Impact of anabolic androgenic steroids on adolescent males

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ABSTRACT

Anabolic androgenic steroid (AAS) use increased dramatically among adolescent males. This review focuses on studies using animal models of AAS exposure during adolescence which is a hormonally sensitive developmental period. AAS exposure during this critical period has wide-ranging consequences, including increased dendritic spine density, altered brain serotonin levels and escalated aggression in response to physical provocation. Human data suggest that AAS induces indiscriminate and unprovoked aggression often described as "'roid rage". However, animal studies indicate that the behavioral impact of AAS is modulated by experiential and social contingencies, a perceived provocation, and the chemical composition of the AAS. The AAS, testosterone increases aggression in juvenile and adult male rats when physically provoked. In contrast, stanzolol, inhibits aggression in both juvenile and adult male rats, even when physically provoked. Nandrolone has minimal effects on aggression, unless preceded by attack training. Exposure to AAS during adolescence may have a host of unintended bio-behavioral consequences. Yet, the perception of harmlessness surrounds AAS use. The perception of harmlessness is promoted by the availability of AAS especially through internet pharmacies. The perception of acceptability is reflected in current cultural ethics that no longer condemn cheating to obtain personal achievement or success. A prevailing conviction is that although AAS are illegal they are not really bad. Reduction of the availability of AAS to adolescents requires ardent legislative and legal intervention. The problem of acceptability can be addressed by educating adolescents about the short-term and long-term effects of AAS on brain and behavior, to increase awareness of the potential consequences of AAS use that apply directly to them.

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1. Introduction

The use of anabolic androgenic steroids (AAS) has increased dramatically in recent years [1,2], particularly among adolescent males. Millions of teenagers currently either use or abuse anabolic steroids [3–5]. Studies estimate that 4%–12% of high school boys have abused AAS, many of whom started by age 11 [1,3,6–10]. AAS are now being used by adolescents for a host of reasons that include gaining body mass and strength to increase their competitive edge at interscholastic sports as well as enhance their appearance and self esteem [11,12].

It is now well documented that organizational events occurring during puberty remodel the brain and influence adult behavioral response patterns [13–18]. Many of the changes in brain structure are mediated by gonadal hormones. For example, changes in the amygdala, hypothalamus, preoptic area, amygdala, and frontal cortex have all been reported [13–16,19]. The importance of androgens in the development of adult behavior patterns has been demonstrated in studies showing that depriving male hamsters of testosterone during adolescence disrupts the display of reproductive behaviors in adulthood [20,21].

The fact that adolescence is a hormonally sensitive developmental period underscores the potential for harmful effects of AAS. Exposure to high levels of androgens during adolescence may alter brain reorganization that is necessary for the acquisition and expression of adaptive adult patterns of behavior. Moreover, the effects of AAS exposure during adolescence may be long-lasting, if not permanent.

2. AAS and aggression

One of the most commonly reported side effects of AAS use in adult males is increased aggression [22,23]. AAS use has also been linked to violence and aggression toward women [24]. A recent report based on data from the National Longitudinal Study of Adolescent Health examined the relationship between AAS use and violence in a large population of young men [25]. The findings from this study suggest that young males who used AAS were more likely to engage in violent acts than were those that did not use AAS.

Anabolic androgenic steroid use has been associated with a propensity for indiscriminate and unprovoked aggression and violence in humans. This gratuitous display of aggression and violence has been referred as "'roid rage", [22,23,26,48]. 'Roid rage has been employed as a legal defense wherein AAS users argued that their behavior was due to the side effects of the AAS which induced either a state of psychosis or paranoia. While this defense has been unsuccessful in the United States

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[27], it raises the issue of whether or not AAS effects are indiscriminate and unprovoked. The relationship between AAS exposure and the factors that may predict aggression has been studied in animal models. Two important issues are: 1] does AAS induce a state of indiscriminate and unprovoked aggression ('roid rage) similar to that reported in humans, and 2] do experiential factors modulate the expression of aggression in AAS-treated male rats.

