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Mad men, women and steroid cocktails: A review of the impact of sex and other factors on anabolic androgenic steroids effects on affective behaviors

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Abstract

Rationale—For several decades, elite athletes and a growing number of recreational consumers have used anabolic androgenic steroids (AAS) as performance enhancing drugs. Despite mounting evidence that illicit use of these synthetic steroids has detrimental effects on affective states, information available on sex-specific actions of these drugs is lacking.

Objectives—The focus of this review is to assess information to date on the importance of sex and its interaction with other environmental factors on affective behaviors, with an emphasis on data derived from non-human studies.

Methods—The PubMed database was searched for relevant studies in both sexes.

Results—Studies examining AAS use in females are limited, reflecting the lower prevalence of use in this sex. Data, however, indicate significant sex-specific differences in AAS effects on anxiety-like and aggressive behaviors, interactions with other drugs of abuse, and the interplay of AAS with other environmental factors such as diet and exercise.

Conclusions—Current methods for assessing AAS use have limitations that suggest biases of both under- and over-reporting, which may be amplified for females who are poorly represented in self-report studies of human subjects and are rarely used in animal studies. Data from animal literature suggest that there are significant sex-specific differences in the impact of AAS on aggression, anxiety, and concomitant use of other abused substances. These results have relevance for human females who take these drugs as performance enhancing substances and for transgender XX individuals who may illicitly self-administer AAS as they transition to a male gender identity.

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Keywords

Aggression; Alcohol; Anabolic Androgenic Steroids (AAS); Anxiety; Corticotropin Releasing Factor (CRF); Diet; Exercise; GABA_A receptors; Serotonin (5-hydroxytryptamine; 5-HT); Sex differences

1. AAS classes and current use

1.1 Profiles of AAS use in human populations

Anabolic androgenic steroids (AAS), a diverse class of synthetic androgens, are credited as the founding fathers of a large and increasingly abused class of illicit performance enhancing drugs (PEDs; Trenton and Currier 2005; Kanayama et al., 2008; Pope et al. 2014a). Use of AAS for non-therapeutic purposes arose in the mid-twentieth century, but was primarily restricted to a cadre of adult male elite athletes. Today, such limitations no longer apply: Spurred on by the ubiquity of information on the AAS through the internet and other media, as well as a growing plethora of sophisticated designer drugs (Labrie et al. 2005; Friedel et al. 2006), illicit users of AAS include women and men, adolescents and adults, athletes and non-athletes (Bahrke et al. 1998; Kanayama et al. 2001; Field et al. 2005; Miller et al. 2005; Parkinson and Evans 2006; Elliot et al. 2001, 2007; vandenBerg et al. 2007; Hallberg 2011; Ip et al. 2011; Johnston et al. 2013; Pope et al. 2014a,b). In addition to the purposeful, albeit illicit, administration of AAS, individuals of all ages and sexes may also unknowingly be exposed to these drugs through the booming business of over-the-counter nutritional supplements (Nutritional Business Journal Supplemental Report 2012) where reports estimate that ~15% of compounds marketed as performance enhancers are laced with AAS (Geyer et al. 2008; Aqai et al. 2013).

Although women and adolescents still constitute only a fraction of illicit AAS users, understanding the influence of sex and age on the impact of these drugs is critical, both for knowing the consequences of use for these identified populations and for better understanding the range of potential untoward actions of the AAS. Sex-specific effects of AAS on behavior, which are reportedly greater in women than in men (O'Connor and Cicero, 1993; Franke and Berendonk, 1997; Wu 1997), may have particular relevance to the development of affective disorders that have a higher prevalence in women (Eaton et al. 2011; Catuzzi and Beck 2014): Approximately 18% of adults (18 and older) in the United States (20% worldwide) suffer from anxiety disorders, however these disorders are twice as prevalent in women than in men (Cameron and Hill 1989; Pigott, 1999; Simonds and Whiffen 2003; Zender and Olshansky 2009; Bao and Swaab 2011). Relevant to these sex-specific differences is the demonstrated sensitivity of affective disorders to steroids. Specifically, anxiety disorders and depression increase with menopause and andropause (Arpels 1996; Lund et al. 1999; Cooper and Ritchie 2000; Eskelinen et al. 2007), and improvement of these symptoms is reported for both sexes with hormone replacement therapy (Cooper and Ritchie, 2000; Yazici et al. 2003; Genazzani et al. 2004; Kumano 2007; Seidman et al. 2009; Amore et al. 2009).

For adolescents, AAS risks may be even greater than for adult women. For example, AAS increase the risk of developing mood disorders such as anxiety, aggression, and depression

(Burnett and Kleiman 1994; Franke and Berendonk 1997) during the developmental epoch when such behaviors often become manifest (Mattsson et al. 1980; Sato et al. 2004; Sato et al. 2008; Sisk and Zehr 2005). Coupled with the fact that these illicit drugs are readily obtained by high school students (Johnston et al. 2013), these reports raise the alarm that AAS use during adolescence may have particularly profound and even permanent effects on the brain and behavior (Sato et al. 2008; Lumia and McGinnis, 2010; Cunningham et al. 2013). Finally, the behavioral impact of illicit AAS use is even greater for sexual minority adolescents, who have an increased prevalence of both affective disorders and AAS use compared to cisgender heterosexual adolescents (Blashill and Safrin 2014). Male to female transgender individuals are also at increased risk for affective disorders and self-medicating at doses of steroids higher than medically recommended (Moore et al. 2003).

1.2 AAS chemistry and administration

There are over 100 known individual AAS, which have been characterized into three major classes based on the modifications made to the testosterone backbone to increase the anabolic to androgenic ratio, increase the duration of effectiveness, and/or make them orally bioavailable (Basaria et al. 2001; Shahidi 2001; Clark and Henderson, 2003; Llewellyn 2007). Illicit users employ elaborate regimens of AAS administration to augment anabolic actions and diminish unwanted side effects. Such strategies include the use of multiple AAS (stacking), complex patterns of variable administration including on-off periods (cycling), and increasing/decreasing doses (pyramiding; Pope and Katz 1994; Gallaway 1997; Sturm and Diorio 1998; Kutscher et al. 2002; Congeni and Millier 2002; Kanayama et al. 2003; Llewellyn 2007; Pope et al. 2014a). The diversity of potential AAS actions depends on the chemical signature, concentrations, and pattern of AAS administered. All AAS [and some of their metabolites] have biological activity at nuclear ARs, albeit with varying degrees of efficacy and potency. Additionally, their ability to act via other members of the nuclear hormone receptor family and through non-genomic mechanisms depends on both their synthetic chemical signatures and the high concentrations at which they are consumed (Clark et al., 2003, Henderson, 2007; Penatti and Henderson 2009; Oberlander and Henderson, 2012a; Oberlander 2012a,b; Figure 1). Taken with the fact that the expression and function of both nuclear hormone receptors and the targets of non-genomic AAS actions (e.g., the molecules that comprise GABAergic, glutamatergic, peptidergic and serotonergic signaling pathways) show significant developmental and sex-specific differences, these variables alone provide an expansive template upon which the AAS may impose age- and sex-specific actions (Jorge and Henderson, 2004; Clark et al., 2006; Henderson, 2007; Oberlander et al., 2012a,b).

