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Supraphysiologic-dose anabolic-androgenic steroid use: a risk factor for dementia?

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Abstract

Supraphysiologic-dose anabolic-androgenic steroid (AAS) use is associated with physiologic, cognitive, and brain abnormalities similar to those found in people at risk for developing Alzheimer's Disease and its related dementias (AD/ADRD), which are associated with high brain β -amyloid ($A\beta$) and hyperphosphorylated tau (tau-P) protein levels. Supraphysiologic-dose AAS induces androgen abnormalities and excess oxidative stress, which have been linked to increased and decreased expression or activity of proteins that synthesize and eliminate, respectively, $A\beta$ and tau-P. $A\beta$ and tau-P accumulation may begin soon after initiating supraphysiologic-dose AAS use, which typically occurs in the early 20s, and their accumulation may be accelerated by other psychoactive substance use, which is common among non-medical AAS users. Accordingly, the widespread use of supraphysiologic-dose AAS may increase the numbers of people who develop dementia. Early diagnosis and correction of sex-steroid level abnormalities and excess oxidative stress could attenuate risk for developing AD/ADRD in supraphysiologic-dose AAS users, in people with other substance use disorders, and in people with low sex-steroid levels or excess oxidative stress associated with aging.

Graphical Abstract

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Supraphysiologic-dose anabolic-androgenic steroid use, which typically commences by the mid-20s, induces early-onset hypogonadism and excess oxidative stress. In turn, these abnormalities alter the function of many proteins involved in A β and tau-P synthesis and elimination. This could result in early-onset accumulation of these proteins in brain and increased risk for developing Alzheimer's Disease and its related dementias.

Keywords

Aging; alcohol; Alzheimer's disease; amyloid; anabolic-androgenic steroid; ApoE; Aquaporin 4; α -secretase; β -secretase; body-building; boldenone; cannabis; cocaine; dementia; estrogen; γ -secretase; GSK3 β ; heroin; homocysteine; hypogonadism; insomnia; insulin degrading enzyme; low-density lipoprotein receptor-related protein1; magnetic resonance imaging; magnetic resonance spectroscopy; menopause; methamphetamine; morphine; muscularity; N-acetylcysteine; nandrolone; neprilysin; neurodegeneration; Nrf2; opioid; oxidative stress; oxymetholone; performance-enhancing drugs; PET imaging; polydrug use; prealbumin; presenilin; protein phosphatase 2A; scyllo-inositol; stanozolol; tau; tobacco; sex-steroid; sleep disturbances; substance use disorder; testosterone; zinc

1. Introduction

Anabolic-androgenic steroids (AAS) are a group of anabolic substances including the naturally occurring sex-steroid hormone testosterone (T) and synthetic T analogs designed for oral or injectable dosing. Synthetic AAS were developed in the 1930s (David et al., 1935; Wettstein, 1935) and by the 1950s, supraphysiologic-dose AAS were widely used by elite athletes (Kanayama et al., 2008, 2010; Pope et al., 2014a). By the 1980s, such use had spread to the general United States (US) population. Supraphysiologic-dose AAS are used almost entirely by men (98% of users) seeking to enhance muscularity. Few women use supraphysiologic-dose AAS because women rarely seek to become extremely muscular and because women are vulnerable to the masculinizing effects of AAS, including beard growth and virilization of secondary sexual characteristics (Kanayama et al. 2007, Kanayama and Pope, 2012a; Pope et al., 2014b). Accordingly, this review focuses primarily on the effects of supraphysiologic-dose (non-medical) AAS exposures in males, although some of the effects we discuss are directly relevant to AAS-nonusers and to women.

Currently, it is estimated that close to 4 million people in the US have used supraphysiologic-dose AAS and about one-third of users become AAS-dependent at some time (Brower, 2009; Kanayama et al., 2009a; Hildebrandt et al., 2011; Kanayama and Pope, 2012b; Pope et al., 2014a). There are nearly 100,000 new supraphysiologic-dose AAS users in the US each year (Kanayama and Pope, 2018) with a median age of initiation of 23 (Pope

et al., 2014b; Sagoe et al., 2014). Surveys in other countries suggest that supraphysiologic-dose AAS use is a substantial global public health problem (Sagoe et al., 2014).

Long-term supraphysiologic-dose AAS exposures are associated with abnormalities in liver and kidney (Modlinski and Fields, 2006; Herlitz et al., 2010), endocrine (Tan and Scally, 2009; de Souza and Hallak, 2011; Coward et al., 2013; Kanayama et al., 2015; Rasmussen et al., 2016; Christou et al., 2017), and cardiovascular (Sullivan et al., 1998; Santora et al., 2006; Achar et al., 2010; Baggish et al., 2010, 2017; Thiblin et al., 2015) systems. Additionally, recent studies from our laboratory and from other groups reporting on physiologic, cognitive, and brain abnormalities in long-term supraphysiologic-dose AAS users (Kanayama et al., 2013; Hildebrandt et al., 2014; Heffernan et al., 2015; Kaufman et al., 2015; Westlye et al., 2016; Bjørnebekk et al., 2017) detected abnormalities similar to those found in people diagnosed with or at risk for developing a family of dementias known as Alzheimer's Disease and its related dementias (AD/ADRD). This suggests that such users may be at increased risk for developing dementia and, consequently, that as they reach the age of 75, the average age of diagnosis of late-onset AD (Barnes et al., 2015), they will experience a higher prevalence of AD/ADRD than the general population. We hypothesize that an increase in incidence of AD/ADRD diagnoses in supraphysiologic-dose AAS users has yet to be detected because the large majority remain under the age of 60 today (Kanayama et al., 2008, 2010) – too young to experience overt symptoms of late-onset AD/ADRD.

This review aims to synthesize published findings on the effects of supraphysiologic-dose AAS use and to highlight key deleterious effects induced by this type of AAS use, hypogonadism, and excess oxidative stress, which accelerate syntheses and brain accumulation of β -amyloid ($A\beta$, including $A\beta_{40}$ and $A\beta_{42}$ forms) and hyperphosphorylated tau (tau-P) proteins. These proteins likely have important causal roles in the pathophysiology of AD/ADRD (Götz and Ittner, 2008). Since supraphysiologic-dose AAS users also use other psychoactive substances, some of which have been independently associated with increased risk for AD/ADRD, we discuss how psychoactive substance use by AAS users and by people who do not take AAS could potentiate risk for developing AD/ADRD. Lastly, we discuss how existing and novel drug therapies, some of which already are being tested as treatments for substance use disorders, could reduce risks for developing AD/ADRD in supraphysiologic-dose AAS users and in other at-risk populations.

2. Supraphysiologic-dose AAS use patterns and effects on androgen levels

2.1 Human studies of AAS effects

Supraphysiologic doses of AAS are self-administered because they increase muscularity and strength. A study of the effects of T-enanthate (3mg/kg, once/week) given for 12 weeks to young/middle-aged men without prior illicit AAS use histories reported an increase in serum T levels to 1.7 μ g/dL (normal physiologic range: approximately 0.3–0.9 μ g/dL), together with increased muscle protein synthesis, but no increase in muscle volume (Griggs et al., 1989). Placebo-controlled laboratory studies in healthy men without supraphysiologic-dose

AAS exposure histories documented that 10 weeks of supraphysiologic T (T-enanthate, 600 mg, intramuscular (IM) once/week, 7.5 mg/kg/week for an 80 kg subject), when combined with exercise, increased weightlifting capacities by more than 20% and increased triceps and quadriceps cross-sectional muscle areas by more than 13% (Bhasin et al., 1996). This AAS regimen increased serum total T concentrations to about 3 µg/dL, nearly 6 times higher than normal levels (Bhasin et al., 1996). Subsequent studies by this group reported that lower weekly T doses induced smaller strength and cross-sectional muscle area increases, and that under the conditions studied, supraphysiologic T promoted strength and muscle volume increases in a dose-related manner (Bhasin et al., 2001). In older men, T supplementation (T-enanthate, 25–600 mg IM, once/week) also increased muscularity in a dose-related manner (Bhasin et al., 2005).