A series of experiments was conducted to determine the extent to which social and environmental factors modulate the expression of aggression following exposure to AAS [33–41]. Male rats are typically most aggressive in defending their home cage and least aggressive in a neutral cage, and are not aggressive towards either castrated males or females [42]. To assess the ability of AAS-treated males to discriminate environmental cues, rats were tested in three different environments: home cage, opponent's cage and neutral cage. AAS-treated males displayed aggression towards an opponent in their home cage [34,37]. However, when AAS-treated males were tested in either the opponent's home cage or a neutral cage the level of aggression exhibited towards opponents, while still elevated, was lower than the level expressed in their home cage [34,37].

To determine the ability to discriminate social cues, AAS-treated rats were tested for aggression with either gonadally intact or castrated males. Studies in both juvenile and adult males indicate that rats exposed to the AAS, testosterone, do not display elevated aggression towards castrated opponents [34,37]. These findings are supportive of the view that while the AAS, testosterone may lower the threshold to elicit aggression, the aggression is discriminative, and is modulated by the environmental context and social cues elicited during an aggressive encounter. In short, AAS-induced aggression is not indiscriminate.

Another key issue surrounding AAS use and "'roid rage" is whether aggression is exhibited in the absence of provocation or challenge. Several studies have addressed this issue. The issue of provocation was tested using a physical provocation in the form of a mild tail pinch. It was found in both juvenile and adult rats that physical provocation potentiates the level of aggression displayed by male rats given the AAS, testosterone [38,39,43]. The enhanced aggression occurred whether the AAS male or the opponent male was provoked, suggesting that AAS-treated males may be sensitized to any perceived threat rather than a heightened sensitivity to the unconditioned or nocioceptive qualities of AAS per se. We have proposed that the AAS, testosterone may lower the threshold to respond to a potential threat or challenge. To test the animals' response to a threatening situation, adolescent, AAS-treated males were tested for intermale aggression in a low threat (smaller male opponent) and a high threat (home cage of a resident male–female pair) condition [44]. Adolescent, AAS-treated males did not attack smaller male opponents in the absence of physical provocation. However, when placed into the home cage of an adult male that was paired with a sexually receptive female they attacked the resident male and copulated with the female.

Aggression toward females is also context specific. Adolescent male rats receiving high doses of the AAS, testosterone, exhibited sexual behavior toward females primed with either estrogen alone or estrogen plus progesterone and were not aggressive [36]. However, AAS-treated males were aggressive toward non-receptive (ovariectomized) females, particularly when provoked. Another notable finding was that adolescent AAS-treated males displayed frustration-induced persistence [35]. When placed with sexually receptive females whose vaginas were occluded with duct tape (preventing intromission and ejaculation), AAS-treated males displayed persistent mounting (Fig. 1). This persistence was not seen in control males.

An example of the role of experiential factors in modulating AAS-induced aggression comes from studies using the AAS, nandrolone. A study by Long et al. [45] reported that nandrolone-treated adult male rats exhibited increased aggression. In subsequent studies nandrolone failed to increase aggression in either adolescent or adult male rats
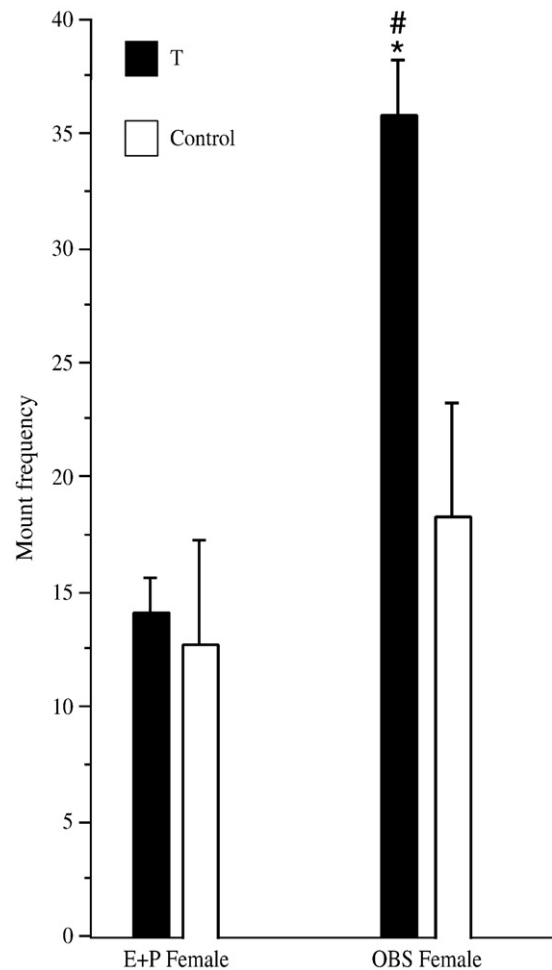