2. AAS use and affective behaviors

The most commonly reported behavioral manifestations of illicit AAS use that pertain to affective states include changes in libido, aggression, anxiety, impulsivity, depression, hostility, mania, and hypomania (Annitto and Layman 1980; Pope et al. 1988; Pope and Katz 1988; O'Connor and Cicero 1993; Su et al. 1993; Burnett and Kleiman 1994; Cooper et al. 1996; Galligani et al. 1996; Franke and Berendonk 1997; Wu 1997; Hall et al. 2005; Pagonis et al. 2006a,b). Moreover different behavioral outcomes observed with illicit AAS

use may be connected. For example, AAS-dependent increases in anxiety may contribute to the etiology of a number of anti-social behaviors, including aggression, hostility, and impulsivity (Annitto and Layman 1980; Pope and Katz 1988; Burnett and Kleiman 1994; Cooper et al. 1996; Hall et al. 2005; Pagonis et al. 2006). Because the deleterious actions of AAS use limit the ability to conduct controlled trials in human subjects and the illicit use of these drugs imposes limitations on data collated from self-reports, much of the information that has been gleaned with respect to the interactions of AAS and other key variables has come from studies in animal models. Previous reviews have highlighted critical aspects of AAS actions on specific behavioral or biological endpoints (Clark and Henderson 2003; McGinnis 2004; Clark et al. 2006; Wood 2008; Lumia and McGinnis 2010; Melloni and Ricci 2010; Oberlander and Henderson 2012a; Oberlander et al. 2012a,b; Cunningham et al. 2013; Table 1). Our focus here is on the known body of work on AAS effects on affective behaviors in mice, rats and hamsters, with an emphasis on the impact of age, sex, treatment regimen, and other key environmental variables on AAS-induced changes in these behaviors (Table 1).

2.1 AAS and aggression

Although the behavioral impact of illicit AAS use is still poorly understood by the general public, the most well publicized aspects of AAS abuse on affective behaviors in humans is the repertoire of poor impulse control, extreme mood swings, and abnormal levels of aggression often called “roid rage” (Trenton and Currier 2005; Pagonis et al. 2006a,b). A myriad of studies has shown that chronic administration of AAS that mimics human abuse paradigms can promote elevated levels of offensive aggression in male rodents that can be directed against both male and female conspecifics (Clark and Henderson 2003; Cunningham and McGinnis 2007; Melloni and Ricci 2010; Oberlander and Henderson 2012a; Robinson et al. 2012; Table 1). As with other behavioral endpoints, the ability of AAS to enhance offensive aggression in male rodents varies with the chemical nature of the AAS (Clark and Henderson 2003; McGinnis et al. 2002a,b; Wesson and McGinnis 2006; Table 1), the environmental conditions under which tests are made (Breuer et al. 2001; McGinnis et al. 2002a,b; Cunningham and McGinnis 2008), species (e.g., see Bronson 1996; Martínez-Sanchis et al. 1998; Pinna et al. 2005; Robinson et al. 2012; Onakomaiya et al. 2014; Table 1 with respect to variable effects in male *mice*), and the age of the animals at the time the AAS are administered (Farrell and McGinnis 2003, 2004; Grimes and Melloni 2006; Salas-Ramirez et al. 2008, 2010; Carrillo et al. 2011; Table 1). In contrast to the wealth of data on AAS-induced aggression in male rodents, there is a paucity of data on AAS effects on aggression in females (Table 1). Early studies indicated that protracted (2.5 to 6 months) treatment of adult female mice with high doses of a mixture of AAS increased aggressive behavior (Bronson et al. 1996; Bronson et al. 1996; Table 1). With more restricted treatment durations, AAS can increase aggression in female mice if environmental conditions are also manipulated. Specifically, increased aggression can be elicited by as few as 3 weeks of moderate dose treatment of female mice maintained in social isolation (Pinna et al. 2005; Pibiri et al. 2006; Table 1). Social variables have also been shown to be important in AAS-induced aggression in males towards females. For example, although male rats do not normally show aggressive behaviors towards females, AAS-treated male rats will show aggressive behaviors towards ovariectomized females when the males are

provoked (Cunningham and McGinnis 2006), and these behaviors are augmented under conditions of “frustration” when these receptive females (treated with estrogen and progesterone) are also vaginally-obstructed (Cunningham and McGinnis 2007; Table 1).

2.2 AAS and neural circuits that underlie aggression

Brain regions implicated in the expression of aggression are widespread and involve both cortical and subcortical regions. While there is some divergence in brain regions implicated in offensive versus defensive aggression, these regions are rich in the expression of androgen and estrogen receptors (Sar et al. 1990; Apostolinas et al. 1999; Mitra et al. 2003; Sarkey et al. 2008; Oberlander and Henderson 2012a; Miczek et al. 2015a). Moreover, these circuits overlap with each other and with brain regions that play key roles in the expression of anxiety-like behaviors (Figure 2). Within these brain regions, a plethora of neurotransmitter systems have been implicated in mediating AAS-induced aggression in male mice, with arginine vasopressin and serotonin (5-HT) being interactive and lead players in this process (Melloni and Ricci 2010; Oberlander and Henderson 2012a). For serotonin, low levels of this indolamine are implicated in the perception of heightened threat and enhanced aggression in novel contexts (Spoont et al. 1992), and AAS-induced changes in serotonergic transmission have assumed particular prominence in AAS-induced male offensive aggression (Lindqvist et al. 2002; Grimes and Melloni 2006; Ricci et al. 2006, 2012; Keleta et al. 2007; Kubala et al. 2008; Schwartz et al. 2009a,b; Ambar and Chiavegatto 2009; Melloni and Ricci 2010; Table 1). Numerous studies have shown, either directly or indirectly, that AAS treatment lowers basal levels of serotonin (Lindqvist et al. 2000; Ricci et al. 2006) and diminishes the expression of 5-HT_{1B} receptors in brain regions that mediate aggression (Grimes and Melloni 2006; Ambar and Chiavegatto 2009; Table 1). Interestingly, pharmacologically lowering serotonin levels alone did not augment standard inter-male aggression in rats (Keleta et al. 2007; Kubala et al. 2008), however combined treatment of AAS with pharmacological depletion of serotonin led to marked increases in aggression under conditions of both low (smaller intruder males when there was provocation; Keleta et al. 2007) and high threat (Kubala et al. 2008; Table 1). Not only are these data consistent with a critical convergence of AAS and serotonin on this behavioral output (Melloni and Ricci 2010), they underscore the importance of other environmental variables in mediating these sophisticated and complex AAS/serotonin interactions on aggression in males (Table 1).

Pharmacobehavioral studies of aggression in female mice may, on the surface, also suggest a pivotal role for serotonin signaling in this sex. Specifically, selective serotonin reuptake inhibitors (SSRIs) countermand the increase in aggression elicited by AAS in socially isolated female mice. However, studies suggest that for both the AAS and the SSRIs, the critical targets are not components of the serotonergic signaling pathway, but rather enzymes that regulate levels of the neurosteroid, allopregnanolone (Pinna et al. 2003, 2005; Pibiri et al. 2006; Agis-Balboa et al. 2009; Table 1). Whether this divergence reflects differences in sex, treatment paradigms, or environmental parameters by which aggression was elicited, remains to be determined.

2.3 AAS effects on anxiety-like behaviors

Sex-specific differences in anxiety and sensitivity of anxiety-like behaviors to endogenous steroids have been amply demonstrated (Palanza 2001; Henderson and Jorge 2004; Nyby 2008; Pinna et al. 2008; Frye 2009; Smith et al. 2009; ter Horst et al. 2012a,b; Donner and Lowry 2013). Indeed, AAS have been shown to influence generalized and social anxiety in both human (Su et al. 1993; Cooper et al. 1996; Galligani et al. 1996; Hall et al. 2005; Pagonis et al. 2006a,b; Kanayama et al. 2008; Lundholm et al. 2010) and non-human (Clark and Henderson 2003; Oberlander and Henderson 2012a) subjects. The expression of different forms of anxiety in animal models has been assessed by a variety of experimental paradigms including the elevated plus maze (EPM), the open field test, the acoustic startle response, the Vogel conflict test, shock-probe and other burying tests, and freezing behavior assays (Crawley 2000; Steimer 2011; Hånell and Marklund 2014). As noted above, there is a marked overlap with respect to brain regions and neurotransmitter signaling systems that contribute to the expression of anxiety and aggression, as well as the steroid sensitivity of those regions (Figure 2 and Section 2.1; Oberlander and Henderson, 2012a). This convergence is likely fundamental to the complex relationship between AAS-induced anxiety and AAS-induced aggression in both human and non-human species.

