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Androgenic anabolic steroid exposure during adolescence: Ramifications for brain development and behavior

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Abstract

Puberty is a critical period for brain maturation that is highly dependent on gonadal sex hormones. Modifications in the gonadal steroid environment, via the use of anabolic androgenic steroids (AAS), have been shown to affect brain development and behavior. Studies in both humans and animal models indicate that AAS exposure during adolescence alters normal brain remodeling, including structural changes and neurotransmitter function. The most commonly reported behavioral effect is an increase in aggression. Evidence has been presented to identify factors that influence the effect of AAS on the expression of aggression. The chemical composition of the AAS plays a major role in determining whether aggression is displayed, with testosterone being the most effective. The hormonal context, the environmental context, physical provocation and the perceived threat during the social encounter have all been found to influence the expression of aggression and sexual behavior. All of these factors point toward an altered behavioral state that includes an increased readiness to respond to a social encounter with heightened vigilance, and enhanced motivation. This AAS-induced state may be defined as emboldenment. The evidence suggests that the use of AAS during this critical period of development may increase the risk for maladaptive behaviors along with neurological disorders.

Keywords

Testosterone; adolescence; HPG; aggression; sex behavior; plasticity

Introduction

This review will address the relationship between the exposure to AAS during adolescence and their neuro-behavioral consequences. We present data in support of AAS-induced changes in neuroplasticity and neurotransmitter activity during adolescence. We also present evidence demonstrating that the neuro-behavioral impact of adolescent AAS is modulated by a host of experiential factors. Finally, we put forth hypotheses that may help to explain the consequences of exposure to AAS use in puberty.

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1. Puberty

Puberty consists of three components: adrenarche, growth axis activation, and gonadarche (Dorn, 2006; Spear, 2000). Adrenarche, which is activation of the hypothalamic-pituitary-adrenal axis (HPA), occurs generally around 6–9 years of age for girls and a year later for boys (Dorn, 2006; Grumbach and Styne, 1998). Generally, growth spurts for girls is at 12 years of age and 14 for boys (Marshall and Tanner, 1969, 1970). Lastly, gonadarche, which is the activation of the hypothalamic-pituitary-gonad axis (HPG), occurs approximately around 8–14 years of age for girls and 9–15 for boys (Susman and Rogol, 2004). In animal studies it has been shown that during these three periods of puberty, organizational events occur that remodel the brain and influence adult behavior patterns (Romeo et al., 2002; Schulz et al., 2009; Sisk et al., 2003; Spear, 2000; Zehr et al., 2008; Zehr et al., 2006). Many of these organizational effects during puberty in boys and girls have been attributed to gonadal steroids, such as testosterone and its metabolite estrogen (Bakker et al., 2003; Keenan et al., 1993; Kerrigan and Rogol, 1992; McCarthy, 2008; Morris et al., 2004).

1.1 Puberty-associated brain remodeling

In humans brain remodeling occurs with puberty. Grey matter volume peaks during puberty, such as amygdala, hippocampal, frontal cortex, temporal cortex, parietal cortex volume (Giedd et al., 1999; Neufang et al., 2009). In addition, white matter increases during puberty (Giedd et al., 1999; Tamnes et al., 2010), with adolescent boys exhibiting a greater increase in white matter compared to girls (Perrin et al., 2009). Interestingly, testosterone has a positive correlation with increased grey matter in adolescent boys (Peper et al., 2009). Similar puberty-associated brain remodeling has been reported in rodent animal models, such as structural changes in the amygdala, hypothalamus, preoptic area, frontal cortex, and striatum (Andersen and Teicher, 2000; Romeo et al., 2002; Sisk et al., 2003; Teicher et al., 2003; Zehr et al., 2006). Therefore these studies indicate that rodents are a viable model for pubertal associated brain and behavior maturation.

1.2 Hyperandrogenism and brain remodeling in adolescents

In humans, genetic forms of hyperandrogenism can be used to examine the effects of supraphysiological levels of androgens on pubertal brain maturation. Adolescent boys diagnosed with familial hyperandrogenism display increased hippocampal activity (Mueller et al., 2009), and increased amygdala activity during fear processing activities (Ernst et al., 2007). These studies suggest that exposure to supraphysiological levels of androgens alter limbic region functions, and offer a window into the possible ramifications of exposure to exogenous supraphysiological levels of androgens, such as anabolic androgenic steroids (AAS), in the adolescent population.