Fig. 1. Mount frequency (mean + SEM) of AAS-treated (testosterone: T) males toward sexually receptive females (estrogen + progesterone: E + P), and E + P females with vaginal obstruction (OBS). T-treated males displayed significantly more mounts toward OBS females compared to controls (*$p < 0.05$). Significantly higher levels of mounting behavior were shown towards OBS females compared with E + P females by T-treated males, but not controls (#$p < 0.05$).
Adapted from Cunningham and McGinnis, 2007.

[32–34,38–40]. However, Long et al. [45] used nadrolone-treated males that were given two weeks of fight training prior to the initiation of nadrolone administration. Males in the other studies had no prior aggressive experience. Thus, the key difference between these studies, that may account for the marked behavioral differences, is experience.

The role of prior experience is further illustrated in a study using male pigeons [46]. In this experiment, socially submissive male pigeons that were given testosterone and returned to their dominant hierarchy did not elevate in social rank. Socially submissive males trained to attack their more dominant cohorts in an operant chamber and returned to their social hierarchy also failed to gain social dominance when returned to their social group. Only when socially submissive males were given both testosterone and trained to attack more dominant male members did they rise in social dominance displacing the previously dominant member. Thus, the effect of the AAS, testosterone, is modulated by experiential factors (training to attack more dominant males).

2.1. Conclusions

It is clear that AAS exposure, in both adolescents and adults, increases aggression. However, the evidence indicates that the behavioral

consequences of AAS in the elicitation of aggression are not determined simply by the presence of very high levels of androgens. In fact it is a general phenomenon that gonadal steroids 'color our world' — endogenous androgens and estrogens in both male and females influence the nervous system and alter the behavioral response to a variety of sensory and social stimuli. So the implications derived from the evidence presented is that the behavioral consequences of AAS, are affected by a multiplicity of factors, including the environmental context, social cues, hormonal condition of the nonspecific, physical provocation and prior social experience. Anabolic androgenic steroids do not induce indiscriminate and unprovoked aggression or violence. As such, it would be difficult to present a case for "roid rage' as a legal defense without taking these mitigating factors into account. Instead, the consequences of AAS use may be better understood as lowering the threshold to respond aggressively to a threatening stimulus, whether real or perceived. The view that AAS directly elicits aggression in humans has recently been revised by Kanayama et al. [28] who reported that men with an AAS dependency were not specifically more violent, but were more likely to have a history of conduct disorder, co-morbid psychopathology and/or drug dependence [29–31]. These more recent human studies reinforce the animal data demonstrating that the behavioral impact of AAS on aggression is modulated by a variety of environmental, experiential and lifestyle factors.

3. Importance of chemical composition of AAS

In humans, AAS users often report alterations in sexual and aggressive behavior as well as changes in activity levels and sleep patterns [1,2,9,47–49]. A major difficulty in determining the neurobehavioral impact of AAS is that most users take several steroids in sequence or concurrently [32]. This form of AAS administration is referred to as 'stacking'. A particular AAS is taken for a specific period followed by a period of abstinence. The rationale for stacking is that a synergistic effect is achieved by combining specific AAS [9].