The influence of AAS treatment on anxiety in a rodent model was first reported for adult male rats by Bitran et al. (1993) who demonstrated that a moderate concentration of testosterone propionate for a relatively brief period (6 days) elicited a transient increase in anxiety-like behavior as measured on the EPM, but was without effect in the open field test. In contrast, in the same year, Minkin et al. (1993) reported that nandrolone decanoate given once a week for 8 weeks to gonadectomized and gonadally intact male rats increased anxiety-like behavior in the open field test. More recent studies have confirmed the anxiogenic actions of high doses of nandrolone decanoate as measured on the EPM in adult male rats and in adult male mice as measured with both the open field test and EPM (Ambar and Chiavegatto 2009; Table 1). However, chronic treatment of male mice during adolescence with a mixture of three AAS failed to elicit anxiety-like behaviors as measured by the acoustic startle response, (although it did so in females: *vide infra*; Onakomaiya et al. 2014). Moreover, a brief exposure of adult male rats to a low dose of methenolone actually elicited anxiolytic effects (Ågren et al. 1999). These studies underscore what has now been observed across a multitude of reports: that the effects of AAS on even a single behavioral endpoint and in a single sex depends on the chemical identity of the individual AAS administered, age, treatment regimen, and environmental variables captured by the different experimental paradigms (Table 1).

Chronic treatment (4 weeks) of female mice during adolescence with a mixture of AAS elicits a consistent increase in anxiety-like behaviors as measured by the acoustic startle response and marble burying assays (Costine et al. 2010; Oberlander and Henderson 2012b; Onakomaiya et al. 2014), reminiscent of results obtained with prolonged treatment of adult female mice with a mixture of AAS and tested in the open field test (Bronson et al. 1996; Table 1). In contrast, a briefer (16 day) treatment of adult female mice with a high dose of a single AAS (17 α -methyltestosterone) was reported to have no effect on anxiety-like behaviors as measured on the EPM, light-dark transitions, or defensive behavior tests

(Barreto-Estrada et al. 2004; Table 1). Similarly, a single exposure to 17 α -methyltestosterone did not increase anxiety-like behaviors in adult female mice (Oberlander et al. 2012c; Table 1). C57Bl/6 mice and the same total concentration of AAS were used in the three more recent studies, suggesting, age, types of AAS administered, duration of treatment, and/or behavioral assays may account for the difference in results. Variable results with females have also been noted with respect to the closely related behavior of fear. AAS treatment increased contextual fear conditioning, albeit only in females subjected to social isolation (Agis-Balboa et al. 2009), but had no reliable effect on fear-potentiated startle (Costine et al. 2010; Table 1).

2.4 Neural correlates of AAS-induced effects on anxiety

Bidirectional communication between key subcortical structures, including regions of the extended amygdala, and other subcortical as well as cortical regions are needed for proper regulation of anxiety (McDonald et al. 1999; Davis and Whalen 2001; Dong et al. 2001; Vertes 2004; Dong and Swanson 2006; Hammack et al. 2009; Kim et al. 2011; Figure 2). Within the extended amygdala, projections from the central nucleus of the amygdala (CeA) to the bed nucleus of the stria terminalis (BnST) are critical in the expression of sustained anxiety-like behaviors (Lee et al. 2008; Walker et al. 2009a,b; Davis et al. 2010). Neurotransmission throughout this anxiety circuit relies not only on the classical neurotransmitters such as GABA, glutamate, serotonin, norepinephrine and dopamine, but also on a host of neuromodulatory peptides, including corticotropin releasing factor (CRF), neuropeptide Y (NPY), substance P, pituitary adenylate cyclase activating peptide (PACAP), nociceptin, and calcitonin gene-related peptide (Shimada et al. 1989; Morilak et al. 2003; Oberlander et al. 2012a; Kormos and Gaszner 2013), many of which are regulated by AAS (Oberlander et al. 2012a).

While expression of anxiety arises from the coordinate actions of many signaling systems, the CRF family of ligands and receptors in the extended amygdala (Walker et al. 2009; Davis et al. 2010) and their interaction with the GABAergic projection from the CeA to the BnST have a prominent role in AAS-induced anxiety and in sex-specific differences in AAS-induced anxiety (Costine et al. 2010; Oberlander and Henderson 2012a,b; Onakomaiya et al. 2014). Elevated levels of CRF in extrahypothalamic areas of the CNS are a hallmark of anxiety and stress disorders in humans (Nemeroff 1988; 1992; Arborelius et al. 1999; Holsboer 1999; Reul and Holsboer 2002; Hauger et al. 2006, 2009; Holsboer and Ising 2008); central infusion of CRF in rodents stimulates anxiety-like behaviors (Bale and Vale 2004); the BnST is the primary site of the anxiogenic action of CRF; and CRF-dependent enhancement of anxiety-like behaviors in rodents is observed in a wide variety of testing paradigms (Bale and Vale 2004; Davis et al. 2010). Beyond the BnST, a key downstream target of CRF signaling is the caudal dorsal raphe, a region rich in serotonin-expressing neurons that also plays a central role in the expression of anxious states (Lowry et al. 2005).

Several aspects of the CRF system have been shown to be sexually differentiated and sensitive to steroid regulation in mammals: CRF mRNA expression in whole CeA tissue of adult male rats is higher than in adult females (Viau et al. 2005); levels of this mRNA are regulated by endogenous gonadal steroids in both the CeA and the PVN (Lund et al. 2004;

Viau et al. 2005); and the promoter region of the CRF gene contains response elements for both androgen and estrogen receptors (Bao et al. 2006; Kageyama and Suda 2010). Although, the specific relationship between genetic sex and levels of stress hormones (including CRF) is variable and depends upon species, brain region examined, level of gonadal steroids, and the type of environmental stressor, as a general rule, females show an exaggerated stress response, especially to psychological stressors, and CRF is implicated in this process (for discussion, Iwasaki-Sekino et al. 2009; Valentino et al. 2012).

CRF modulation of GABA_A receptor-mediated transmission in anxiety circuits of the extended amygdala and the dorsal raphe, may be a critical conduit for mediating AAS effects on anxiety-like behaviors observed in female subjects for the following reasons: GABA_A receptors play a central role in the expression of anxious states and are primary targets for many anxiolytic drugs (Möhler 2012); CRF modulation of GABAergic signaling in the CeA, BnST, and the dorsal raphe has been implicated in the expression of anxiety (Nie et al. 2004, 2009; Lowry et al. 2005; Kash and Winder 2006; Bajo et al. 2008; Kirby et al. 2008; Oberlander and Henderson 2012b); and neurons in these regions express a high level of androgen receptors (Simerly et al. 1990; Hamson et al. 2004).

Consistent with these observations, the increase in anxiety-like behaviors observed in female mice treated throughout adolescence with a mixture of AAS was accompanied by increased levels of CRF within the extended amygdala (Costine et al. 2010; Oberlander and Henderson 2012b; Onakomaiya et al. 2014; Table 1); CRF-induced changes in CeA activity, coordinate changes in GABA_A receptor-mediated inhibition and action potential activity in the BnST, as well as increased levels of serum corticosterone following startle testing. CRF signaling through CRF type 1 receptor (CRF₁) was required for expression of AAS-induced anxiety and for the associated changes in neural signaling in the BnST, and the increase in serum corticosterone following startle (Costine et al. 2010; Oberlander et al. 2012b; Onakomaiya et al. 2014; Table 1).

Surprisingly, studies of male and female mice tested concurrently under the same experimental paradigms demonstrated that although baseline levels of CRF are higher in the extended amygdala of male than female mice, AAS treatment of males had no effect on this peptide or on the expression of anxiety-like behaviors (Onakomaiya et al. 2014). These data are consistent with previous studies illustrating sex-specific differences in CRF signaling in the rodent brain (Bangasser et al. 2010, Bangasser and Valentino 2012) and provide a cautionary note to human users that the untoward behavioral effects of AAS administration are likely to elicit significantly different effects in men and women.

3. Interactions of AAS and exercise

As suggested above, the ability of chronic AAS to modify behaviors is likely to depend not only on intrinsic parameters (e.g., sex, age, and genetic background), but also on a host of extrinsic or environmental factors. External variables that may be particularly germane to the effects of AAS on affective behaviors include exercise, diet, and the use of other abused drugs.