2.2 Supraphysiologic AAS self-administration patterns

Supraphysiologic-dose AAS self-administration involves complex, customized patterns of AAS intake including concurrent use of supraphysiologic T plus other AAS to achieve even larger strength and muscle mass gains (e.g., Graham et al., 2008; Ip et al., 2011), a practice termed “stacking.” Illicit AAS users take substantially higher T doses than used clinically to treat male hypogonadism, which typically are ~100 mg/week (Surampudi et al., 2014), and many users take substantially higher AAS doses than those administered in the experimental studies described above. For example, self-reported weekly T or T-equivalent (via self-administration of multiple AAS) doses range from 250 to 5000 mg/week (Pope and Katz, 1994; Yu et al., 2014). Online surveys of large numbers of supraphysiologic dose AAS users have found that up to 60% of respondents reported taking more than 1000 mg/week of AAS (Parkinson and Evans, 2006; Ip et al., 2011; Westerman et al., 2016), or up to 10 mg/kg/week for a 100 kg subject. Thus, self-administration of extremely high AAS doses is prevalent. Systemic total T levels reported in such users range from concentrations of 2.8 µg/dL (Rasmussen et al., 2016), a level similar to those achieved in some laboratory studies, up to much higher levels exceeding 8 mg/dL (Hengevoss et al., 2015), ~16 times normal serum total T levels in men.

Users typically self-administer supraphysiologic-dose AAS in alternating cycles of AAS ingestion (“on-cycle”) and AAS abstinence (“off-cycle”) (Graham et al., 2008; Kanayama et al., 2009a). Users cycle off of AAS to reduce side effects and risks associated with prolonged supraphysiologic-dose AAS use, including infertility and gynecomastia (Pope and Katz, 1994; Christou et al., 2017). AAS on-cycle durations are typically on the order of several months but in long-term users, virtually continuous AAS use persisting for years has been reported (Brower, 2002; Kanayama et al., 2009a; Ip et al., 2011; Westerman et al., 2016). Those using supraphysiologic-dose AAS for years despite experiencing adverse medical or psychiatric consequences meet formal DSM criteria for AAS dependence (Kanayama et al., 2009b). Among supraphysiologic-dose AAS users as a whole, the prevalence of AAS dependence has been reported to range from 14% (Malone et al., 1995) to 57% (Brower et al., 1991), with a median prevalence across studies of 30% (Pope et al., 2014b).

2.3 Supraphysiologic AAS exposure-induced hypogonadism

Although hypogonadism in men is rare under the age of 60 (Bhasin et al., 2011), supraphysiologic-dose androgen use results in feed-back suppression of the hypothalamic-pituitary-testicular (HPT) axis, which leads to decreased production of natural T and thereby induces hypogonadism. When male supraphysiologic-dose AAS users suspend AAS use, previously suppressed HPT axis function slowly returns in some users (Alèn et al., 1987). However, other users apparently do not spontaneously recover HPT axis function and their ability to produce T, resulting in a chronic hypogonadal state defined as a serum total T concentration of <348 ng/dL (Bhasin et al., 2011). AAS-induced hypogonadism has been described in case reports (reviewed by Kanayama et al., 2015; Rasmussen et al., 2016) and has been reported after as few as 12 weeks of supraphysiologic-dose AAS use (Martikainen et al., 1986). A study of all-cause male hypogonadism found that 20% of cases were associated with prior supraphysiologic-dose AAS use and that hypogonadism occurring before age 50 was strongly associated with prior supraphysiologic-dose AAS use (Coward et al., 2013). Among former users, hypogonadism is prevalent and persistent, ranging from 27% in subjects abstinent for 1.7 to 3.7 years (Rasmussen et al., 2016) to 53% in subjects abstinent for 3 months to over 10 years (Kanayama et al., 2015). Accordingly, a substantial proportion of supraphysiologic-dose AAS users experience very high systemic androgen levels (while on-cycle) and subphysiologic/hypogonadal systemic T levels for prolonged periods after suspending AAS use (Figure 1). Thus, most supraphysiologic-dose AAS users rarely experience physiologically normal (that is, eugonadal) androgen levels.

T also is synthesized in brain. In male rat brain, T concentrations up 4 times higher than systemic T levels have been reported (Hojo et al., 2009; Caruso et al., 2010; Tobiansky et al., 2018). However, gonadectomy substantially depletes T levels in male rat whole brain cortex, medial frontal cortex, hippocampus, ventral tegmentum, nucleus accumbens, and cerebellum (Hojo et al., 2009; Caruso et al., 2010; Tobiansky et al., 2018). Brain T and DHT levels also decline with aging in men and in male mice (Rosario et al., 2009, 2011; Caruso et al., 2013). Thus, male systemic hypogonadism is accompanied by hypogonadal brain T levels. Importantly, as discussed below, significant departures from eugonadal T levels, systemically and in brain, can trigger deleterious effects, including increased A β and tau-P accumulations, which could increase risk for developing AD/ADRD.

3. Supraphysiologic-dose AAS exposures are associated with cognitive, cardiovascular, and sleep abnormalities similar to those found in people diagnosed with or at increased risk for developing AD/ADRD

3.1 Cognitive effects of supraphysiologic-dose AAS exposures

Chronic supraphysiologic-dose AAS use by men has been associated with the development of spatial memory impairments similar to those found in people with AD/ADRD. Using the Cambridge Neuropsychological Test Automated Battery (CANTAB) paired associates learning (PAL) and the pattern recognition memory (PRM) tasks, we detected visuospatial memory impairments in a British cohort of supraphysiologic-dose AAS users (Kanayama et al., 2013). Error numbers on these tasks were higher in men with higher self-reported

lifetime cumulative AAS doses, suggesting a cumulative dose-effect relationship between supraphysiologic-dose AAS use and visuospatial memory impairment (Kanayama et al., 2013). The PAL and PRM tasks have been shown to differentiate individuals with mild dementia from healthy individuals and individuals with mild dementia those with AD, respectively (Swainson et al., 2001), suggesting that the cognitive abnormalities we found in supraphysiologic-dose AAS users could reflect increased risk for AD/ADRD. Another study found that on-cycle supraphysiologic-dose AAS users displayed a diminished ability to shift attention on a cognitive attention and set-shifting task as compared to off-cycle users, and also found that adolescent-onset supraphysiologic-dose AAS users displayed poorer spatial-planning efficiency on cognitive testing than individuals with adult onset use (Hildebrandt et al., 2014). A study of young-adult (18–30 years old) AAS-using respondents to an online questionnaire reported higher levels of retrospective and prospective memory and executive function deficits (Heffernan et al., 2015). Subsequently, we reported a possible impairment of CANTAB visuospatial memory performance on the PAL, albeit not reaching statistical significance ($P = 0.052$), in American middle-aged supraphysiologic-dose AAS users (Kaufman et al., 2015), consistent with our earlier finding in a British cohort (Kanayama et al., 2013).

Animal studies of the effects of supraphysiologic-dose AAS exposures in males report cognition abnormalities comparable to those found in humans. Nandrolone (15 mg/kg, subcutaneous: SC) given daily for 6 weeks impaired rat social memory (Kouvelas et al., 2008) and when given either daily for 2 weeks or every third day for 4 weeks reduced Morris Water Maze task spatial memory performance (Magnusson et al., 2009; Tanehkar et al., 2013). Morris Water Maze task spatial memory retention was impaired in rats given nandrolone or stanozolol (5 mg/kg, SC) for 4 weeks (Pieretti et al., 2013). Rats given chronic T (7.5 mg/kg/day, SC, 5 days/week) exhibited reversal learning and set shifting task deficits (Wallin and Wood, 2015).