To circumvent the limitations inherent in determining AAS effects in humans, a number of animal studies have been conducted using an AAS "cocktail". An advantage of the cocktail, rather than individual AAS, is that it mimics, to some extent, the human style of dosing. The use of the AAS "cocktail" has proven valuable within an animal paradigm to show that AAS increases aggression [50–53]. One of the disadvantages of the AAS "cocktail" is that it does not contain one of the most widely used AAS, stanozolol. Because stanozolol has high anabolic (muscle building) and lower androgenic properties, it is frequently used in AAS stacking paradigms [54]. The major limitation of the cocktail, however, is that it prevents the determination of individual AAS effects. The impact of anabolic steroid use and abuse cannot be fully understood without knowledge of the effects of individual AAS on brain and behavior.

Since all anabolic steroids have both anabolic and androgenic properties, they are now referred to as anabolic androgenic steroids (AAS) [2]. One of the most commonly abused AAS is the endogenous androgen, testosterone. Testosterone is highly sought after because it is not only androgenic, but has excellent anabolic properties as well [55]. Another commonly abused AAS is stanozolol. Stanozolol is a 17alpha-alkylated, synthetic androgen that is prized for its high anabolic properties [55]. Nandrolone, which is a 19-nor testosterone has the highest affinity for the androgen receptor and has both androgenic and anabolic properties. These three commonly used AAS have been the most widely studied in animal models. It is important to bear in mind that in most studies, AAS-treated animals were compared to gonadally intact males, not castrates, which makes these results more comparable to human data.

Animal studies using testosterone have shown that exposure to high levels of this AAS during adolescence has several effects on behavior. It's ability to facilitate aggression has been well documented [32] (see Fig. 2). Testosterone also enhances many androgen-sensitive
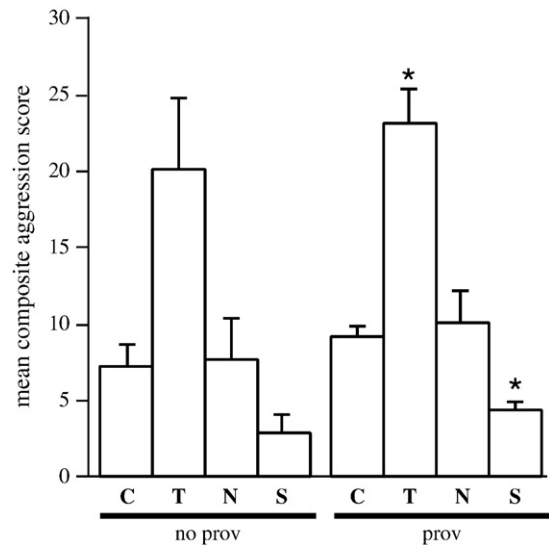

Fig. 2. Mean composite aggression score with (prov), and without (no prov), physical provocation, for males treated with testosterone (T), nandrolone (N), stanozolol (S) or control injections (C). All animals were gonadally intact. $N = 10$–12 rats/group $^*p < .01$ compared to controls.
Adapted from Wesson and McGinnis, 2006.

behaviors in adolescent rats, including copulation, partner preference, scent marking and 50 kHz ultrasonic vocalizations [32–34,38–40,56]. High doses of testosterone have also been found to affect the adolescent brain. For example, testosterone alters serotonin levels in several brain regions, decreases SRC-2 expression in the hypothalamus, and increases dendrite spine density in both the amygdala and hippocampus [43,44,57,58]. Some experiments have examined the long-term effects of adolescent AAS exposure. Evidence from these studies suggests that exposure to testosterone during this critical period of brain development exerts a long-term and possibly permanent effect on both behavior and brain maturation, including serotonin levels and hippocampal dendritic spine density [33,44,57].

In general, studies on non-social behaviors, such as locomotion and nose poke for a food reward have indicated that testosterone does not influence these behavioral patterns [43,44,59]. An exception to this is running wheel activity [58]. Wheel running activity was significantly increased in male rats exposed to testosterone during late puberty when compared to gonadally intact control males. These results from animal studies show that the AAS, testosterone is a powerful modulator of brain and behavioral maturation in the adolescent brain.