2. Anabolic Androgenic Steroids (AAS) and Puberty

In recent years, AAS abuse has increased, especially in the adolescent male population (Stilger and Yesalis, 1999; Uzych, 1992). The Centers for Disease Control and Prevention reported that 4.3% high school boys have used AAS (Centers for Disease Control and Prevention, 2009), with many reporting the age of first AAS use at 11 years (Anderson et al., 1997; Bahrke et al., 1998; Buckley et al., 1988; Faigenbaum et al., 1998; Rogol and Yesalis, 1992; Stilger and Yesalis, 1999; Tanner et al., 1995). A current study about AAS use in experienced male weightlifters found that 6% had initiated AAS during adolescence, and risk factors for AAS use included conduct disorder, adolescent body image disorder, and male gender (Pope et al., 2012). These risk factors are consistent with the variety of reasons for AAS abuse reported by adolescents, such as increased body mass and strength, competitive edge, appearance, and self-esteem (Berning et al., 2004; Denham, 2009).

AAS abuse in adolescents has been associated with a spectrum of behavioral effects, such as increased physical and verbal aggression, irritability, and impulsiveness (Olweus et al., 1980; Olweus et al., 1988; Scott et al., 1996), similar to what has been reported for adult AAS users (Choi and Pope, 1994; Galligani et al., 1996; Pope and Katz, 1990; Pope and Katz, 1994). Although similar behavioral effects of AAS abuse have been reported in the adolescent and adult populations, it is highly disconcerting that adolescents are abusing AAS, especially since adolescence is a critical time period involving gonadal steroid-mediated brain remodeling (Bakker et al., 2003; Keenan et al., 1993; Kerrigan and Rogol, 1992; McCarthy, 2008; Morris et al., 2004; Romeo et al., 2002; Schulz et al., 2009; Sisk et al., 2003; Spear, 2000; Zehr et al., 2008; Zehr et al., 2006). Currently, knowledge of the effects of AAS abuse in the adolescent population on brain and behavior is limited. However, animal studies suggest that AAS may have a more prominent effect on brain and resulting behavior in adolescents than adults.

2.1 AAS and neurotransmitters

Pubertal AAS exposure in rodent models has been shown to induce structural changes in the hippocampus and amygdala, along with increased activity of the amygdala (Costine et al., 2010; Cunningham et al., 2007; Oberlander and Henderson, 2012). However, more studies have examined the effects of pubertal AAS exposure on brain neurotransmitters. Pubertal AAS exposure has been shown to alter serotonin (5-HT), catecholamine levels, vasopressin, GABA, and glutamate (Table 1).

5-HT has been associated with mood, cognition, anxiety, aggression, and reproduction (Barnes and Sharp, 1999; van Erp and Miczek, 2000; Young, 2007). AAS exposure decreased 5-HT and 5-HT metabolites levels in the hypothalamus, amygdala, striatum, and hippocampus of pubertal rodents (Bonson et al., 1994; Grimes and Melloni, 2006; Keleta et al., 2007; Kubala et al., 2008) and in adult rodents (Ambar and Chiavegatto, 2009). However, an age-associated difference in AAS-induced 5-HT levels was found in the cortex, in which pubertal AAS exposure increased 5-HT and 5-HT metabolite levels (Frahm et al., 2011; Keleta et al., 2007; Kubala et al., 2008), whereas adult AAS exposure decreased 5-HT levels in male rodents (Ambar and Chiavegatto, 2009). Interestingly, decreased 5-HT levels in the cortex have been associated with aggression (van Erp and Miczek, 2000), suggesting that AAS could exacerbate 5-HT-mediated aggression.

Catecholamines, such as dopamine and norepinephrine, are associated with cognition, motivation, movement, mood, attention, and aggression (Schultz, 2007; van Erp and Miczek, 2000). Studies have examined catecholamine levels in several brain regions. AAS exposure in adult rodents increased dopamine and its metabolites levels/expression in striatum, cortex, and hypothalamus (Kindlundh et al., 2002; Kindlundh et al., 2004; Kurling et al., 2005; Thiblin et al., 1999). Fewer studies have examined catecholamine levels in pubertal AAS-exposed rodents. These studies found a different expression pattern than adult rodents. Specifically, pubertal AAS exposure did not increase catecholamine levels in the striatum and cortex (Frahm et al., 2011). However, pubertal AAS exposure did increase dopamine metabolite and norepinephrine levels in the brainstem (Frahm et al., 2011), and increased dopamine neuronal expression in the hypothalamus (Ricci et al., 2009) (Table 1).