3.2 Cognitive effects of low androgen levels

The cognitive effects of AAS-induced hypogonadism have not been assessed. However, low androgen levels accompanying other health conditions, including normal aging (van den Beld et al., 2000; Moffat et al., 2002; Muller et al., 2003; Bhasin et al., 2005, 2011; Rosario et al., 2011; Yeap et al., 2012; Caruso et al., 2013), have been associated with cognitive dysfunction. In otherwise healthy older men, nearly half of whom were hypogonadal, associations were found between serum T levels and working memory, although no associations were found between T levels and spatial cognition (Matousek and Sherwin, 2010). Men with low T levels due to idiopathic hypogonadotrophic hypogonadism were impaired on several tests of spatial cognition (Hier and Crowley, 1982). In individuals with prostate cancer, therapeutic androgen ablation was associated with impaired spatial cognition and working memory (Cherrier et al., 2003, 2009). Thus, a number of studies, but not all (e.g., Matousek and Sherman, 2010), report associations between low circulating T levels and impaired spatial cognition in men. Low serum T or bioavailable T levels in older men have been associated with increased risk for developing mild cognitive impairment or dementia (Chu et al., 2008, 2010; Carcaillon et al., 2014), and postmortem frontal cortex T levels are substantially lower in men diagnosed with mild cognitive impairment (MCI) or

AD than T levels in men without these conditions (Rosario et al., 2004). Similarly, animal studies of castrated male rats have reported impaired spatial working memory (Gibbs and Johnson, 2008; McConnell et al., 2012; Locklear and Kritzer, 2014) and/or impaired memory retention (Sandstrom et al., 2006; Hawley et al., 2013; Locklear and Kritzer, 2014). Thus, hypogonadism, including that associated with supraphysiologic-dose AAS use, may increase risk for developing spatial memory and other cognitive impairments.

3.3 Cardiovascular abnormalities associated with supraphysiologic-dose AAS exposures

Supraphysiologic-dose AAS use doubles the risk for experiencing cardiovascular morbidity and mortality (Thiblin et al., 2015). Professional bodybuilders with supraphysiologic-dose AAS use histories averaging more than 12 years had increased coronary artery calcium levels (Santora et al., 2006). Subsequently, we reported reduced left ventricular ejection fractions and ventricular diastolic impairments in middle-aged long-term users of supraphysiologic-dose AAS (Baggish et al., 2010), effects that we and others confirmed in subsequent larger-scale studies (Angell et al., 2012; Luijckx et al., 2013; Baggish et al., 2017; Rasmussen et al., 2018a). Other groups also have reported finding right ventricular abnormalities (Angell et al., 2014; Alizade et al., 2016; Rasmussen et al., 2018a), apoptosis-related fibrotic changes in the heart (Cecchi et al., 2017), increased systolic blood pressure and aortic stiffness (Rasmussen et al., 2018b), and a pro-coagulant state (Chang et al., 2018) in long-term supraphysiologic-dose AAS users. In an echocardiography study in male rabbits, 6 months of supraphysiologic nandrolone administration (SC, 4 or 10 mg/kg, twice/week) was associated with impaired global myocardial performance in a dose-related manner (Vasilaki et al., 2016). These cardiovascular abnormalities have been independently linked to cognitive (including visuospatial memory) impairments, accelerated cognitive aging, dementia, and AD (Hoth et al., 2010; Jefferson et al., 2011; Quinn et al., 2011; Arangalage et al., 2015; Walker et al., 2017; Cui et al., 2018). Accordingly, supraphysiologic-dose AAS-induced cardiovascular abnormalities could amplify risk for developing AD/ADRD.

3.4 Sleep abnormalities associated with supraphysiologic-dose AAS exposures

Sleep disturbances, including insomnia, are among the most common symptoms reported by supraphysiologic-dose AAS users, occurring in 25–50% of cases (Korkia and Stimson, 1997; Bolding et al., 2002; Eklöf et al., 2003; Parkinson and Evans, 2006; Ip et al., 2011), and are more common among men who “stack” by using multiple AAS (Bolding et al., 2002). On-cycle AAS users exhibited lower sleep efficiency and increased wakefulness after sleep onset (Venâncio et al., 2008). In a laboratory study in healthy elderly men without prior AAS use histories, short-term high dose T (Sustanon, a mixture of T esters, 250–500 mg/week IM, for 2 weeks) reduced sleep time by an average of 1 hour (Liu et al., 2003a). Placebo-controlled studies in former supraphysiologic-dose AAS users or never-users found that 6 weeks of stepped T administration culminating in supraphysiologic T exposures (T-cypionate, 2 weeks at 150 mg IM once/week, 2 weeks at 300 mg once/week, 2 weeks at 600 mg once/week) induced manic or hypomanic symptoms in some subjects (Pope et al., 2000). Similarly, oral methyl-T (up to 240 mg/day) taken by healthy male AAS non-users for several days induced mania or hypomania in 2 (10%) of 20 subjects (Su et al., 1993). By reducing the need for sleep, mania/hypomania could contribute to sleep abnormalities in

AAS users. Sleep disturbances have been linked to increased cortical and precuneus A β levels in healthy elderly adults (Spira et al., 2013) and sleep abnormalities worsen the pathophysiology underlying AD (Vanderheyden et al., 2018). Even one night of sleep deprivation of healthy young adults increased plasma and brain A β levels (Wei et al., 2017; Shokri-Kojori et al., 2018) and self-reported sleep duration in healthy subjects was associated with decreased precuneus A β levels (Shokri-Kojori et al., 2018). Accordingly, sleep disturbances in supraphysiologic-dose AAS users and in other groups may increase A β accumulation.

4. Brain structural, functional, and chemical effects of supraphysiologic-dose AAS exposures

4.1 Supraphysiologic-dose AAS exposures are associated with abnormal brain structure and functional connectivity

In a structural MRI study of long-term users of supraphysiologic-dose AAS (mean use duration = 9.3 years), we detected increased mean right amygdala volumes (Kaufman et al., 2015). The right lateralization of this structural abnormality prompted us to conduct a right amygdala seed-point analysis of resting state (task independent) functional MRI (fMRI) connectivity data collected from these same subjects. We found lower connectivity between the right amygdala and several cortical areas (dorsolateral prefrontal cortex, anterior cingulate cortex, superior frontal gyrus, precuneus, and cuneus), subcortical areas (caudate nucleus, putamen, nucleus accumbens, and hippocampus), and cerebellum. By contrast, few left amygdala connectivity differences were detected (Kaufman et al., 2015). Thus, both amygdala structural and functional connectivity abnormalities were right-lateralized. These findings are consistent with a human brain developmental study reporting that right amygdala volume in both sexes is sensitive to sex-steroid hormone levels and predicted by T levels (Herting et al., 2014), as well as with animal studies reporting that adult amygdala volume is sensitive to androgens (Cooke et al., 1999; Johnson et al., 2012), an effect limited to right amygdala in males (Johnson et al., 2012).

A subsequent large-scale structural MRI study of users of long-term supraphysiologic-dose AAS (mean use duration = 9.1 years) reported smaller cortical, gray matter, putamen, and corpus callosum volumes, but did not detect a total amygdala (right + left hemisphere) volume abnormality (Bjørnebekk et al., 2017). This study also reported widespread cortical thinning, including in the occipital pole (cuneus), precuneus, precentral gyrus, posterior cingulate gyrus, temporal lobe, and superior frontal cortex (Bjørnebekk et al., 2017). Greater cortical thinning was detected in long- versus short-term AAS users, suggesting a cumulative dose-effect relationship between AAS and cortical thickness (Bjørnebekk et al., 2017). This research group also analyzed resting state fMRI connectivity data from their subjects using a whole brain data-driven independent components analysis (ICA) approach (Westlye et al., 2016). Low amygdala connectivity with the default mode network (DMN) was found in current but not former AAS users, as was low connectivity between the dorsal attention network (DAN) and the superior frontal gyrus in former and current AAS users (Westlye et al., 2016). DMN-amygdala connectivities were reduced to a greater extent in AAS users taking higher versus lower AAS doses and in on- versus off-cycle AAS users,

while DAN-superior frontal gyrus connectivities were reduced to a greater extent in dependent versus nondependent AAS users and in AAS users taking higher versus lower AAS doses (Westlye et al., 2016). Collectively, the structural and functional connectivity findings in supraphysiologic-dose AAS users implicate amygdala network disruption and widespread cortical thinning induced by long-term high-dose AAS use, possibly in a dose- or duration-dependent manner. Notably, the brain areas affected by AAS include regions in which the earliest increases in A β levels are reported, including amygdala (Sepulcre et al., 2013), precuneus (Gordon et al., 2018), and posterior cingulate cortex, which is an A β propagation hub (Sepulcre et al., 2018).