The effects of the AAS, stanozolol, stand in stark contrast to those of testosterone. In adolescent rats, stanozolol actually inhibits androgen-sensitive behaviors, including sexual behavior, aggression toward both males (Fig. 2) and females, scent marking and ultrasonic vocalizations [32–36,38–40]. This behavioral inhibition is a health concern, particularly because stanozolol is often taken by adolescents and has the potential for disrupting normal brain development. The behavioral effects of stanozolol appear to be long-lasting and possibly permanent as the suppression of both sexual behavior and aggression has been shown to be present for many weeks after cessation of stanozolol exposure [33]. While these data lend support to the view that stanozolol may have permanent effects on the brain maturation, the effect of stanozolol on parameters such as spine density and neurotransmitters has not been studied.

In adolescent male rats, few effects of the AAS, nandrolone, have been found. Males receiving nandrolone treatment were similar to gonadally intact controls with regard to sexual behavior, aggression (Fig. 2), scent marking and vocalizations [33,34,38]. Paradoxically, nandrolone had an inhibitory effect on wheel running, a non-social behavior, in adolescent

male rats [58]. It may be noted that most nandrolone studies have been conducted on adult males and the results have been equivocal, sometimes increasing aggression and sometimes not [37,39–41,45,60]. However, changes in dopamine and serotonin have been reported in adult animals suggesting that nandrolone alters brain neurochemistry, at least in adults [60,61]. Neurochemical changes resulting from nandrolone exposure have not been assessed in adolescent males.

Only one study has examined the effect of combining different AAS in a controlled stacking paradigm [38]. In this experiment, adolescent male rats received testosterone, nandrolone and stanozolol alone or in combination: testosterone + nandrolone, testosterone + stanozolol, or nandrolone + stanozolol. One of the most interesting findings from this study was that stacking testosterone with stanozolol prevented the inhibitory effects of stanozolol on virtually all behavioral measures. In contrast, nandrolone did not prevent the inhibitory effects of stanozolol on sexual behavior or scent marking. Cell nuclear androgen receptor binding in brain was measured to determine if the changes in behavior were correlated with the binding characteristics of these three AAS. As previously reported [62], nandrolone had the highest affinity for the androgen receptor, followed by testosterone, and then stanozolol with the lowest. Despite its low affinity for the androgen receptor, when stanozolol was combined with either nandrolone or testosterone it reduced androgen receptor binding. Thus, there was no direct correlation between AAS-induced changes in behavior and levels of androgen receptor binding.

AAS also differentially affect the endocrine system. As one might expect, testes weights were smaller in adolescent males receiving exogenous testosterone treatment [38,56,58] (Fig. 3). Nandrolone and stanozolol also significantly decreased testes weights [38,58] (Fig. 3). Both prostate and seminal vesicle weights were significantly increased by adolescent exposure to testosterone, but significantly decreased by exposure to nandrolone and stanozolol [38,56,58] (Fig. 3). There have been few reports of the long-term effects of AAS on the endocrine system. In one study prostate weights remained elevated 18 weeks after withdrawal from testosterone, (Fig. 3). In another study [56] there were no effects of testosterone on prostate weights 13 weeks after withdrawal of the hormone, but a lower T dose was used, suggesting the effects of AAS may be dose dependent. No long-term effects were found following withdrawal from either nandrolone or stanozolol (Fig. 3). Other endocrine measures were similarly unaffected by adolescent AAS exposure. Table 1 shows that the fertility rate was significantly lower in stanozolol-treated males, probably because of their poor ejaculatory response [33,38]. However, litter size was unaffected in stanozolol-treated males that impregnated females. Interestingly, testosterone had no effect on serum estradiol levels, but serum estradiol levels were significantly elevated in nandrolone-treated males and significantly reduced in stanozolol-treated males. The significance of this finding remains to be determined. None of these AAS resulted in long-term effects on any of the above measures (Table 2). It has been suggested in humans that AAS exposure during adolescence may stunt growth by inducing premature epiphysial closure [8,9]. Our results show that tibia and femur length in adulthood were consistently lower than controls though this did not reach statistical significance ($p < .07$) with an n of 6. This corresponds with results in adolescent non-exercised male rats indicating that T decreases body weight [38,43,58]. These data, while intriguing, should be interpreted with caution and would benefit from further research. In general, it appears that the endocrine effects eventually return to normal following withdrawal from AAS exposure in rats. However, the time course of the endocrinological recovery is currently not known.