Pubertal AAS exposure in male rodents has been shown to increase vasopressin receptor expression in the hypothalamus, bed nucleus of the stria terminalis (BNST), and the septum (DeLeon et al., 2002; Harrison et al., 2000). Interestingly, vasopressin has been associated with increased aggression (Ferris et al., 1984) and stress (Aguilera et al., 1993; Yates et al., 1971).

AAS has been shown to modulate the main excitatory and inhibitory neurotransmitters, GABA and glutamate, respectively. Pubertal AAS can enhance excitatory neurotransmission by increasing vesicular glutamate transporter expression in the hypothalamus, BNST, and amygdala in pubertal rodents (Carrillo et al., 2011), along with increasing spine density, a measure of excitatory potential, in the hippocampus and amygdala (Cunningham et al., 2007). Similarly, in adults AAS can enhance excitatory neurotransmission through increased phosphorylation of the glutamate NMDA receptor in adult rodents (Rossbach et al., 2007). In contrast, pubertal AAS can have region-specific effects on inhibitory neurotransmission, such as decreased or no effect on GABA-A subunit expression in the hypothalamus and increased GABA-A subunit expression in the amygdala in male rodents (McIntyre et al., 2002; Penatti et al., 2005). In adult rodents, AAS decreased GABA-A subunit expression in the amygdala and hypothalamus (McIntyre et al., 2002) (Table 1). These findings indicate that AAS can modulate neurotransmission through the glutamatergic and GABAergic systems, but the effects of AAS on the GABAergic system varies for pubertal and adult animals.

Taken as a whole, these studies indicate that pubertal AAS exposure can alter brain plasticity in the limbic regions of the brain via neurotransmitters and structural changes. The limbic regions, such as the hypothalamus, amygdala, and hippocampus, support a broad range of functions that include aggression, reproductive behaviors, learning, and appropriate responses to external stimuli (Sokolowski and Corbin, 2012). Modulation of this region of the brain, especially by AAS exposure during the critical period of puberty, may increase the likelihood of behavioral and emotional disorders. While these areas also contain high concentrations of androgen receptors, it is notable that androgen receptor binding levels were not correlated with AAS-induced changes in behavior (Wesson and McGinnis, 2006). Changes in serotonin and dopamine found in non-limbic structures such as the striatum, frontal cortex and brainstem, which are not high in cell nuclear androgen receptor levels, support a potential role for exposure to supraphysiological levels of AAS, acting perhaps via membrane receptors or other cellular mechanisms. Interpretation of the neurotransmitter effects is complicated by the fact that different studies examined different brain areas, employed different techniques, and AAS exposure times. Despite the anatomical and experimental variability, it is clear that exposure to AAS during adolescence, when structural brain maturation is occurring, alters neurotransmitter function and dendritic spine density in these same limbic structures that are important for androgen-dependent adult behavior patterns.

2.2 Pubertal AAS exposure and behavior

The majority of AAS behavioral studies on adolescent animals have been performed on rats and hamsters. In hamsters, aggressive behavior has generally been the dependent variable (DeLeon et al., 2002; Ricci et al., 2009), though one study has tested the effect of AAS on sexual behavior (Salas-Ramirez et al., 2008). In rats, aggression has been studied in detail (Cunningham and McGinnis, 2006, 2007; Farrell and McGinnis, 2003; Frahm et al., 2011; Keleta et al., 2007; Kubala et al., 2008; Wesson and McGinnis, 2006). In addition, the effects of AAS on sexual behavior and two androgen-dependent behaviors, scent marking and ultrasonic vocalizations have been examined.

2.2.1 Aggression

2.2.1a Chemical composition of AAS and increased aggression: In both rats and hamsters, the most common measure used for assessing inter-male aggression is the resident-intruder paradigm, where the experimental male is introduced into the cage of a conspecific animal (Farrell and McGinnis, 2003; Harrison et al., 2000). Species typical aggressive responses are recorded for the experimental animal (offensive aggression). Using