3.1 AAS use and exercise

Most individuals who use AAS as performance enhancing drugs, whether elite athletes or not, do so in conjunction with an exercise regimen (Parkinson and Evans 2006; Wood and Stanton 2012; Eisenberg et al. 2012; Fitch 2012; Buckman et al. 2013). AAS users also exercise at a higher rate than non-users (Kokkevi et al. 2008; Ip et al. 2011). Most studies assessing the interaction of AAS and exercise have focused on peripheral physiological functions and on the impact on voluntary exercise itself (Hickson et al. 1990; Bronson 1996; Riezzo et al. 2011; Shokri et al. 2012; Seynnes et al. 2013). Bronson and colleagues (Bronson 1996; Bronson et al. 1996; *vide supra*, Section 2.1) demonstrated that prolonged exposure of adult mice to a mixture of AAS significantly decreased wheel running in females, but not males. In contrast, shorter treatment with an AAS mixture during adolescence decreased wheel running in male, but not female mice (Onakomaiya et al. 2014; Figure 3; Table 1). Exposure to a single AAS also diminished wheel running in male rats (McGinnis et al. 2007; Tanehkar et al. 2013), although the impact of AAS was compound-specific (McGinnis et al. 2007; Table 1).

Exercise by itself has a significant impact on affective behaviors and, depending on the circumstances, can decrease anxiety in human subjects of both sexes (Raglin and Morgan 1987; Youngstedt et al. 1998; Fox 1999; Manger and Motta 2005; Herring et al. 2010, 2012). Although the majority of studies in rodents report that voluntary wheel running decreases anxiety-like behaviors in both sexes (Binder et al. 2004; Duman et al. 2008; Fox et al. 2008; Salam et al. 2009), anxiogenic effects have also been noted (Burghardt et al. 2004; Fuss et al. 2010), and results are context-dependent and appear more variable in females than in males (Novak et al. 2012). Few studies have assessed potential neural mechanisms underlying the interactions of AAS and exercise in the expression of anxiety, but those that have been performed point to regulation in the hippocampus as having an important role. For example, Gomes et al. (2014) reported that anti-apoptotic and pro-proliferative processes in the hippocampus that were elicited by strength exercise and were presumed to contribute to the anxiolytic actions of exercise were impaired by AAS exposure in adult male rats. In male mice, both wheel running and AAS influenced the levels of mRNA encoding the presumed anxiolytic molecule, brain-derived neurotrophic factor (BDNF; Pedersen et al. 2009; Zoladz and Pilc 2010; Novak et al. 2012) when mice were treated during adolescence; however, the interactions of AAS and exercise did not necessarily correlate well with changes in hippocampal BDNF mRNA (Onakomaiya et al. 2014). These results are consistent with data from male rats where exercise induced increases in BDNF, but did not ameliorate AAS-induced deficits in a hippocampal-dependent test of spatial learning (Tanehkar et al. 2013).

As with other aspects of AAS effects on behavior, sex-specific differences were apparent in the effects of wheel running on anxiety-like behaviors in male versus female mice treated and assayed under identical conditions. Specifically, although wheel running promoted anxiolytic effects in male mice, it neither ameliorated AAS-induced anxiety nor altered CRF levels in the extended amygdala in female mice (Figure 3). Moreover, neither AAS treatment nor wheel running altered hippocampal BDNF mRNA levels in females (Onakomaiya et al. 2014). The lack of effect of exercise on this molecular endpoint in

females is consistent with previous studies looking at exercise alone (Engesser-Cesar et al. 2007; Alvarez-López et al. 2013; c.f. Zajac et al. 2010; Marlatt et al. 2013).

4. AAS reward and drugs of abuse

Wood and colleagues have demonstrated that the AAS themselves may be considered a rewarding drug, and that animals will self-administer AAS even with deleterious consequences. (Johnson and Wood 2001; Peters and Wood 2005; Triemstra and Wood 2004; DiMeo and Wood 2006; Wallin and Wood 2015; Table 1). Whether AAS “prime” reward pathways and in so doing alter responsiveness to other substances is still unknown, but concurrent use of other substances, including marijuana, opioids, stimulants, and alcohol, is common in AAS users (Brower et al. 1991; Wichstrøm 2006; Elliot et al. 2007; McCabe et al. 2007; Kokkevi et al. 2008; Lundholm et al. 2010; Dodge and Hoagland 2011; Hakansson et al. 2012; Buckman et al. 2013) despite the fact that many of these drugs have no beneficial effects on physical performance (Buckman et al. 2013). Interactions between AAS and other drugs of abuse including cannabinoids (Célérier et al. 2006), cocaine (Kailanto et al. 2011; Table 1), opioids (Wood 2008; Nyberg and Hallberg 2012), and alcohol (Rojas-Ortiz et al. 2006; Etelälahti and Eriksson 2013; Table 1) on behavioral endpoints have been assessed in rodents, although few studies have contrasted or compared effects between the sexes.

4.1 AAS and alcohol

The co-occurrence of AAS and alcohol use is particularly germane as both influence anxietylike behaviors and aggression, and both alter signaling along critical pathways in the extended amygdala and associated projection regions (Rashid 2000; Miczek et al. 2015a,b; Pagonis et al. 2006; Morrow et al. 2009; Costine et al. 2010; Oberlander and Henderson 2012a, b; Table 1). Of particular note, both alcohol and AAS converge on key molecular components of anxiety and aggression circuits, including CRF₁-, GABA_A receptor- and serotonin-mediated signaling (Lindqvist et al. 2002; Nie et al. 2004, 2009; Bajo et al. 2008; Sommer et al. 2008; Roberto et al. 2010; Ambar and Chiavegatto 2009; Chiavegatto et al. 2010; Costine et al. 2010; Gilpin et al. 2012, 2015; Oberlander and Henderson 2012b; Onakomaiya et al. 2014; Miczek et al. 2015a,b; Pleil et al. 2015; Quadros et al. 2015; Table 1).

In human subjects, alcohol is reported to have more profound effects in females than in males (Lynch et al. 2002), and there is a significantly higher incidence of alcohol-related anxiety disorders in women compared to men (Zilberman et al. 2003; Epstein et al. 2007). In rodents, females generally consume more ethanol than males (Lancaster et al. 1996; Middaugh et al. 1999; Rojas-Ortiz et al. 2006; Morrow et al. 2009; Strong et al. 2010), and a role for sex steroids, rather than genetic sex, has been suggested in underlying this phenomenon (Barker et al. 2010). Studies on the interactions of AAS and alcohol in animal models have been scarce, and no published reports have compared across the sexes. In one study, treatment of male rats with a high dose of nandrolone decanoate was found to abolish the effects of ethanol on motor behavior, but the impact of AAS on ethanol consumption and preference was not determined (Lindqvist et al. 2002; Table 1). In another study, chronic treatment of male mice with the single AAS, 17 α -methyltestosterone, did not alter ethanol

consumption (Rojas-Ortiz et al. 2006; Table 1). A direct comparison of male and female mice in work from our laboratory suggests that chronic AAS treatment with a mixture of three commonly abused AAS was also without effect on ethanol consumption in male mice, but decreased consumption in female mice, negating a basal sex-specific difference. Furthermore, although female mice treated with AAS drank less than female controls, ethanol-dependent anxiolysis was significantly greater in AAS-treated female, but not control mice (Onakomaiya, Demidenko and Henderson, unpublished data).