3.1. Conclusions

The results of these studies demonstrate that the chemical composition of individual AAS is an important factor in determining
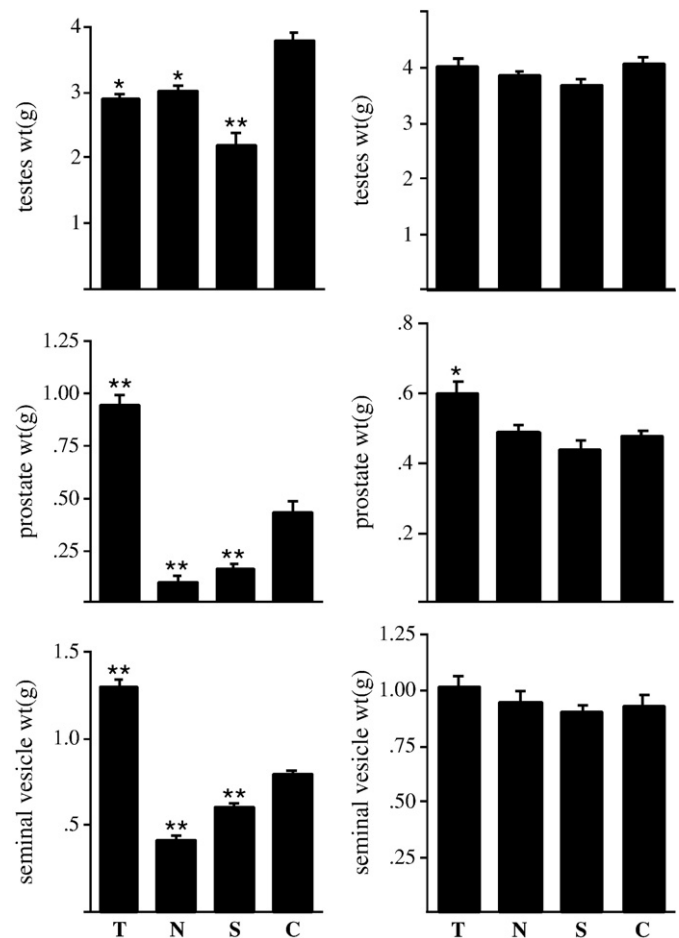

Fig. 3. Mean weights ($\pm$SEM) of reproductive tissues following long-term exposure to AAS (left panel) and 18 weeks after withdrawal from AAS exposure (right panel). Groups were testosterone (T: $n = 10$), nandrolone (N: $n = 12$), stanozolol (S: $n = 12$) or vehicle control (C: $n = 12$). During AAS exposure, testes weights were significantly lower than controls in all three groups (T, N, and S). Prostate and seminal weights were significantly higher in the T group, and were significantly lower in the N and S groups compared with controls. By 18 weeks after cessation of AAS exposure testes and seminal vesicle weights had returned to control levels. Prostate weights returned to control levels in N and S males, but remained significantly elevated in males treated with T during adolescence. $^*p < 0.001$, $^{**}p < 0.0001$.

AAS's effects on behavior. The systematic study of the effects of stacking [38] was important in demonstrating that the inhibitory effect of stanozolol could be prevented by concurrent exposure to testosterone. A major difference between these two AAS is that stanozolol is not aromatized to an estrogen. Since both testosterone and estrogen are vital for normal pubertal development [13] this has critical implications for adolescent humans. Stanozolol suppresses endogenous testosterone levels in rats [58] (Table 1). Therefore, adolescent exposure to stanozolol, in the absence of testosterone, may

Table 1
Fertility tests and serum hormone assays following chronic AAS exposure.

