79–88. [PubMed: 24721625]
- Ramos-Pratts K, Rosa-González D, Pérez-Acevedo NL, Cintrón-López D, Barreto-Estrada JL. Sex-specific effect of the anabolic steroid, 17 α -methyltestosterone, on inhibitory avoidance learning in periadolescent rats. *Behavioural Processes*. 2013; 99:73–80. [PubMed: 23792034]
- Ricci LA, Morrison TR, Melloni RH. Serotonin modulates anxiety-like behaviors during withdrawal from adolescent anabolic-androgenic steroid exposure in Syrian hamsters. *Hormones and Behavior*. 2012; 62(5):569–578. [PubMed: 23026540]
- Ricci LA, Morrison TR, Melloni RH. Adolescent anabolic/androgenic steroids: Aggression and anxiety during exposure predict behavioral responding during withdrawal in Syrian hamsters (*Mesocricetus auratus*). *Hormones and Behavior*. 2013; 64(5):770–780. [PubMed: 24126136]
- Ricci LA, Rasakham K, Grimes JM, Melloni RH. Serotonin-1A receptor activity and expression modulate adolescent anabolic/androgenic steroid-induced aggression in hamsters. *Pharmacology, Biochemistry, and Behavior*. 2006; 85(1):1–11.
- Ricci LA, Schwartz JJ, Melloni RH. Alterations in the anterior hypothalamic dopamine system in aggressive adolescent AAS-treated hamsters. *Hormones and Behavior*. 2009; 55(2):348–355. [PubMed: 19014946]
- Rocha VM, Calil CM, Ferreira R, Moura MJCS, Marcondes FK. Influence of anabolic steroid on anxiety levels in sedentary male rats. *Stress (Amsterdam, Netherlands)*. 2007; 10(4):326–331.

- Rojas-Ortiz YA, Rundle-González V, Rivera-Ramos I, Jorge JC. Modulation of elevated plus maze behavior after chronic exposure to the anabolic steroid 17alpha-methyltestosterone in adult mice. *Hormones and Behavior*. 2006; 49(1):123–128. [PubMed: 16026788]
- Romeo RD, Schulz KM, Nelson AL, Menard TA, Sisk CL. Testosterone, puberty, and the pattern of male aggression in Syrian hamsters. *Developmental Psychobiology*. 2003; 43(2):102–108. [PubMed: 12918089]
- Scerbo AS, Kolko DJ. Salivary testosterone and cortisol in disruptive children: relationship to aggressive, hyperactive, and internalizing behaviors. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1994; 33(8):1174–1184. [PubMed: 7982868]
- Schaal B, Tremblay RE, Soussignan R, Susman EJ. Male testosterone linked to high social dominance but low physical aggression in early adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1996; 35(10):1322–1330. [PubMed: 8885586]
- Schalling, D. Personality correlates of plasma testosterone levels in young delinquents: an example of person-situation interaction. In: Mednick, SA.; Moffitt, TE.; Stack, SA., editors. *The Causes of Crime: New biological approaches*. Cambridge: Cambridge University Press; 1987. p. 283-291.
- Steroid Tips. 2014 from <http://www.steroidtips.com/>.
- Strauss, RH. *Drugs and Performance Sports*. 1st ed.. Philadelphia: W.B. Saunders Company; 1987. Anabolic Steroids; p. 59-67.
- Strauss RH, Wright JE, Finerman GAM. Side-effects of anabolic steroids in weight trained men. *The Physician and Sports Medicine*. 1983; 11:87–96.
- Su TP, Pagliaro M, Schmidt PJ, Pickar D, Wolkowitz O, Rubinow DR. Neuropsychiatric Effects of Anabolic Steroids in Male Normal Volunteers. *JAMA*. 1993; 269:2760–2764. [PubMed: 8492402]
- Toufexis D, Davis C, Hammond A, Davis M. Sex differences in hormonal modulation of anxiety measured with light-enhanced startle: possible role for arginine vasopressin in the male. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*. 2005; 25(39):9010–9016. [PubMed: 16192392]
- Zotti M, Tucci P, Colaianna M, Morgese MG, Mhillaj E, Schiavone S, Trabace L. Chronic nandrolone administration induces dysfunction of the reward pathway in rats. *Steroids*. 2014; 79:7–13. [PubMed: 24490270]
- Zuloaga DG, Morris JA, Jordan CL, Breedlove SM. Mice with the testicular feminization mutation demonstrate a role for androgen receptors in the regulation of anxiety-related behaviors and the hypothalamic-pituitary-adrenal axis. *Hormones and Behavior*. 2008; 54(5):758–766. [PubMed: 18775430]
- Zuloaga DG, Poort JE, Jordan CL, Breedlove SM. Male rats with the testicular feminization mutation of the androgen receptor display elevated anxiety-related behavior and corticosterone response to mild stress. *Hormones and Behavior*. 2011; 60(39):380–388. [PubMed: 21801726]

HIGHLIGHTS

1. Anabolic steroids are anxiogenic during withdrawal in adolescents, but not adults
2. Adult exposure to anabolic steroids may be anxiolytic over the long term
3. Anabolic steroids do not alter aggression in adults during exposure or withdrawal
4. In Adolescent-anabolic steroid withdrawal, aggression is low while anxiety is high

Adolescent AAS

Figure 1.

Adolescent AAS exposure produced increased rump/belly targeted attacks and decreased latency to attack during adolescent exposure testing period (P57) (a - Left), but not during withdrawal (P77) (b - Left). There were no changes in entries into the open arms or duration of time spent in the open arms of the EPM during AAS exposure (P57) (a - Right), but decreases in the number of entries into the open arms and a reduction in the amount of time spent in the open arms of the EPM were observed following withdrawal from adolescent AAS exposure (P77) (b - Right). (** $p < 0.01$, *** $p < 0.001$).

Adult AAS

(a) AAS Exposure (P95)

(b) AAS Withdrawal (P115)

Figure 2.

During the AAS-exposure testing period (P95), adults administered AAS showed no differences in targeted attacks, latency to attack, entries or time spent in the open arms of the EPM compared to vehicle-treated controls (a). During the AAS-withdrawal testing period (P115), AAS adults showed no differences in aggression measures, but did have a greater number of entries into- and spent significantly more time than vehicle treated controls within- the open arms of the EPM (b) (* $p < 0.05$, ** $p < 0.01$).