5. Future directions: sex-specific interactions of AAS use and diet

In concert with exercise, many AAS users consume a high protein diet often augmented by protein supplements such as casein and whey powders, in order to maximize skeletal muscle gains (Blake et al. 2000; Tipton et al. 2004; Roth 2008; Tipton and Ferrando 2008; Lollo et al. 2011) and minimize the natural catabolic processes that follow vigorous exercise (Shimomura et al. 2004; Roth 2008). Strenuous exercise markedly accelerates catabolic processes (Shimomura et al. 2004; Roth 2008), increasing the recommended daily requirement of protein (Lemon et al. 1981; Lemon 1997, Phillips et al. 1997; Tipton and Ferrando 2008). AAS users are reported to routinely consume almost quadruple the recommended daily amount of protein when on an AAS cycle, with average daily intakes of approximately 2g/lb (4.4g/kg) (<http://www.bodybuilding.com/fun/planet4.htm>). High protein diets promote an agonistic interaction of peptide YY3-36 (PYY3-36) with NPY Y2 receptors. These receptors are co-expressed with CRF receptors in the extended amygdala and have been implicated in producing anxiogenic effects (Nakajima et al. 1998; Sajdyk et al. 2002; Tasan et al. 2010) as well as modulating signaling through the mesolimbic dopaminergic reward pathways (Stadlbauer et al. 2013a,b; 2015). In addition, as with components of the CRF signaling pathway, expression of NPY and its signaling components show sex-specific differences (Forbes et al. 2012). Taken together, these studies suggest that males and females may manifest highly divergent affective responses to AAS exposure that reflect a highly complex and sex-specific matrix of both intrinsic and extrinsic factors, inclusive of diet and exercise. These data also raise provocative questions with respect to parallels between illicit AAS use and eating disorders, including shared peptide targets, sex-specific differences, and underlying disturbances in the expression of anxiety and distortion of body image (Kaye et al. 1987, 2009; Rohman 2007; Kanayama et al. 2010; Oberlander et al. 2012a; Smink et al. 2012). Such sex-specific interactions may raise a particularly cautionary note for high school and college-age women, where unhealthy approaches to eating, exercise, and obsession with body image may prove a recipe for disaster when combined with AAS use.

6. Conclusions

AAS use is no longer the domain of a limited number of elite male athletes taking a limited number of drugs. Over the past three decades there has been a marked expansion in the number of AAS available, the sophistication in the patterns of AAS self-administration, and the number of “everyday” men, women, and children who are taking them. The boundaries to assessment of these complicated interactions in humans are obvious, but as this review highlights, those who work in animal models need to attend to the generalization of results

with care. Of interest, a review (Piacentino et al. 2015) published during the preparation of our own manuscript mirrors the same diversity of effects in the human population, providing a valuable bookend to the work presented here. As illustrated in Table 1, many of the behavioral studies have not been coupled with determinations of changes in neural systems. Moreover, when such assessments have been made, they have, by necessity, focused on a handful, not a broad spectrum of endpoints. It should also be noted that a demonstrated contribution of one set of parameters does not preclude a critical role for others, and that when translating results in animal work to the human population, we as investigators need to be direct in acknowledging the danger in over-interpretation. This is particularly true when considering sex- and age-specific effects on both neural signaling systems and the behaviors they engender.

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Figure 1. Known Mechanisms of Action of Anabolic Androgenic Steroids (AAS)

All AAS are androgens and have direct action through binding to nuclear androgen receptors (AR), as well as estrogen receptor α and β (ER α ;ER β) and progestin receptors (PR) [1.], promoting receptor dimerization, translocation to the nucleus, and regulation of gene expression through interactions with cognate hormone response elements (HRE) [2.]. Some AAS (such as nandrolone decanoate) may also be aromatized to estrogens [3.] providing an alternate pathway for interactions with classical ER α and β . AAS also promote effects in the nervous system through non-genomic mechanisms including putative actions through G protein-coupled metabotropic receptors linked to second messenger signaling pathways [4.]; direct allosteric modulation of gating of GABA_A receptors [5.]; direct allosteric inhibition of aromatase by some AAS (such as 17 α -methyltestosterone) [6.]; an action that can then indirectly affect classical signaling through ER α and β and regulation of MAPK-dependent phosphorylation of NMDA receptors [7].

Figure 2. The Mind's Metro of Anxiety and Aggression

The neural circuitry implicated in the expression of both aggression and anxiety-like behaviors exhibits striking overlap. These neural areas are presented as train stations on different train lines of a subway or metro map, to illustrate the overlap and complexity of affective and aggressive circuitry: medial pre-frontal cortex (mPFC); dorsal raphe nuclei (DRN); bed nucleus of the stria terminalis (BnST); shell of the nucleus accumbens (NAc(s)) parts of the amygdala proper [the lateral and basolateral (LA/BLA) nuclei, the medial nucleus (MeA), and the central nucleus (CeA)]; ventral hippocampus (vHF), lateral septum (LS); ventromedial nucleus of the hypothalamus (VMN); lateral anterior hypothalamic areas (LAH); paraventricular nucleus (PVN); medial preoptic area (mPOA); midbrain central gray (MCG); periaqueductal gray area (PAG). Figure is reproduced with permission from Oberlander et al (2012a; Nature Publishing Group).

Figure 3. Effects of voluntary exercise on anxiety-like behavior

(A) Representative photograph of experimental set-up of voluntary wheel running showing a mouse on a wheel in the home cage. (B) Representative actogram of daily running activity. Each horizontal line represents a 24 hr period and each green block represents running activity in 5 min bins over that day. AAS treatment did not change the circadian patterning of running; all groups were most active in the dark cycle. (C) Representative average running activity for the first 6 hours of the dark cycle (7:00 PM to midnight) binned in 30-minute blocks demonstrating that AAS treatment significantly decreased average running activity in male mice but did not significantly alter running in female mice. (D) Average acoustic startle response (ASR; which may be used to gauge changes in anxiety) demonstrate that there was neither a significant effect of AAS treatment nor an interaction of treatment and exercise on the ASR in males. In contrast, ASR amplitudes were significantly higher with AAS treatment whether female mice had access to running wheels or not ($p < 0.0001$). Data are modified from Onakomaiya et al. 2014.

Table 1

Effects of Anabolic Androgenic Steroids on Rodent Behaviors: Sex, Age, and AAS Regimen.

Publication	Species	Age at Treatment Onset	AAS	Effect of AAS on Behavioral Endpoints	Brain Regions/Signaling Mechanisms
Both Sexes					
Barreto-Estrada et al. 2004	Mice	Adult	17MeT (~7.5 mg/kg; pump); ~16 days	<i>Social interactions</i> : changes observed <i>Anxiety</i> : No changes on EPM, light-dark transition, and defensive behavior tests. Some effects on the modified Vogel conflict test	None assessed
Bronson 1996	Mice	Adult	Mixture (capsules) TC, 17MeT, NE; varying doses (mm); 6 months	<i>Aggression</i> : increased in females but not males <i>Wheel running</i> : decreased significantly in females, marginally in males <i>Sexual behavior</i> : blocked ejaculation in most males; elicited male-like sexual behaviors in some females	None assessed
Onakomaiya et al. 2014	Mice	Adolescent	Mixture: 2.5 mg/kg/day each of MT, ND, TC; 5 days/week, 4 weeks	<i>Anxiety</i> : increased in females, no effect in males <i>Wheel running</i> : augmented the sex-specific effects on anxiety <i>Social interaction</i> : no changes	CeA, BnST, hippocampus/BDNF, CRF
Peters and Wood 2005	Hamsters	Adult	T (ICV self-administration @ 1 µg/µL); 4-5 days	<i>Self-administration</i> : death in up to 70% of hamsters when self-administration exceeded 60ug/day <i>Locomotion</i> : >20ug/day depressed central autonomic function	None assessed
Pinna et al. 2005	Mice	Adult	TP (0.5 mg/kg); daily; 3 weeks	<i>Aggression</i> : increased aggression in socially isolated females and males	Olfactory bulb/allopregnanolone, 5α-R
Females Only					
Agis-Balboa et al. 2009	Mice	Adult	Testosterone (1.45µmol/kg/day); daily; 4 weeks	<i>Fear conditioning</i> : excessive contextual fear no change in cued fear responses	Glutamatergic corticolimbic neurons in: basolateral amygdala, hippocampus, PFC/allopregnanolone, 3α-hydroxysteroid dehydrogenase, 5α-R
Barreto-Estrada et al. 2007	Mice	Adult	17MeT (~7.5 mg/kg; osmotic pump); 17 days	<i>Sexual behavior</i> : male-like sexual behaviors towards control female mice	None assessed
Blasberg and Clark 1997	Rats	Adult	Single: 17MeT, MT, ND, OXM, ST, TC (7.5 mg/kg); daily; 15 days	<i>Sexual behavior</i> : 17MeT, MT, ND and ST interfered with the display of sexual receptivity; OXM and TC had no effect	None assessed
Blasberg et al. 1997	Rats	Adult	Single: 17MeT; MT, ST (various concentrations); daily; 2 weeks	<i>Sexual behavior</i> : the highest doses of 17MeT (7.5 mg/kg) and ND (5.6 mg/kg) disrupted behavioral and vaginal cyclicity; the highest dose of MT (3.75 mg/kg) had less robust effects	None assessed