4.2 Supraphysiologic-dose AAS exposures are associated with neurochemical abnormalities

In our study of long-term AAS users cited above (Kaufman et al., 2015), we also acquired proton [^1H] magnetic resonance spectroscopy (MRS) scans of dorsal anterior cingulate cortex. We detected an abnormally high glutamine/glutamate metabolite ratio (Kaufman et al., 2015). Because glutamine is a catabolite of glutamate, we interpreted the high glutamine/glutamate ratios in AAS users to reflect increased glutamate turnover (e.g., higher glutamate release and/or lower glutamate reuptake, leading to increased glutamate catabolism to glutamine). This interpretation is consistent with the finding that prolonged administration of a supraphysiologic dose of the AAS nandrolone (15 mg/kg, SC, 19 days) to male mice decreased expression of the astrocyte glutamate transporter (GLT-1), decreased hippocampal and cortical glutamate uptake, and increased hippocampal extracellular glutamate levels (Kalinine et al., 2014)—effects that likely increase glutamate availability for catabolism to glutamine. Nandrolone, like a number of other AAS, induces excess oxidative stress (see section 6.1 and Table 1), which reduces GLT-1 expression and function (Trotti et al., 1996, 1997; Blanc et al., 1998; Keller et al., 1997). High glutamate levels inhibit protein phosphatase 2A (Yi et al., 2005, 2008), an enzyme that reduces tau-P levels by dephosphorylation (see section 7.7), and thus high glutamate levels in AAS users could increase tau-P levels and risk for developing AD/ADRD.

We also found a low scyllo-inositol (sI) signal in AAS users (Kaufman et al., 2015). This finding was intriguing to us because sI complexes with and prevents clumping and accumulation of A β protein (McLaurin et al., 2000; Li et al., 2013a; Jin and Selkoe, 2015). Further, sI prevents tau hyperphosphorylation (Jin and Selkoe, 2015). These potentially beneficial effects have prompted development of sI and close sI analogs as potential treatments for AD/ADRD (Salloway et al., 2011; Morrone et al., 2016; Lee et al., 2017; Liu et al., 2018). A possible mechanism to explain the low sI signal in supraphysiologic-dose AAS users is that its synthetic enzyme, inositol epimerase, which converts myo-inositol to sI, may be inhibited by AAS. Inositol epimerase utilizes nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor for sI synthesis (Hipps et al., 1977) and NADPH thus could be depleted by AAS activation of NADPH oxidase (NOX1) (Fu et al., 2013; Frankenfeld et al., 2014; Chignalia et al., 2015; Gomes et al., 2016; Tofighi et al., 2017; Table 1). Consistent with this possibility, AAS users in our MRS study exhibited a possible increase, albeit not statistically significant ($P = 0.092$), in anterior cingulate cortex myo-inositol levels (Kaufman et al., 2015), which could reflect a shift in the inositol epimerase

equilibrium to favor myo-inositol over sI formation. Increased myo-inositol levels have been detected with MRS in association with increased A β plaque load (Voevodskaya et al., 2016). Thus, the low sI signal that we detected in supraphysiologic-dose AAS users may reflect sI depletion, which could accelerate A β and tau-P accumulation.

Another mechanism that could explain the finding of a low sI signal in AAS users is that they may have higher levels of A β protein. If so, a higher proportion of sI could be complexed with A β , which would result in an attenuation of the sI MRS signal by the so-called line-broadening effect (Fischer and Jardetzky, 1965). MRS line-broadening occurs when a relatively large molecule (e.g., A β monomer or oligomer, molecular weight $\cong$ 4,200 or multiples thereof) complexes with a relatively small one (e.g., sI, molecular weight = 180). During an MRS scan, this protein-protein interaction results in an acceleration of small molecule (e.g., sI) magnetic relaxation and an apparent reduction in its MRS signal. Molecular modeling studies suggest that sI complexes cooperatively with A β (Li and Pomès, 2013), meaning that several sI molecules may complex with each A β monomer or oligomer, which could substantially reduce the MRS signal intensity of sI. Importantly, the anterior cingulate cortex from which we obtained our sI measurement is an early region of A β accumulation in AD (Grothe et al., 2017; Gordon et al., 2018; Sepulcre et al., 2018), and so the low sI signal we found there in supraphysiologic-dose AAS users (Kaufman et al., 2015) could reflect a line-broadening effect resulting from higher A β levels. This possibility is supported by preclinical studies reporting that acute or short-term administration of supraphysiologic-dose AAS increase brain A β levels (Wahjoepramono et al., 2008; Ma and Liu, 2015; and see section 5 below). Thus, MRS measurement of sI could be very sensitive as a screen for detecting early increases in A β levels without the use of ionizing radiation.

By contrast, an MRS study reported *higher* brain sI levels in people with more advanced dementia (e.g., mild AD versus mild cognitive impairment) (Griffith et al., 2007). Although this finding would appear to be at odds with the line-broadening effect noted above, myo-inositol levels and sI levels tend to increase with dementia severity (Griffith et al., 2007), whereas brain A β levels tend to stabilize or even decline with dementia severity (Villemagne et al., 2013; Mishra et al., 2018). The net result of these effects could be higher sI/A β ratios in people with greater dementia severities, which would be accompanied by less sI line-broadening and a greater sI MRS signal. Although further studies are necessary to clarify whether the low sI signal we found in AAS users reflects low sI concentration, a low sI/A β ratio, or a combination of these effects, any of these scenarios – via reduction of sI availability to complex with and help eliminate A β – could lead to or reflect increased A β burdens and risk for developing AD/ADRD. Because sI also prevents clumping of other neurotoxic proteins, including α -synuclein and Huntingtin proteins associated with the development of Parkinson's and Huntington's diseases, respectively (Vekrellis et al., 2009; Lai et al., 2014), the low sI signal we found in long-term supraphysiologic-dose AAS users could indicate that they are at increased risk for developing other neurodegenerative disorders.

Collectively, the cognitive, physiological, cardiovascular, sleep and neural disturbances induced by supraphysiologic-dose AAS use, which also have been reported in people diagnosed with or at increased risk for developing AD/ADRD, suggest that

supraphysiologic-dose AAS users may be at increased risk for developing dementias. Below, we describe additional molecular effects of AAS that could increase risk for developing AD/ADRD.

5. Abnormal androgen levels increase A β levels and A β toxicity

To our knowledge, no human studies have been published that describe effects of supraphysiologic-dose androgen exposures on A β or tau-P levels. In animals, a single IM dose of the commonly used AAS 17 β -trenbolone (up to 5 mg/kg) given to male rats induces rapid, dose-related plasma, whole brain, and hippocampal A β 42 increases (Ma and Liu, 2015). Similarly, supraphysiologic T (20 mg/kg/day, 4–6 weeks) given to castrated male guinea pigs increases CSF and plasma A β 40 levels (Wahjoepramono et al., 2008). Thus, the available evidence suggests that supraphysiologic-dose AAS administration rapidly increases brain, CSF, and plasma A β levels.

Similarly, low T levels, which are prevalent in older men (van den Beld et al., 2000; Moffat et al., 2002; Muller et al., 2003; Bhasin et al., 2005; Rosario et al., 2011; Yeap et al., 2012) and in hypogonadal former AAS users (Kanayama et al., 2015; Rasmussen et al., 2016), are associated with elevated A β levels. Decreased serum T levels are associated with increased plasma A β 40 levels in older men with memory loss or dementia (Gillett et al., 2003), and decreased plasma free T levels are associated with increased plasma A β 42 in older men with memory problems (Verdile et al., 2014). In postmortem frontal cortex samples from men with AD-related neuropathological changes, decreased T levels were associated with increased A β 42 levels (Rosario et al., 2011). In aged male rats, decreased levels of the potent androgen 5 α -dihydro-T (DHT) were associated with increased whole brain A β 40 levels (Rosario et al., 2009).

More extreme androgen reductions, induced by therapeutic castration of men, substantially increased plasma A β 40 levels (Gandy et al., 2001; Almeida et al., 2004) and nearly doubled the risk for developing AD within four years (Nead et al., 2016; Jhan et al., 2017). Similarly, brain, CSF, and plasma A β levels were elevated in castrated male rats, guinea pigs, and Alzheimer's model 3xTg mice, and androgen normalization with T or DHT attenuated A β increases in these models (Ramsden et al., 2003; Rosario et al., 2006, 2010, 2012; Wahjoepramono et al., 2008). T and DHT treatments also substantially reduced tau-P deposits in castrated mice (Rosario et al., 2010), possibly by inhibiting glycogen synthase kinase 3 β , which phosphorylates tau protein (see section 6.3).