this paradigm, increased aggression has been consistently reported in adolescent males exposed to AAS (DeLeon et al., 2002; Farrell and McGinnis, 2003; Farrell and McGinnis, 2004; Harrison et al., 2000; Ricci et al., 2009; Salas-Ramirez et al., 2008), unlike adult AAS-treated males that show variable aggressive responses (Breuer et al., 2001; McGinnis et al., 2002a; Salas-Ramirez et al., 2008, 2010) (Table 1). In the case of hamsters, a cocktail consisting of testosterone, nandrolone and boldenone has been employed (DeLeon et al., 2002; Grimes and Melloni, 2006; Ricci et al., 2009; Salas-Ramirez et al., 2008). However, studies in rats have shown that the chemical composition of the AAS is a critical factor in determining whether or not aggression will be displayed. For example, testosterone increases aggression, whereas stanozolol inhibits aggression (Farrell and McGinnis, 2003; Wesson and McGinnis, 2006). Nandrolone's effect is equivocal, sometimes increasing and sometimes having no effect on aggression (Farrell and McGinnis, 2003; Farrell and McGinnis, 2004; Wesson and McGinnis, 2006). One study examined the effect of stacking AAS in adolescent male rats (Wesson and McGinnis, 2006). Males received testosterone, nandrolone or stanozolol alone or in combination. Testosterone, alone, increased aggression, while combining testosterone with nandrolone did not alter behavior. However, stacking paradigms that included stanozolol inhibited virtually all androgen- mediated behaviors measured. It is clear from these results that in spite of the differences in AAS composition, use of different species, and different exposure times, that adolescent AAS exposure, particularly to testosterone, increases aggression.

2.2.1b Experiential factors that influence AAS-induced aggression: Several studies have been designed to investigate a variety of variables that might influence aggressive responses in adolescent males exposed to AAS. The intent of these studies was A] to determine if AAS-induced aggression was indiscriminant as has been proposed for human males and B] to identify experiential factors that might modulate the expression of AAS induced aggression (Cunningham and McGinnis, 2007, 2008; Farrell and McGinnis, 2003; Farrell and McGinnis, 2004; Feinberg et al., 1997; Keleta et al., 2007; Kubala et al., 2008). The data derived from these studies have been instrumental in demonstrating that a number of experiential factors influence the display of aggression in AAS-treated males. Factors that have been identified are the hormonal status, the environmental context, physical provocation and the perceived threat during the social encounter.

The hormonal status of the conspecific rat plays a crucial role in determining whether aggression will be exhibited. It has been demonstrated that adolescent AAS-treated males can discriminate the hormonal states of their opponents, as evidenced by increased aggression towards gonadally intact males, but not castrated male rats (Farrell and McGinnis, 2003).

The ability of AAS-treated adolescent males to make appropriate hormonal discriminations extends to females as well. AAS and control animals both display sexual behavior toward sexually receptive female rats. Notably, when AAS males were provoked by tail pinch, they continued to display sexual behavior and were not aggressive (Cunningham and McGinnis, 2007). A plausible interpretation is that the hormonal and behavioral cues emanating from the females were sufficient to suppress aggression that typically follows physical provocation in AAS-treated pubertal males. In contrast, when AAS treated males were paired with sexually unreceptive females, that are devoid of both the hormonal and behavioral sexual qualities necessary to induce male copulation (i.e., proceptive, receptive or attraction), the AAS-treated males displayed aggression towards the females (Cunningham and McGinnis, 2007). Thus, the absence of sexually eliciting stimulus qualities emanating from the female can induce a state of frustration that leads to an escalation in aggression (Amsel, 1962, 1990). The inability to copulate does not induce aggression towards females by AAS-treated males, as evidenced by lack of aggression by pubertal AAS-treated males

towards sexually receptive females with occluded vaginas (Cunningham and McGinnis, 2007). Instead, they continued to mount the female even though they were prevented from achieving either intromissions or ejaculation. This may be an indication that AAS induces an altered motivational state that is reflected in persistence of behavior in the absence of reward.

The environmental context is another critical factor in determining whether an animal will respond aggressively (Farrell and McGinnis, 2003). Adolescent males treated with AAS were more aggressive than controls when tested against an opponent of similar age and weight in their home cage environment. However, they displayed less aggression when tested in either the opponent's home cage or a neutral cage (Farrell and McGinnis, 2003). These findings, in conjunction with the studies on hormonal cues, show that adolescent AAS exposure does not induce indiscriminate aggression as has been reported in humans ('roid rage'). Instead, the evidence indicates that the impact of AAS during puberty is modulated in part by the environmental context in which the social interaction occurs.