Publication	Species	Age at Treatment Onset	AAS	Effect of AAS on Behavioral Endpoints	Brain Regions/Signaling Mechanisms
Blasberg et al. 1998	Rats	Adults	Single: DHTP (7.5 mg/kg), 3x/d (3.75 mg/kg), 17MeT (7.5 mg/kg), ST (7.5 mg/kg), ND (7.5 mg/kg); daily; 15 days	<i>Sexual behavior</i> : inhibited sexual receptivity	Androgen receptors
Bronson et al. 1996	Mice	Adult	Mixture (capsules) TC, 17MeT, NE; varying doses (mm); 20 days	<i>Aggression</i> : increased <i>Wheel running</i> : decreased spontaneous use; no effect on recovery time after forced treadmill running <i>Locomotion</i> : depressed open-field activity <i>Sexual behavior</i> : eliminated the rejection of genital inspection	None assessed
Clark et al. 1998	Rats	Adult	Single: ST (5 mg/kg), OXM (12 mg/kg), TC (7.5 mg/kg); daily; 2 weeks	<i>Sexual behavior</i> : highest doses disrupted the cyclical display of sexual receptivity	None assessed
Costine et al. 2010	Mice	Adolescent	Mixture: ND, TC, MT (2.5 mg/kg each); 5 days/week; 4 weeks	<i>Anxiety</i> : increased ASR <i>Fear</i> : no effect <i>Sensorimotor gating</i> : no effect	BnST, CeA/CRF
Oberlander et al. 2012c	Mice	Adult/Adole scent	17MeT (7.5 mg/kg); single injection	<i>Anxiety</i> : no effect <i>Thermoregulatory behavior</i> : impaired nest building in diestrus but not in estrus	mPOA/GABA-A receptors (protein kinase C-mediated phosphorylation)
Oberlander and Henderson 2012b	Mice	Adolescent	Mixture: MT (2.5 mg/kg); ND (2.5 mg/kg); TC (2.5 mg/kg); 6 days/week; 4 weeks	<i>Anxiety</i> : increased ASR	BnST, CeA / CRF, GABA
Pibiri et al. 2006	Mice	Adult	TP (0.15 to 43.5 µmol/kg); daily; up to 4 weeks	<i>Aggression</i> : increased with social isolation	Olfactory bulb/GABA-A receptors
Rivera-Arce et al. 2006	Rats	Adult	17MeT (unknown); acute ICV infusion	<i>Anxiety</i> : increase in latency to display the appetitive reaction in the Vogel conflict test, while increasing the number of punished responses; no changes on EPM <i>Social interaction</i> : increased	Dorsomedial hypothalamus/GABA-A receptors
Triemstra and Wood 2004	Hamsters	Adult	T (ICV self-administration @0.1, 1.0, and 2.0 µg/µL); daily; 8 days	<i>Reward</i> : OVX and intact hamsters showed a significant operant response preference for ICV testosterone <i>Partner preference</i> : no effect	None assessed
Males Only					
Ågren et al. 1999	Rats	Adult	ME (0.01 mg/kg); 1 st day of 3 consecutive weeks; tested Day 4 following treatment	<i>Anxiety</i> : decreased anticipatory anxiety in a modified OFT	None assessed
Anbar and Chiavegatto 2009	Mice	Adult	15mg/kg ND; daily; 28 days	<i>Anxiety</i> : increased in novel environments <i>Aggression</i> : increased <i>Locomotion</i> : increased <i>Depression</i> : reduced immobility in the FST	Amygdala, hippocampus, hypothalamus, PFC/5-HT

Publication	Species	Age at Treatment Onset	AAS	Effect of AAS on Behavioral Endpoints	Brain Regions/Signaling Mechanisms
Ballard and Wood 2005	Hamsters	Adult	Single: D, N, OXM, ST (0.1, 1.0, and 2.0 µg/µL each); daily; 8 day	<i>Reward</i> : higher operant self administration of injectable AAS (D, N) compared with orally active AAS (OXM, ST)	None assessed
Breuer et al. 2001	Rats	Adult	Single: ND, ST, TP (5mg/kg); 5 days/week; 12 weeks	<i>Aggression</i> : TP increased aggression, ND had no effect, and ST decreased aggression	None assessed
Carrillo et al. 2011	Hamsters	Adolescent	Mixture: TC (2 mg/kg), ND (2 mg/kg), BD (1 mg/kg); daily; 7, 14, 21, 28, or 30 days	<i>Aggression</i> : progressively increased after 2 weeks of exposure	BnST, CeA, LAH, LS, MeA, VLH/vesicular glutamate transporter 2
Clark and Barber 1994	Rats	Adult	ST (400 µg/day); 17MeT (3 mg/day); TP (400 µg/day); 3 weeks	<i>Aggression</i> : TP and 17MeT increased aggression in GDX rats; ST had no effect <i>Locomotion</i> : no effect	None assessed
Clark and Fast 1996	Rats	Adult	17MeT, MT, ND (various concentrations)	<i>Sexual behavior</i> : ND > MT > 17MeT in maintaining male sexual behavior in GDX rats <i>Locomotion</i> : no effect	None assessed
Clark and Harrold 1997	Rats	Adult	Single: ST, OXM, TC (various concentrations); daily; 6 weeks	<i>Sexual behavior</i> : in GDX rats, all doses of ST failed to maintain ejaculation; OXM failed to maintain ejaculation above control; all doses of TC sustained ejaculation	None assessed
Clark et al. 1997	Rats	Adult	Single: 17MeT, MT, ND, ST, OXM, TC (various concentrations); daily; 12 weeks	<i>Sexual behavior</i> : in intact males, the high doses of 17MeT, ST, and OXM, eliminated male sexual behavior. MT, ND, and TC had minimal effects on sexual behavior at any dose tested	None assessed
Cooper and Wood 2014	Rats	Adult	7.5 mg/kg T; 5 days/wk; > 4 weeks	<i>Reward</i> : no effect on morphine self-administration <i>Locomotion</i> : no effect; decreased rearing behavior	None assessed
Cooper et al. 2014	Rats	Adolescent	7.5 mg/kg T; 5 days/wk; > 4 weeks	<i>Risk tolerance</i> : increased on a risk decision-making task <i>Impulsivity</i> : no effect on a go/no-go task	None assessed
Cunningham and McGinnis 2006	Rats	Adolescent	Single or two: TP (5 mg/kg); ST (5 mg/kg) or TP+ST; 5 days/week; 9 weeks	<i>Aggression</i> : only increased with provocation towards OVX females with no estrogen replacement	None assessed
Cunningham and McGinnis 2007	Rats	Adolescent	Single or two: TP (5 mg/kg); ST (5 mg/kg) or TP+ST; 5 days/week; 9 weeks	<i>Aggression</i> : increased towards OVX females; frustration-induced persistence in response to vaginally-obstructed receptive females	None assessed
Cunningham and McGinnis 2008	Rats	Adolescent	TP (5 mg/kg); 5 days/week; 5 weeks	<i>Aggression</i> : increased even after 12 weeks of withdrawal <i>Social behavior</i> : increased aggression but had no long term effects when combined with TP treatment	None assessed
Farrell and McGinnis 2003	Rats	Adolescent	Single: N, ST, T (5mg/kg); 5 days/week; 12 weeks	<i>Aggression</i> : T increased; N had no effect; ST inhibited	None assessed