These effects also occur in neuronal culture preparations, in which androgens reduce A β levels and its toxicity. T supplementation (0.2–1.0 μ M) of murine N2a neuroblastoma cells or primary cortical neuronal cultures increases production of the soluble amyloid precursor protein- α (sAPP α), a nonamyloidogenic (α -secretase) enzyme product, and decreases A β release (Gouras et al., 2000). Low-dose T (10 nM) also increases sAPP α production in hypothalamic GT1–7 cells (Goodenough et al., 2000) and lowers A β 42 levels in hippocampal neurons (Ma and Liu, 2015). Addition of up to 100 nM T or DHT to hippocampal neuronal cultures attenuates toxicity of a shortened A β fragment (A β 25–35) (Pike, 2001). Similarly, in cortical neuronal cultures, 10 nM T protects against A β 25–35

toxicity in a flutamide- (androgen receptor antagonist) and formestane- (aromatase inhibitor) sensitive manner (Caraci et al., 2011). By contrast, the potent AAS methandrostenolone supplemented at higher concentration (100 nM) exacerbates A β 25–35 toxicity (Caraci et al., 2011). Collectively, these studies illustrate that A β and tau-P levels and A β toxicity are moderated by androgen levels and are increased in the presence both of abnormally high and low androgen concentrations.

6.0 Abnormal androgen levels and sleep disturbances increase oxidative stress

6.1 Supraphysiologic-dose AAS exposures increase oxidative stress

Generation of oxidative stress is a normal cellular signaling mechanism linked to a number of key biological processes including synaptic plasticity, learning, and memory (Kishida and Klann, 2007; Hidalgo et al., 2016; Kumar et al., 2018a). However, in healthy subjects, oxidative stress generally is maintained within a narrow range to minimize its deleterious effects (Yan, 2014), including mitochondrial impairments associated with increased A β and tau-P levels and with the development of AD/ADRD (Zhu et al., 2005; Grimm et al., 2016). Several of the most commonly used AAS induce excess oxidative stress in men and/or in male animals, as well as in cell culture models. In healthy men without AAS use histories, a single supraphysiologic dose of T (T-enanthate, 500 mg, IM) decreases urine total antioxidant capacity (TAC), reflecting increased systemic oxidative stress (Skogastierna et al., 2014). Among strength-trained men with histories of supraphysiologic-dose AAS use for at least 1 year, blood biomarkers indicative of elevated oxidative stress are found (Arazi et al., 2017a), including 8-hydroxy-2'-deoxyguanosine: (8-OHdG), a DNA oxidation product, malondialdehyde (MDA), a lipid peroxidation product, catalase (CAT), which neutralizes hydrogen peroxide (H₂O₂), and glutathione peroxidase (GPx), which utilizes glutathione (GSH), the most abundant endogenous small molecule antioxidant (Wu et al., 2004), to neutralize oxidative species. Homocysteine (HCY), levels of which are elevated in active long-term supraphysiologic-dose AAS users (Graham et al., 2006), is rapidly oxidized (Starkebaum and Harlan, 1986; Blom, 2000) and in brain, HCY increases levels of reactive oxygen species (ROS, which mediate oxidative stress), MDA, and protein carbonyls (oxidized proteins), while decreasing GSH levels (Kumar et al., 2018b). HCY levels also are elevated in female to male transsexuals therapeutically administered high-dose androgens (250 mg of Sustanon administered biweekly for 4 months) (Giltay et al., 1998) and in men with Klinefelter's syndrome administered high-dose androgens (250 mg of Sustanon biweekly for 6 months) (Yesilova et al., 2004), suggesting that supraphysiologic androgen levels increase HCY levels. High HCY levels also are associated with AD/ADRD (Clarke et al., 1998; McCaddon et al., 1998; Seshadri et al., 2002; Genedani et al., 2004; Agnati et al., 2005; Guidi et al., 2006; Cascalheira et al., 2009).

The pro-oxidative effects of supraphysiologic-dose AAS reported in humans are consistent with findings in numerous animal studies of the effects of supraphysiologic-dose AAS given over a wide range of exposure conditions (except for years-long durations). Animal studies report abnormal levels of many different biomarkers of oxidative stress including thiobarbituric acid reacting substances (TBARS, lipid peroxidation byproducts), lipid

peroxides, advanced glycation endproducts (AGEs), advanced oxidation protein products (AOPP), superoxide dismutase (SOD, which neutralizes superoxide anion), nicotinamide adenine dinucleotide phosphate (NADPH) Oxidase 1 (NOX1, the primary producer of ROS in some tissues and a depletor of inositol epimerase cofactor (Hipps et al., 1977)), Nuclear factor (erythroid-derived 2)-like 2 (Nrf2, the master antioxidant response transcription factor), and glutathione reductase (GR, which regenerates GSH from its oxidized form, glutathione disulfide, GSSG). Results from animal studies are summarized below in brief and additional study details are provided in Table 1.

Supraphysiologic doses of T in the forms of T, methyl-T, or Sustanon increase oxidative stress biomarkers in male reproductive tissues or cells (Hwang et al., 2011; Tóthová et al., 2013), in liver or hepatocytes (Welder et al., 1995; Arazi et al., 2017b; Sadowska-Krpa et al., 2017), in cultured dopaminergic cells (Cunningham et al., 2009) and in hippocampus (Joksimović et al., 2017). Supraphysiologic-dose boldenone increases oxidative stress in male reproductive tissues (Bueno et al., 2017b), in liver (Dornelles et al., 2017), and in brain cortex and hippocampus (Bueno et al., 2017a). Supraphysiologic-dose nandrolone increases oxidative stress in blood (Nikolic et al., 2016), in male reproductive tissues (Ahmed, 2015; Gomes et al., 2016) in liver (Frankenfeld et al., 2014), kidney (Frankenfeld et al., 2014; Riezzo et al., 2014; Tofighi et al., 2018), and cardiac tissues (Frankenfeld et al., 2014; Tofighi et al., 2017), as well as in prefrontal cortex and hippocampus (Tugyan et al., 2013; Turillazzi et al., 2016), striatum and cerebellum (Turillazzi et al., 2016), and in whole brain (Ahmed and El-Awdan, 2015). Supraphysiologic-dose oxymetholone increases oxidative stress in liver cells (Welder et al., 1995). Supraphysiologic-dose stanozolol increases oxidative stress in blood (Tahernejad et al., 2017), liver (Pey et al., 2003; Dornelles et al., 2017), muscle (Delgado et al., 2010) and cardiac (Barbosa Dos Santos et al., 2013; Kara et al., 2018) tissues, and in brain cortex, hippocampus, and whole brain (Camiletti-Moirón et al., 2015; Bueno et al., 2017a). Collectively, these findings indicate that supraphysiologic-dose AAS increase oxidative stress in blood, brain, and throughout the body. Comparable increases in oxidative stress biomarkers have been reported in association with low T levels, as described below.

6.2 Low T levels are associated with elevated oxidative stress

Low systemic and brain T levels are common in older men (van den Beld et al., 2000; Moffat et al., 2002; Muller et al., 2003; Bhasin et al., 2005; Rosario et al., 2011; Yeap et al., 2012) and are associated with excess oxidative protein modifications in cultured human fibroblasts and in postmortem human brain (Oliver et al., 1987, Smith et al., 1991). Low systemic T levels also are associated with excess oxidative stress in middle-aged men with erectile dysfunction and in young men with congenital hypogonadotropic hypogonadism (Yasuda et al., 2008; Haymana et al., 2017).

In animals, older male rhesus macaques with low T levels have elevated blood oxidative stress biomarkers and older females with low estradiol (E2) levels exhibit similar effects (Ibáñez-Contreras et al., 2018). Orchidectomy lowers and elevates serum and testicular antioxidant and oxidative stress levels in rat, respectively (Deyhim et al., 2006, 2007; Bae et al., 2017); it increases brain and serum oxidative stress in rats (Pintana et al., 2015; Meydan

et al., 2010); and it can be attenuated by daily low dose (0.5 mg/kg, SC) T administration (Meydan et al., 2010). Collectively, the literature indicates that both high and low departures from the eugonadal state induce excess oxidative stress.