AAS exposure has been found to alter the aggressive response to physical provocation. To test the impact of physical provocation on the expression of AAS-induced aggression, a brief, mild tail pinch has been administered (Farrell and McGinnis, 2004). Adolescent males were tested in an inter-male aggression paradigm against a gonadally intact opponent of similar age and weight in the experimental rats home cage. When AAS treated males were physically provoked there was an elevated level of aggression towards the opponent male. However, the proclivity towards aggression was not limited to the unconditioned stimulus qualities of the tail pinch, per se. When the opponent male was tail pinched the AAS treated male still reacted by attacking the opponent, though there was no physical consequence of the tail pinch. In short, the exposure to physical provocation, experiential or observed, appears to induce a state of heightened readiness to respond to a potentially threatening stimulus (ie. vigilance).

An important factor that influences aggression in adolescent AAS-treated males is the magnitude of the perceived threat. When pubertal AAS-treated males were exposed to a threatening situation, an increased likelihood towards aggression was observed. To assess the role of perceived threat, adolescent males were tested for aggression in two conditions: low threat and high threat. In the low threat test, males were paired with smaller, immature, gonadally intact opponents with and without physical provocation (Kubala et al., 2008). Testing took place in the AAS-treated rats home cage. In the absence of physical provocation, AAS-treated males did not attack the smaller opponents, even though the opponent was the intruder. In this test, AAS treated males did not differ from control males. This is significant because, even non-AAS treated gonadally intact males will display aggression in defense of their home cage when the male is an adult (Barfield et al., 1972; Breuer et al., 2001). These data suggest that in adolescent AAS-treated males, the absence of a perceived threat is sufficient to attenuate the proclivity towards displaying an adaptive species typical response in the defense of territory. When AAS-treated males were tested with gonadally intact opponents of similar age and weight, physical provocation elicited a significant increase in aggression (Keleta et al., 2007). When adolescent AAS-treated males were tested in a low threat condition with younger, smaller gonadally intact males, physical provocation elicited aggression, but they did not differ from controls. Thus, the perception that the opponent was non-threatening was sufficient to attenuate the unconditional stimulus properties of the physical provocation.

In the high threat test, males were placed in the home cage of a resident-pair that consisted of a gonadally intact male and a sexually receptive female (Kubala et al., 2008). In this test condition the AAS treated male was not only the intruder, he was smaller and younger than

his opponent, and he was entering the established home cage of a larger, older male that had been cohabitating with a sexually receptive female. In this situation the adolescent AAS-treated males, were extremely aggressive and dominant towards the resident male. In addition, the AAS-treated males successfully copulated with the resident female. In contrast, control males not only failed to display aggression, but also were rendered submissive and did not copulate with the resident female. The readiness of the adolescent AAS-treated male to emerge dominant in this aggressive encounter, rendering the resident male submissive, and to successfully copulate with the cohabitating female in this highly threatening condition, suggests that AAS may induce a state of heightened vigilance and motivation. This may be conceptualized as 'emboldenment'.

The notion of vigilance in this review is defined operationally as a heightened state of awareness or alertness induced by AAS to the diversity of stimuli that include the physical, social and experiential conditions in which the social interactions take place. The concept of vigilance is also used to denote the fact that AAS treated males display a heightened capacity to attend to the salient qualities of the social milieu that includes, such factors as the potential threat of an opponent and the hormonal status of a female. Overall, the hormonal cues emitted by the conspecific, whether male or female, as well as the environmental context are discriminated and determine the nature of the behavioral response of the AAS-treated male. In addition, the level of aggression displayed is commensurate with the perceived level of threat in a particular social encounter. Therefore, the AAS-treated male displays a keen sense of the potential threat posed by an opponent. Based on the evidence we propose AAS emboldens the animal by inducing a heightened state of vigilance to the both environmental and social cues that are present during an interaction with another individual.

2.2.2 Reproductive behaviors—The two most commonly reported paradigms to assess reproductive behavior are copulation and partner preference. Copulatory behavior is typically measured via a timed test with a sexually receptive female (Cunningham and McGinnis, 2006, 2007; Feinberg et al., 1997), while partner preference is considered a measure of sexual motivation (Everitt, 1990).