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Farrell and McGinnis 2004	Rats	Adolescent	Single: N, ST, T (5mg/kg); 5 days/week; 5 weeks	<i>Sexual behavior:</i> T increased scent-marking; ST inhibited <i>Aggression:</i> ST increased inter-male aggression without tail-pinch; all increased tail-pinch induced aggression even after prolonged withdrawal <i>Sexual behavior:</i> ST and N reduced vocalizations and scent-marking; ST reduced copulation; T had no effect	None assessed
Feinberg et al. 1997	Rats	Adolescent	TP (1 mg/cc); 3x/week; varying durations	<i>Sexual behavior:</i> enhanced sexual performance and sexual motivation in peripubertal but not prepubertal rats. Effect was gone after 13 weeks of AAS withdrawal	None assessed
Fernandez-Guasti and Martinez-Mota 2005	Rats	Adult	TP; 3cd; single and mixture; varying concentrations; acute and chronic (4 x, once every 48 hrs); 72 hrs	<i>Anxiety:</i> Chronic (but not acute) TP decreased anxiety in the burying behavior test without changes in reactivity; 3cd and mixture had no effect	Androgen receptors, GABA-A receptors
Fischer et al. 2007	Hamsters	Adolescent	Mixture: TC (2 mg/kg), N (2 mg/kg), DHTU (1 mg/kg); daily; 30 days	<i>Aggression:</i> increased in the resident-intruder test	AH, BnST, LS, MeA VLH/glutamate receptor 1, phosphate-activated glutaminase
Frahm et al. 2011	Rats	Adolescent	TP (5 mg/kg); 5 days/week;	<i>Aggression:</i> more threats towards OVX females <i>Sexual behavior:</i> increased mounts towards sexually receptive, vaginally-obstructed females	Brainstem, PFC/5-HIAA, DA, dihydroxyphenylacetic acid, NE
Grimes and Melloni 2006	Hamsters	Adolescent	Mixture: TC (2 mg/kg), NT (2 mg/kg), DHTU (1 mg/kg); daily; 30 days	<i>Aggression:</i> increased; returned to control levels at 18 days withdrawal of AAS	AH, MeA, VLH/5-HT, 5-HT1B
Harrison et al. 2000	Hamsters	Adolescent	Mixture: TC (2 mg/kg), ND (2 mg/kg), BD (1 mg/kg); daily; 30 days	<i>Aggression:</i> increased intensity and initiation of aggressive behavior	AH/AVP
Johansson et al. 2000	Rats	Adult	ND (15 mg/kg); daily; 14 days	<i>Aggression:</i> increased <i>Fear:</i> decreased fleeing and freezing Ethanol consumption: increased at 1 and 3 weeks of AAS withdrawal	Hypothalamus, NAc, periaqueductal gray/dynorphin B and met-enkephalin-Arg-Phe (MEAP)
Johansson-Steensland et al. 2002	Guinea pigs	Adult	ND (15 mg/kg); daily; 14 days	<i>Aggression:</i> increased biting behavior	CeA, NAc (shell), PFC, supraoptic nucleus/c-Fos, Fos-related antigen
Johnson and Wood 2001	Hamsters	Adult	Oral T (200 or 400 µg/mL); two - bottle test	<i>Reward:</i> moderate preference for T over vehicle	None assessed
Kailanto et al. 2011	Rats	Adult	ND (20 mg/kg), every other day; 10 days	<i>Stereotyped behavior and Locomotion:</i> attenuated cocaine-induced behavior	NAc/5-HT, DA
Kalinine et al. 2014	Mice	Adult	ND (15 mg/kg); daily; 4, 11 or 19 days	<i>Aggression:</i> decreased the latency to first attack and increased the number of attacks in the resident-intruder test.	Fronto-parietal cortex, hippocampus excitatory amino acid transporter 2 (Glt-1), glutamate, NMDA receptor

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Keleta et al. 2007	Rats	Adolescent	TP (5 mg/kg); 5 days/wk; 9 weeks	<i>Anxiety</i> : no effect on OFT <i>Spatial memory</i> : no effect on MWM <i>Aggression</i> : increased <i>Partner preference</i> : increased <i>Irritability, locomotor activity, and sexual behavior</i> : no effects	Brainstem, frontal cortex, hypothalamus, striatum/5-HT, 5-HIAA
Kim and Wood 2014	Rats	Adult	T (7.5 mg/kg); 5 days/wk; > 4 weeks	<i>Sexual behavior</i> : no effect on operant responding for access to an estrous female	None assessed
Kouvelas et al. 2008	Rats	Adult	ND (15 mg/kg); daily; 6 weeks	<i>Anxiety</i> : decreased on EPM <i>Memory</i> : increased social olfactory memory	Androgen receptors
Kubala et al. 2008	Rats	Adolescent	TP (5 mg/kg); 5 days/wk; 45 days	<i>Aggression</i> : increased in both low- and high-threat Situations <i>Locomotor activity and food reinforcement</i> : no effects	Brainstem, frontal cortex, hippocampus, hypothalamus, striatum/5-HT, 5-HIAA
Kurling et al. 2008	Rats	Adult	ND (5 or 20 mg/kg); every 2 nd day; 10 days	<i>Reward</i> : modulates behavioral effects of MDMA and amphetamine	NAC/5-HT, DA
Lindqvist et al. 2002	Rats	Adult	ND (15 mg/kg); daily; 14 days	<i>Competitive behavior</i> : enhanced dominant behavior <i>Locomotion</i> : prevented sedative effects of ethanol on locomotion	Basal forebrain, dorsal striatum/5-HT
Long et al. 1996	Rats	Adult	ND (2 or 20 mg/kg); daily; 4 weeks	<i>Aggression</i> : increased with and without co-administration of cocaine	None assessed
Lumia et al. 1994	Rats	Adult	TP (1 mg/kg); 3×/week; 5-10 weeks	<i>Aggression</i> : increased <i>Sexual behavior</i> : no effect on copulation	None assessed
Martínez-Sanchis et al. 1998	Mice	Adult	TP (3.75, 7.5, 15, 30 mg/kg); weekly; 10 week	<i>Aggression</i> : only the highest dose (30 mg/kg) led to shorter latency of "threat" but not "attack"	None assessed
Matriciano et al. 2010	Rats	Adult	Single: ND, ST (5 mg/kg); daily; 28 days	<i>Depression</i> : increased immobility in the FST	Hippocampus, PFC/BDNF, glucocorticoid receptor
McGinnis et al. 2002a	Rats	Adult	Single: N, ST, TP (5mg/kg); 5 days/week; 12 weeks	<i>Aggression</i> : TP increased in all social and environmental conditions; ND did not increase tail-pinch induced aggression; ST decreased aggression	Amygdala, hypothalamus, POA, septum/androgen receptors (nuclear)
McGinnis et al. 2002b	Rats	Adult	Single: ND, ST, TP (5mg/kg); 5 days/week; 12 weeks	<i>Aggression</i> : TP (but not ND or ST) sustained increased aggression after 3 weeks (but not at 12 weeks) of AAS withdrawal	None assessed
McGinnis et al. 2007	Rats	Adult	T, ND, ST (~ 3.3 mg/animal/day -pellet); 60 days	<i>Wheel running</i> : significantly elevated by T; significantly depressed by ND, and unaffected by ST	Amygdala, hypothalamus/Steroid receptor coactivator -1 & -2
Melloni et al. 1997	Hamsters	Adolescent	Mixture: TC (2 mg/kg), ND (2 mg/kg), BD (1 mg/kg); daily; 14 days	<i>Aggression</i> : increased offensive aggression without changes in total activity in the resident-intruder test	None assessed