	Testosterone	Nandrolone	Stanozolol	Control
Fertility success rate, %	100 (5)	100 (6)	42** (12)	80 (10)
Litter size	15.8 ± 1.1 (5)	12.8 ± 1.1 (6)	8.8 ± 2.2 (4)	13.0 ± 1.1 (8)
Testosterone (ng/ml)	27.25 ± 2.74*** (10)	4.83 ± 1.11 (12)	0.06 ± 0.03 (12)	1.02 ± 0.23 (10)
Estradiol (pg/ml)	42.46 ± 7.35 (10)	186.98 ± 24.91** (11)	29.68 ± 7.05* (10)	95.47 ± 36.85 (9)

Values are mean ± SEM except for fertility success rate, with numbers of animals per group in parentheses. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.0001$ compared with controls.

Table 2
Fertility tests, serum hormone assays, and bone lengths following withdrawal from AAS.

	Testosterone	Nandrolone	Stanozolol	Control
Fertility success rate (%)	63 (8)	88 (8)	58 (12)	75 (8)
Litter size	14.0 ± 2.4 (5)	15.0 ± 0.9 (7)	13.29 ± 0.47 (7)	13.8 ± 1.5 (5)
Testosterone (ng/ml)	1.70 ± 0.28 (9)	1.45 ± 0.39 (10)	1.12 ± 0.26 (11)	2.75 ± 0.91 (9)
Estradiol (pg/ml)	166.08 ± 49.79 (11)	111.05 ± 40.71 (9)	86.58 ± 28.05 (8)	110.63 ± 39.12 (9)
Tibia length (cm)	4.42 ± 0.05 (6)	4.53 ± 0.04 (6)	4.52 ± 0.03 (6)	4.55 ± 0.06 (6)
Femur length (cm)	4.00 ± 0.04 (6)	4.10 ± 0.03 (6)	4.10 ± 0.04 (6)	4.10 ± 0.06 (6)

Values are mean ± SEM except for fertility success rate, with numbers of animals per group in parentheses.

have negative consequences for normal neural and behavioral development [9,63,64]. Another significant consequence of adolescent AAS exposure with direct human relevance is that AAS have long-term effects on behavior, neurochemistry and neural function [33,44,57].

4. AAS and the perception of harmlessness

This review presented unambiguous evidence implicating the use of AAS during adolescence with a host of unintended neural and behavioral consequences. While the palpable consequences of AAS exposure on neurobehavioral development are apparent, the perception of harmlessness surrounds their use. This appears to be based on several factors, including availability and acceptability.

In 1990, the Anabolic Steroid Control act was passed into law and many AAS were given a schedule III classification. Despite the fact that AAS are now illegal they are readily available online. In a 2006 report issued by the National Center on Addiction and Substance Abuse at Columbia University [65] it was reported that no prescription was required to purchase drugs from many of the websites that sell controlled drugs. Any teenager with a credit card can obtain AAS without the permission of a physician [66]. This easy access contributes to the perception of harmlessness.

A second factor that has advanced the perception of harmlessness is the ethical climate that pervades our culture with regard to personal or athletic achievement. A striking example of the ethical justification surrounding personal achievement is presented by Berning et al. [11]. These authors reported that coaches had a tendency to feel that it was not cheating and was justified if everyone was doing it. This attitude of acceptability, particularly in adult role models adds to the perception of harmlessness.

In conclusion, the use of AAS has not abated, particularly in teenagers [12]. One of the core beliefs of youth is that they are invincible and that medical catastrophes happen to others [67]. The effects of AAS use have the highest potential for long-term consequences in the adolescent population. The extent to which effective education concerning the consequences of early AAS use, combined with early medical intervention, legislative and legal intercession will affect the perception of harmlessness remains to be seen.

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