2.2.2a Sexual behavior: Sexual behavior has been assessed in adolescent AAS-treated male rodents. In hamsters, AAS significantly increased both intromissions and ejaculations in adolescent males (Salas-Ramirez et al., 2008). In pubertal rats, AAS exposure increased sexual behavior in some studies but had no effect in others (Farrell and McGinnis, 2003; Keleta et al., 2007; Wesson and McGinnis, 2006). A closer inspection suggests that this may to be due to prior sexual experience. The pubertal AAS-treated rats that had prior sexual experience were not different from controls (Farrell and McGinnis, 2003; Farrell and McGinnis, 2004; Keleta et al., 2007). However, in studies where animals did not have prior sexual experience, AAS exposure during puberty increased male sexual behavior (Feinberg et al., 1997; Wesson and McGinnis, 2006). This difference is most likely due to the fact that the controls copulated at a level below normal in their first sexual encounter, whereas the AAS-treated males copulated at normal high levels even without sexual experience. Thus, prior sexual experience plays a role in the enhancement of male sexual behavior in AAS-treated adolescent males. In contrast to the increased sexual behavior seen in AAS-treated adolescent males, AAS exposure in adults decreased sexual behaviors in hamsters (Salas-Ramirez et al., 2008) and had no effect in rats (Lumia et al., 1994) (Table 1).

2.2.2b Partner preference: The partner preference test is performed by placing the experimental male in a three-compartment apparatus. A sexually receptive female is in one compartment and an ovariectomized sexually non-receptive female is in the other compartment. The middle compartment is empty and considered neutral. The amount of

time spent in each compartment is measured (Everitt, 1990; Feinberg et al., 1997). Gonadally intact males will typically spend significantly more time with the sexually receptive female (Feinberg et al., 1997). Adolescent males receiving AAS treatment consistently showed a significantly greater preference for the sexually receptive female compared to control males (Feinberg et al., 1997; Keleta et al., 2007; Wesson and McGinnis, 2006). Thus, AAS exposure during adolescence increases sexual motivation. However by 13 weeks after withdrawal, partner preference returned to within normal levels (Feinberg et al., 1997). To our knowledge, partner preference has not been tested in AAS-treated adult males.

In sum, the data suggest that adolescent AAS exposure increases male sexual behavior, but this is influenced by prior sexual experience. Furthermore, AAS exposure increases sexual motivation as evidenced by the increase in partner preference (Feinberg et al., 1997; Keleta et al., 2007; Wesson and McGinnis, 2006). Two other androgen-dependent behaviors, scent marking and 50 kHz ultrasonic vocalizations have been measured, but the results have been equivocal significantly increasing these behaviors in one case and having no effect in the other (Farrell and McGinnis, 2003; Wesson and McGinnis, 2006). The evidence suggests that the primary effect of adolescent AAS exposure on reproductive behaviors is sexual motivation. However, this may also reflect a heightened state of sensitivity to social cues.

2.4 Long-term effects of pubertal AAS use

Long-term effects of AAS in humans have not been widely studied. In adult AAS users the long-term effects of AAS are controversial with physiological and behavioral effects ranging from months to years (Bahrke et al., 1996; Choi et al., 1990; Pope and Katz, 1988), but knowledge about the long-term effects of AAS in adolescents are currently unknown. However, animal studies have shown that pubertal AAS exposure can lead to long-term behavioral and structural changes in the brain (Table 2). Aggression has been shown to remain elevated several weeks (2–17 weeks) following suspension of pubertal AAS treatment (Carrillo et al., 2011; Farrell and McGinnis, 2004; Grimes and Melloni, 2006; Grimes et al., 2006; Salas-Ramirez et al., 2010), whereas in adults AAS had no long lasting effects on aggression following withdrawal (McGinnis et al., 2002b; Salas-Ramirez et al., 2010). With the exception of the AAS, stanozolol (Farrell and McGinnis, 2003), no long-term effects of pubertal AAS exposure were observed on sexual behaviors or sexual motivation in male rats (Feinberg et al., 1997), whereas in male hamsters decreased sexual behaviors were observed (Salas-Ramirez et al., 2010). Interestingly, long lasting changes to the structure of the brain, in response to pubertal AAS exposure, have also been shown. Spine density, a measure of excitatory potential, remained elevated in hippocampus four weeks after pubertal AAS withdrawal in rats (Cunningham et al., 2007), consistent with the time period that long-term aggressive behavioral effects were found (Farrell and McGinnis, 2004). Further, long lasting changes to the glutamate system in the hypothalamus, BNST, and amygdala were found following three-week cessation from pubertal AAS (Carrillo et al., 2011). These long lasting effects of pubertal AAS on brain structure and function suggest that AAS abuse by human adolescents may permanently alter the normal trajectory of brain development.