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Morrison et al. 2015a	Hamsters	Adult/Adole scent	Mixture: BU, ND, TC (5 mg/kg); 30 days	<i>Anxiety</i> : in adolescents, decreased on the EPM; increased during AAS withdrawal; no effect in adults <i>Aggression</i> : increased	None assessed
Morrison et al. 2015b	Hamsters	Adolescent	Mixture: BU (2 mg/kg), ND (2 mg/kg), TC (1 mg/kg); 30 days	<i>Aggression</i> : increased	LAH/AVP receptor, DA D2 receptor
Morrison et al. 2015c	Hamsters	Adolescent	Mixture: BU, ND, TC (2 mg/kg each); 30 days	<i>Anxiety</i> : decreased on the EPM <i>Aggression</i> : increased	BnST, CeA, LAH, LS, MeA, VLH/5-HT3 receptors
Olivares et al. 2014	Rats	Adolescent	TP (5 mg/kg); 5 days/week; 5 weeks	<i>Aggression</i> : increased in adolescence <i>Anxiety</i> : increased on EPM in adulthood <i>Locomotion</i> : increased horizontal and vertical exploration in adulthood	None assessed
Parrilla-Carrero et al. 2009	Mice	Adult	Single: TD, ND, 17MeT (various concentrations; daily; 2 weeks)	<i>Reward</i> : all doses of TP and two of ND, but not 17MeT, altered place preference <i>Anxiety</i> : only low dose ND decreased light-dark transitions	None assessed
Ricci et al. 2006	Hamsters	Adolescent	Mixture: TC (2 mg/kg), N (2 mg/kg), DHTU (1 mg/kg); daily; 30 days	<i>Aggression</i> : increased offensive aggression	AH, BnST, CeA, LS, MeA, VLH/5-HT 1A receptors
Ricci et al. 2007	Hamsters	Adolescent	Mixture: TC (2 mg/kg), N (2 mg/kg), DHTU (1 mg/kg); daily; 30 days	<i>Aggression</i> : increased	AH, LS/FOS
Ricci et al. 2012	Hamsters	Adolescent	Mixture: TC (2 mg/kg), N (2 mg/kg), DHTU (1 mg/kg); daily; 30 days	<i>Anxiety</i> : 21 days after withdrawal, increased anxiety on the EPM and dark-light transitions, but no effect on seed finding <i>Aggression</i> : no effects in resident-intruder test during withdrawal	AH, CeA, MeA/5-HT
Ricci et al. 2013	Hamsters	Adolescent	Mixture: TC (2 mg/kg), N (2 mg/kg), DHTU (1 mg/kg); daily; 30 days	<i>Aggression</i> : increased <i>Anxiety</i> : decreased during treatment; increased during AAS withdrawal <i>Social interaction</i> : no effect <i>Locomotion</i> : no effect	None assessed
Robinson et al. 2012	Mice	Adult	Mixture: 17MeT, TC, ND (2.5 mg/kg each 17); 5 days/week; 3 weeks; ~4-7 weeks	<i>Aggression</i> : increased when AR is present during development; less frequent in AR-deficient mice	Androgen receptors
Rocha et al. 2007	Rats	Adult	ND (5 mg/kg); 2x/week; 6 weeks	<i>Anxiety</i> : increased on the EPM	None assessed
Rojas-Ortiz et al. 2006	Mice	Adult	17MeT (Osmotic pump; 7.5 mg/kg); 17 days	<i>Anxiety</i> , <i>locomotor activity</i> , and <i>ethanol consumption</i> : no effects	None assessed
Salas-Ramirez et al. 2008	Hamsters	Adult/Adole scent	Mixture: TC (2 mg/kg), ND (2 mg/kg); BD (1 mg/kg); daily; 2 weeks	<i>Aggression</i> : increased in adolescents but not adults <i>Sexual behavior</i> : increased in adolescents; decreased in adults	None assessed

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Salas-Ramirez et al. 2010	Hamsters	Adult/Adole scent	Mixture; TC (2 mg/kg), ND (2 mg/kg); BD (1 mg/kg); daily; 2 weeks	<i>Aggression</i> : during AAS withdrawal, increased in both adults and adolescents <i>Risk assessment</i> : adolescents did not show any submissive or risk-assessment behaviors <i>Sexual behavior</i> : decreased potential to reach sexual satiety	None assessed
Schwartz et al. 2009a	Hamsters	Adolescent	Mixture; TC (2 mg/kg), NT (2 mg/kg), DHTU (1 mg/kg); daily; 30 days	<i>Aggression</i> : increased offensive aggression in resident-intruder test	LAH/5-HT type 2A receptors
Schwartz and Melloni 2010a	Hamsters	Adolescent	Mixture; TC (2 mg/kg), ND (2 mg/kg), BD (1 mg/kg); daily; 30 days	<i>Aggression</i> : increased	AH/DA receptors (D2)
Schwartz and Melloni 2010b	Hamsters	Adolescent	Mixture; TC (2 mg/kg), ND (2 mg/kg), BD (1 mg/kg); daily; 30 days	<i>Aggression</i> : increased	AH, LAH/DA receptors (D2 & D5)
Steensland et al. 2005a	Rats	Adult	ND (15 mg/kg); daily; 2 weeks	<i>Aggression</i> : after 3 weeks of AAS withdrawal, increased defensive aggression with amphetamine challenge	None assessed
Steensland et al. 2005b	Rats	Adult	ND (pellets, 15 mg/kg/day); 6 weeks (tests @ 9 weeks)	<i>Aggression</i> : increased in dominant rats towards subordinate cage-mate <i>Fear</i> : decreased in subordinate rats	None assessed
Svensson 2010	Rats	Adult	T (silastic capsules); 6 days	<i>Anxiety</i> : behavioral disinhibition on the modified Vogel conflict test	Aromatase
Wallin and Wood 2015	Rats	Adolescent	T (7.5 mg/kg); 5 days/wk; > 4 weeks	<i>Set-shifting, and reversal learning</i> : impaired behavioral flexibility	None assessed
Wesson and McGinnis 2006	Rats	Adolescent	Mixture or Single: T, N, ST (5 mg/kg) or mixture @ 10 mg/kg; 5 days/week; ~35 days	<i>Aggression and sexual behavior</i> : T increased; ST decreased; N had no effect; ST + T prevented decrease	Amygdala, hypothalamus, POA, septum/androgen receptor occupation
Wood et al. 2013	Rats	Adolescent	T (7.5 mg/kg); 5 days/week, ~ 9 weeks	<i>Aggression</i> : increased <i>Impulsivity</i> : no change	Caudate-putamen, medial PFC, NAc/Tyrosine hydroxylase
Zotti et al. 2014	Rats	Adult	ND (5 mg/kg); 5 days/wk; 4 weeks	<i>Depression</i> : increased on sucrose preference test <i>Social interaction, and anxiety</i> : no effect	Amygdala, NAc/DA, 5-HT, NE

Abbreviations: intracerebroventricular (ICV); gonadectomized (GDX); ovariectomized (OVX); for AAS: boldenone undecylenate (BD); 3 α -diol (3 α D); drostanolone (D); dihydrotestosterone propionate (DHTP); dihydrotestosterone undecylenate (DHTU); 17 α -methyltestosterone (17MeT); metenolon (ME); nandrolone (N); nandrolone decanoate (ND); norethandrolone (NE); nortestosterone (NT); oxymetholone (OXM); stanozolol (ST); testosterone (T); testosterone cypionate (TC); testosterone propionate (TP); for behavioral tests: Acoustic Startle Response (ASR); Elevated Plus Maze (EPM); Forced Swim Test (FST); Morris Water Maze (MWM); Open Field Test (OFT); for brain regions: anterior hypothalamus (AH), bed nucleus of the stria terminalis (BnST), central amygdala (CeA), latero-anterior hypothalamus (LAH), lateral septum (LS), medial amygdala (MeA), medial preoptic area (mPOA), nucleus accumbens (NAc), prefrontal cortex (PFC), ventrolateral amygdala (VlH); for signaling mechanisms: 5 α -reductase type I (5 α -RI), 5-Hydroxyindoleacetic acid (5-HIAA), arginine-vasopressin (AVP), brain-derived neurotrophic factor (BDNF) corticotropin releasing factor (CRF), dopamine (DA), gamma-Aminobutyric acid (GABA), N-methyl-D-aspartate (NMDA), norepinephrine (NE), serotonin (5-HT).