6.3 Low sex-steroid hormone levels increase activity of glycogen synthase kinase 3 β (GSK3 β), an enzyme at the nexus of oxidative stress, A β , and tau-P regulation

Glycogen synthase kinase 3 β (GSK3 β) is a key enzyme involved in cell death and survival pathways (Maurer et al., 2014) and in the formation of amyloid plaques and tau tangles (Llorens-Martín et al., 2014). Brain GSK3 β levels are increased in people with AD (Leroy et al., 2007). GSK3 β activity is suppressed by normal androgen levels, while abnormally low T levels increase GSK3 β activity (Papazosomenos, 1997; Papazosomenos and Shanavas, 2002; Gu et al., 2014; Maurer et al., 2014; Duran et al., 2016). A GSK3 β target relevant to the regulation of oxidative stress is the master antioxidant transcription factor Nrf2, which is inhibited by GSK3 β (Salazar et al., 2006; Rojo et al., 2008; Correa et al., 2011; Rada et al., 2012; Zou et al., 2013; Shang et al., 2015; Chen et al., 2016; Pang et al., 2016; Ebrahimi et al., 2018). Thus, in the presence of low T (e.g., in aging men (van den Beld et al., 2000; Moffat et al., 2002; Muller et al., 2003; Bhasin et al., 2005; Rosario et al., 2011; Yeap et al., 2012) and perhaps in hypogonadal off-cycle AAS users (Kanayama et al., 2015; Rasmussen et al., 2016)), high GSK3 β activity inhibits Nrf2, leading to increased oxidative stress. Low Nrf2 protein and mRNA levels have been reported in rodent brain and spinal cord with aging (Suh et al., 2004; Duan et al., 2009; Zhang et al., 2013, 2016; Cui et al., 2017), which could underlie the age-associated reduction in Nrf2 antioxidant response efficiency (Zhang et al., 2015). Similarly, low brain Nrf2 expression occurs in hypogonadal 21-month-old male rats, an effect countered by low dose T administration (Zhang et al., 2016; Cui et al., 2017), while chemical castration of rats lowers testicular Nrf2 protein expression (Bae et al., 2017). Because excess oxidative stress itself increases GSK3 β protein expression (Shin et al., 2006; Barbisan et al., 2018), excess oxidative stress may act in a feed-forward manner to increase GSK3 β activity, inhibit Nrf2 activity, and further increase oxidative stress. GSK3 β also upregulates A β production (Ryder et al., 2003) and it increases tau hyperphosphorylation (Papazosomenos, 1997; Papazosomenos and Shanavas, 2002). Accordingly, higher GSK3 β activity accompanying low T levels in aging or other conditions associated with hypogonadism could increase oxidative stress and A β and tau-P levels, which could increase risk for developing AD/ADRD. Because Nrf2 not only attenuates oxidative stress but also reduces tau-P levels (Jo et al., 2014), GSK3 β -induced Nrf2 downregulation in the presence of low T could increase tau-P levels.

Substantially less is known about how supraphysiologic-dose androgens affect GSK3 β or Nrf2 activity, although supraphysiologic-dose nandrolone administration downregulates brain Nrf2 protein expression (Ahmed and El-Awdan, 2015). It remains to be determined whether nandrolone's effect generalizes to other AAS.

E2 also inactivates GSK3 β (Cardona-Gomez et al., 2004; Goodenough et al., 2005; Chen et al., 2013) and thus may enhance Nrf2 activity and inhibit A β and tau-P formation. Thus, the E2 decline in postmenopausal women, which occurs much more rapidly than the gradual T decline in otherwise healthy older men (Grimm et al., 2016), could more strongly disinhibit

GSK3 β activity in women than men, leading to more rapid A β increases and the higher AD/ADRD prevalence observed in women (Grimm et al., 2016). Abnormally low E2 levels also are found males after surgical or chemical castration (Resko et al., 2000; Almeida et al., 2004; Salminen et al., 2005; Hojo et al., 2009; Guerrieri et al., 16), in older men or males with low T levels (van den Beld et al., 2000; Rosario et al., 2009; Yeap et al., 2012), and in supraphysiologic-dose AAS users soon after suspending AAS use (Alèn et al., 1987). Accordingly, GSK3 β activity and its deleterious effects may be increased in hypogonadal men due to depletion of T and E2. Collectively, the effects described above illustrate important interrelationships among T, E2, oxidative stress, A β , and tau-P levels, which are regulated by GSK3 β activity, and indicate that physiological levels of T or E2 may help limit oxidative stress, A β , and tau-P formation.

6.4 Sleep disturbances increase oxidative stress

Sleep disturbances, independent of AAS exposures, increase oxidative stress. Individuals with insomnia exhibit abnormally elevated oxidative stress (Gulec et al., 2012; Liang et al., 2013a; Zhao et al., 2017) and even brief (overnight) sleep deprivation in healthy young adults is sufficient to increase systemic oxidative stress levels (Trivedi et al., 2017; Wei et al., 2017). Sleep studies in rodents also report increases in brain or liver oxidative stress after short- (3–4 day) (D’Almeida et al., 1998; Silva et al., 2004; Singh et al., 2008) and longer-duration (5–21 days) deprivation (Ramanathan et al., 2002; Chang et al., 2008; Süer et al., 2011; Feng et al., 2016), while eye movement (REM) sleep deprivation in rats for 6 weeks increases hippocampal oxidative stress (Alzoubi et al., 2012). Sleep deprivation upregulates GSK3 β activity (Xia et al., 2018), which could be a basis for sleep deprivation-induced oxidative stress, A β , and tau-P increases. Together, these human and animal findings support the possibility that sleep disturbances, which are common in supraphysiologic-dose AAS users (see section 3.4), contribute to AAS-induced oxidative stress, A β , and tau-P increases.

7. Androgen abnormalities and excess oxidative stress alter activities of a number of proteins involved in A β synthesis and tau-P turnover, and may increase A β and tau-P accumulation

Many proteins are involved in the regulation of A β and tau-P syntheses and elimination. Androgens and oxidative stress alter the expression and/or function of a number of these proteins including the amyloidogenic β - and γ -secretases (including Presenilins 1 and 2: PS1 and PS2). Androgens and oxidative stress also alter the expression and/or function of proteins involved in directing amyloid precursor protein (APP) toward the nonamyloidogenic processing pathway (α -secretase) and of proteins mediating turnover or elimination of A β or tau-P including transthyretin, insulin-degrading enzyme, neprilysin, the aquaporin 4 water channel, protein phosphatase 2A, apolipoprotein E, and the low-density lipoprotein receptor-related protein-1. The effects of androgens and excess oxidative stress on these proteins are outlined below.

7.1 α - and β -secretases

Under normal conditions, amyloid precursor protein (APP) is catabolized primarily by the α -secretase enzyme (Bouillot et al., 1996) to form soluble amyloid precursor protein- α (sAPP α), which is nonamyloidogenic and neuroprotective. Physiologic-dose T administered to hypogonadal male guinea pigs increases α -secretase activity and sAPP α synthesis and decreases A β synthesis and release (Gouras et al., 2000; Goodenough et al., 2000; Wahjoepramono et al., 2008; Ma and Liu, 2015). The apparent inverse relationship between sAPP α and A β production may result from sAPP α inhibition of amyloidogenic β -secretase (Obregon et al., 2012; Deng et al., 2015) and from β -secretase product A β 42 inhibition of the ADAM10 α -secretase (Chinchalongporn et al., 2018). Excess oxidative stress also reduces α -secretase expression, increases β -secretase activity, and leads to higher β -secretase mRNA levels and higher A β 40 and A β 42 levels (Tamagno et al., 2008; Oda et al., 2010; Arimon et al., 2015; Hernández-Zimbrón and Rivas-Arancibia, 2015). In postmortem AD brain, the higher oxidative stress associated higher β -secretase activity (Tayler et al., 2010). A β 42 itself increases oxidative stress (Huang et al., 1999; Yatin et al., 1999; Kim et al., 2003; Boyd-Kimball et al., 2005) and may thus act in a feed-forward manner to increase oxidative stress and A β levels. A β also upregulates GSK-3 β activity resulting in greater amyloid plaque formation, tau hyperphosphorylation (Terwel et al., 2008; Hu et al., 2009; DaRocha-Souto et al., 2012; Deng et al., 2015; Chinchalongporn et al., 2018), and Nrf2 inhibition (see section 6.3), with the latter effect potentially amplifying oxidative stress and A β and tau-P formation.