3. Possible association between neurological disorders and pubertal AAS use

Psychopathological disorders have been associated with abnormal brain development (Arango et al., 2008; Courchesne et al., 2011; Wallace et al., 2010). Further, increased psychopathology is associated with puberty (Kessler et al., 2007; Paus et al., 2008) with males more vulnerable to behavioral disorders, such as attention deficit hyperactivity

disorder (ADHD), conduct disorder, and oppositional defiant disorder (ODD) (American Psychiatric Association, 2000). Additionally, precocious puberty in males has been associated with earlier onset of schizophrenia, while early puberty is associated with delayed schizophrenia onset in females (Cohen et al., 1999).

The increased vulnerability for males during puberty for psychopathology indicates a role for androgens. Interestingly, ADHD and conduct disorder have been associated with the androgen receptor (Comings et al., 1999), while adolescent males and females with hyperandrogenism (familial male precocious puberty and congenital adrenal hyperplasia) have an increased incidence of ADHD diagnosis (Mueller et al., 2010). It is possible that the higher proportion of neuropsychiatric disorders in adolescent males may be a contributing or mediating factor responsible for the display of indiscriminate and unprovoked aggression and violence reported in some young AAS abusers.

4. Conclusions

The conclusion derived from the evidence presented is that AAS exposure during adolescence, a critical period of brain organization, alters the normal pattern of brain development as well as neurotransmitter function and adult behavior patterns. In both humans and animal models, AAS exposure induces changes in neural structure and neurotransmitter function. This suggests an influence of AAS on brain remodeling during this critical period that can have long lasting effects on behavior. A hallmark feature of AAS exposure is an increase in aggression. With regard to the relationship between adolescent AAS exposure and aggression, several factors that influence the expression of aggression are the chemical composition of the AAS, the hormonal context, the environmental context, physical provocation and the perceived threat during the social encounter. All of these factors point toward an altered behavioral state that includes an increased readiness to respond to a social encounter with heightened vigilance, and enhanced motivation. We propose that AAS induces this neurobehavioral state, which may be defined as emboldenment. This concept is consistent with the results for reproductive behaviors. For example, AAS-treated males show increased sexual motivation in a partner preference test, continue copulatory attempts with sexually receptive females having vaginal occlusion, and copulate with sexually receptive females in a high threat test. The results of these studies have directs implications for humans. Specifically, pubertal AAS abuse may contribute to abnormal brain development, or at least alter the normal trajectory of brain development, resulting in increased vulnerability for psychopathological and disorders and maladaptive behaviors.

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Highlights

- Pubertal anabolic androgenic steroid (AAS) exposure alters normal brain remodeling.
- Most common reported effect of pubertal AAS is aggression.
- External stimuli influence expression of AAS-induced behaviors.
- Pubertal AAS may increase the risk for neurological disorders.

Table 1

AAS effects on physiology and behavior

	Puberty	Adult
Neurotransmitters		
Serotonin		
amygdala	↑	↑
cortex	↑	↓
hippocampus	↑	↑
hypothalamus	↑	↑
striatum	↑	↑
Dopamine		
brain stem	↑	**not tested**
cortex	**no change**	↑
hypothalamus	↑	↑
striatum	**no change**	↑
Vasopressin		
bed nucleus of stria terminalis	↑	**not tested**
hypothalamus	↑	**not tested**
septum	↑	**not tested**
Glutamate		
amygdala	↑	**not tested**
bed nucleus of stria terminalis	↑	**not tested**
hippocampus	**not tested**	↑
hypothalamus	↑	**not tested**
GABA-A		
amygdala	↑	↓
hypothalamus	**variable**	↓
Plasticity		
Spine density		
amygdala	↑	**not tested**
hippocampus	↑	**not tested**
Behavior		
aggression	↑	**variable**
sexual behavior	↑	**variable**
sexual motivation	↑	**not tested**

Table 2

Long-term effects of AAS

	Puberty	Adult
Behavior		
aggression	+	–
sexual behavior	**variable**	–
Neurotransmitters		
Glutamate		
amygdala	+	**not tested**
bed nucleus of stria terminalis	+	**not tested**
hypothalamus	+	**not tested**
Plasticity		
Spine density		
amygdala	-	**not tested**
hippocampus	+	**not tested**

+ = present, - = not present