7.2 γ -secretase

The γ -secretase enzyme is a complex of proteins involved in A β processing including presenilins 1 and 2 (PS-1, PS-2). In young gonadectomized male mice, T replacement suppresses PS-1 mRNA and protein levels (Ghosh and Thakur, 2008) and in aged male hpg (lifelong hypogonadal) mice, hippocampal PS-1 and A β 42 levels are elevated (Drummond et al., 2012). These findings suggest that in males, subphysiologic T levels may increase PS-1 expression or activity and promote A β accumulation. GSK3 β also increases PS-1 activity leading to higher A β 42 levels (Ryder et al., 2003), and thus hypogonadism, by upregulating GSK3 β , may increase PS-1 activity. Excess oxidative stress increases activities and alters efficiencies of the γ -secretase and its components, leading to higher A β 42 levels (Tamagno et al., 2008; Arimon et al., 2015; Hernández-Zimbrón and Rivas-Arancibia, 2015).

7.3 Transthyretin

Transthyretin (TTR), also known as prealbumin, is a serum and CSF transport protein that complexes with, catabolizes, and helps eliminate A β (Schwarzman et al., 1994; Alshehri et al., 2015; Silva et al., 2017). TTR levels are reduced by 40% after androgen ablation therapy in individuals with prostate cancer (Wang et al., 2012) and are substantially reduced in gonadectomized male mice (Reuter and Kennes, 1966). By contrast, in individuals with spinal cord injury, therapeutic oral administration of the AAS oxandrolone (~1.75 mg/kg/week) increases serum TTR levels (Bauman et al., 2013) as does low-dose T administration to gonadectomized male mice (Reuter and Kennes, 1966). TTR most effectively complexes with and eliminates A β monomers and oligomers by assembling into tetramers (Li et al.,

2013a), a conformation that is inhibited by excess oxidative stress (Zhao et al., 2013). Notably, the proportion of oxidized CSF TTR in individuals with AD and MCI is nearly twice that found in healthy individuals (Poulsen et al., 2014). Further, serum TTR levels are 16% lower in individuals with AD (Elovaara et al., 1986) and low CSF TTR levels are associated with increased dementia severity in individuals with AD (Riisøen, 1988). Thus, low androgen levels and excess oxidative stress may impair TTR expression and its ability to complex with and catabolize A β .

7.4 Neprilysin

Neprilysin (NEP, also known as neutral endopeptidase) is a metallo-endopeptidase that inactivates several peptide hormones and that catabolizes soluble A β 40 and soluble and insoluble A β 42 (Iwata et al., 2000, 2001; Eckman et al., 2006). Low-dose DHT (10 nM) rapidly increases NEP expression in hippocampal neuronal culture in an androgen receptor-dependent manner (Yao et al., 2008) and in transgenic AD mice, aromatase knockout (effectively doubling endogenous T levels) increases NEP expression and decreases A β pathology and cognitive dysfunction (McAllister et al., 2010). By contrast, gonadectomy substantially reduces brain NEP expression in male rats, an effect that is normalized by DHT treatment or by treatment with NEP28, a selective androgen receptor modulator (SARM) that also reduces brain A β 40 levels (Yao et al., 2008; Akita et al., 2013). Co-treatment of male gonadectomized 3xTg AD mice with the SARM ACP-105 and with AC-186, a selective estrogen receptor β modulator (SERM), increases NEP, decreases brain A β levels, and improves cognition (George et al., 2013). Oxidative stress also inhibits NEP activity (Shinall et al., 2005; Wang et al., 2010), an effect that is attenuated by the antioxidant N-acetylcysteine (Wang et al., 2010). Thus, physiologic androgen levels upregulate, and oxidative stress inhibits NEP activity.

7.5 Insulin degrading enzyme

Insulin degrading enzyme (IDE) is a peptidase that complexes with and catabolizes A β (Kurochkin and Goto, 1994). In prostate cells, nuclear IDE expression and function are lowered by castration, an effect counteracted by T treatment (Udrisar et al., 2005). In aromatase knockout AD mice with elevated endogenous T levels, IDE is upregulated and A β pathology and cognitive dysfunction are decreased (McAllister et al., 2010). In gonadectomized male 3xTg AD mice, the SARM ACP-105 and the SERM AC-186 increase IDE, decrease brain A β levels, and improve cognition (George et al., 2013). Further, oxidative stress inhibits IDE activity (Shinall et al., 2005; Yui et al., 2015). Thus, IDE activity is upregulated by T and downregulated by hypogonadism and oxidative stress.

7.6 Aquaporin 4

Aquaporin-4 (AQP4) is an astrocyte water channel protein involved in glymphatic system fluid movements that participate in A β clearance (Iliff et al., 2012; Yang et al., 2012). In cultured astrocytes, physiologic T (100 nM) doubles AQP4 protein expression while E2 is without effect, indicating that AQP4 is upregulated by physiologic levels of androgens (Gu et al., 2003). By contrast, supraphysiologic T (500 nM) reduces astrocyte AQP protein expression (Gu et al., 2003). Although the effects of orchidectomy on astrocyte AQP4 expression have yet to be described, orchidectomy decreases kidney AQP4 channel

expression in male rats (Loh et al., 2017). Thus, it appears that eugonadal androgen levels are needed for normal AQP4 channel expression and function. While oxidative stress reportedly upregulates AQP4 channel expression (Bi et al., 2017), OS also liberates zinc ion (Zn^{2+}), an inhibitor of AQP4 channel function (Yukutake et al., 2009), from redox-sensitive intracellular Zn^{2+} sequestration sites (Kröncke and Klotz, 2009; Furuta et al., 2017). Amyloid plaques contain high Zn^{2+} concentrations and Zn^{2+} levels are high postmortem in hippocampal neurons from individuals with AD (Lovell et al., 1998; Suh et al., 2000). Accordingly, abnormal androgen levels and excess oxidative stress directly, and indirectly via Zn^{2+} mobilization, limit A β elimination by AQP4 channels.

7.7 Protein phosphatase 2A

Protein phosphatase 2A (PP2A) dephosphorylates and regulates activities of a number of proteins including tau-P (Goedert et al., 1992; Gong et al., 2000) and GSK3 β (Qian et al., 2010). GSK-3 β also phosphorylates and downregulates PP2A (Qian et al., 2010; Yao et al., 2012). Excess oxidative stress inhibits PP2A (Foley et al., 2007, 2011; Raghuraman et al., 2009) as does Zn^{2+} (Sun et al., 2012; Xiong et al., 2013), perhaps by upregulating GSK3 β activity (Kwon et al., 2015). PP2A expression also is inhibited by excess glutamate (Yi et al., 2005, 2008). PP2A is inhibited by the pro-oxidant molecule HCY (Vafai and Stock, 2002; Sontag et al., 2007; Zhang et al., 2008; Shirafuji et al., 2018), the levels of which are elevated in active long-term supraphysiologic-dose AAS users (Graham et al., 2006), and HCY rapidly decreases and increases rat brain PP2A and tau-P levels, respectively (Luo et al., 2007). High systemic HCY levels are associated with AD/ADRD (Clarke et al., 1998; McCaddon et al., 1998; Seshadri et al., 2002; Genedani et al., 2004; Agnati et al., 2005; Guidi et al., 2006; Cascalheira et al., 2009) and PP2A activity and hippocampal mRNA levels are low in AD (Gong et al., 1995; Vogelsberg-Ragaglia et al., 2001; Sontag et al., 2004). Although it has yet to be determined whether physiologic concentrations of androgens alter PP2A expression or function, this effect is hypothesized since androgens inhibit GSK3 β activity (see section 6.3); and E2, via ER α receptors, increases brain PP2A activity (Ueda et al., 2018). E2 and E2 analogs that do not bind to estrogen receptors also preserve PP2A levels under conditions of excess glutamate (Yi et al., 2005, 2008). Therefore, the rapid E2 declines that occur in postmenopausal women (Grimm et al., 2016) could facilitate tau-P accumulation. Thus, AAS-induced oxidative stress and hypogonadism (through GSK-3 β upregulation), as well as hypogonadism in women, likely inhibit PP2A activity and increase tau-P levels.

7.8 Apolipoprotein E

Apolipoprotein E (ApoE) complexes with A β and plays a role in its elimination (Strittmatter et al., 1993; Verghese et al., 2013). The ApoE ϵ 4 gene polymorphism is associated with increased risk for developing AD/ADRD (Corder et al., 1993). ApoE genotype determines A β accumulation in humans and in mice, with highest A β levels occurring in people possessing an ϵ 4 allele (Castellano et al., 2011). In human ApoE ϵ 4 carriers, T levels are associated with hippocampal volume and verbal episodic memory recall, suggesting that androgens modify risk for AD/ADRD in ApoE ϵ 4 carriers (Panizzon et al., 2010, 2014). In otherwise healthy elderly male ApoE ϵ 4 carriers, T levels are lower than in noncarriers and the combination of low T and ApoE ϵ 4 increases risk for AD (Hogervorst et al., 2002). In

cultured microglial cells, oxidative stress activates and reduces microglial ApoE levels and A β uptake, respectively (Feng et al., 2017), which could reduce microglial clearance of A β . Lipid peroxidation products of oxidative stress crosslink e3 and e4 proteins in culture, which reduces their ability to catalyze A β turnover (Montine et al. 1996). Thus, ApoE interactions with A β may be impaired by low T levels and/or high oxidative stress, resulting in increased A β accumulation.

7.9 Low-Density Lipoprotein Receptor-related protein-1

The low-density lipoprotein receptor-related protein-1 (LRP1) complexes with and helps clear A β both by transporting it out of the brain and into the blood and by transporting A β out of the blood and into the liver (Kang et al., 2000; Shibata et al., 2000; Liu et al., 2017b). A soluble fragment of LRP1 (sLRP1), which is excreted into the blood, complexes with and delivers A β to the liver for elimination, thereby preventing circulating A β from entering or re-entering the brain (Sagare et al., 2007). LRP1 also alters neuronal localization of β -secretase and enhances its degradation, which reduces neuronal A β synthesis capacity (Tanokashira et al., 2015). Acute induction of oxidative stress in mice decreases LRP1-dependent A β 42 transport out of the brain (Erickson et al., 2012). One night of total sleep deprivation in humans, which increases oxidative stress (see section 3.4), decreases sLRP levels and increases plasma A β 40 levels (Wei et al., 2017). Although the effects of androgen abnormalities on LRP1 expression and function have not been reported, ovariectomy lowers liver LRP1 mRNA levels and E2 supplementation attenuates this effect (Ngo Sock et al., 2014), perhaps by activating ER α receptors (Hwang et al., 2015). In people with AD, sLRP1 binding is low and sLRP1 is substantially oxidized (Sagare et al., 2007) as is hippocampal LRP1 (Owen et al., 2010). Individuals with mild cognitive impairment also exhibit low hippocampal LRP1 density (Sultana et al., 2010). Thus, excess oxidative stress and hypogonadal E2 levels impair the A β -clearing effects of LRP1/sLRP1 and may increase risk for developing AD/ADRD.

Collectively, these subsections demonstrate that many proteins are involved in a complex orchestration of A β and tau-P syntheses and elimination, which when out of balance as a consequence of abnormal sex-steroid levels and/or excess oxidative stress (Figure 2, red pathways), favors A β and tau-P accumulation and increases risk for developing AD/ADRD.

8. Other abused substances induce androgen abnormalities, excess oxidative stress, increased GSK3 β activity, and may increase risk for developing AD/ADRD

Supraphysiologic-dose AAS users typically use other psychoactive substances including alcohol, tobacco, methamphetamine, cocaine, opioids, and cannabis (Skarberg et al., 2009; Ip et al., 2011; Lindqvist et al., 2013; Sagoe et al., 2015; Kanayama et al., 2018). Several of these substances have been independently linked to increased risk for developing AD/ADRD and several induce excess oxidative stress, and/or hypogonadism, and/or activate GSK3 β . Known effects of several of these substances that could modify risk for developing AD/ADRD in supraphysiologic-dose AAS users and non-users alike are outlined below.

8.1 Alcohol Use Disorder

Alcohol use disorder has been established as a risk factor for AD/ADRD (Schwarzinger et al., 2018). Alcohol drinking typically commences by age 18 and the likelihood of developing alcohol use disorder substantially increases in people who consumed their first drink by 16 years of age (Hingson et al., 2006). In rats, chronic alcohol drinking increases brain expression of APP, β -secretase, and nicastrin (a component of the γ -secretase complex) (Kim et al., 2011) and alcohol withdrawal increases PS-1 expression and A β 40 and A β 42 levels (Ryou et al., 2017). Chronic alcohol drinking in mice increases brain levels of A β 40 and A β 42 (Gong et al., 2017) and in a mouse AD model, alcohol increases oxidative stress of APP, β -secretase, A β 40 and A β 42, and amyloid plaque (Huang et al., 2018a). Several blood oxidative stress biomarkers are abnormal in individuals with alcohol use disorder (Lecomte et al., 1994; Kalousova et al., 2004; Chen et al., 2011; Sandhya et al., 2016) and rats or mice chronically exposed to alcohol or its withdrawal exhibit brain, liver, and systemic biomarkers indicative of excess oxidative stress (Montoliu et al., 1994; Sun et al., 2001; Aydin et al., 2002; Das et al., 2007; Waly et al., 2011; Zeng et al., 2014; Gong et al., 2017; Ryou et al., 2017). Inflammatory processes, some of which are mediated by excess oxidative stress, also have been implicated as linking alcohol use to AD (Venkataraman et al., 2017). Acute and chronic heavy alcohol exposures decrease plasma T levels (Mendelson and Mello, 1974; Mendelson et al., 1978; Gordon et al., 1976; Persky et al., 1977) while chronic heavy alcohol use has been associated with hypogonadism (Castilla-García et al., 1987) and menstrual cycle dysfunction (Mello et al., 1989). Prolonged heavy alcohol exposure increases liver and kidney GSK3 β expression and/or activity (Li et al., 2013b; Zeng et al., 2014; Wang et al., 2017). While light to moderate alcohol drinking by humans may be protective by increasing TTR expression (Jono et al., 2016), heavy alcohol use decreases TTR levels (Kalousova et al., 2004).

8.2 Tobacco Use Disorder

The association between tobacco smoking and dementia has been confirmed by a recent meta-analysis reporting a 50% increase in risk for developing AD/ADRD among tobacco smokers (Niu et al., 2018). Regular tobacco smoking typically is established before the age of 20 and in some smokers before they reach 15 years of age (Kendler et al., 2013). Tobacco use disorder has been associated with cortical thinning in brain areas that exhibit early atrophy in AD (Durazzo et al., 2018) and with higher brain levels of A β and higher risk for developing AD/ADRD (Durazzo et al., 2014a; Zhong et al., 2015). Smoking and having an ApoE ϵ 4 genotype appear to exert additive effects on brain A β levels (Durazzo et al., 2016b). Conversely, tobacco smoking cessation reduces risk for developing AD/ADRD (Choi et al., 2018). Tobacco smoke is a potent oxidative stressor (Pryor and Stone, 1993) that induces systemic oxidative stress (Sandhya et al., 2016) and depletes Nrf2 expression (Naha et al., 2018). Smoking-induced oxidative stress has been demonstrated in humans by quantifying a CSF biomarker, F2-isoprostane (iPF2 α -III), levels of which are elevated in both cognitively normal elderly smokers and in probable AD smokers (Durazzo et al., 2014b, 2016a). Cigarette smoke extracts increase GSK3 β activity and reduce Nrf2 expression and function (Borgas et al., 2016; Ebrahimi et al., 2018). Tobacco smoke contains high concentrations of cadmium and smoking substantially increases systemic cadmium levels (McKelvey et al., 2007). Cadmium in turn induces oxidative stress and activates

GSK3 β activity (Wang et al., 2009) and inhibits PP2A activity (Chen et al., 2008). Other tobacco smoke components, especially metal ions and polycyclic aromatic hydrocarbons, stimulate A β aggregation (Wallin et al., 2017). Tobacco smoke also triggers NOX activity (Kim et al., 2014), which as noted above lowers NADPH levels and could lower inositol epimerase activity and sI synthesis (Hippis et al., 1977). In this regard, chronic smokers have low blood sI levels (Gu et al., 2016). Since systemic sI concentration predicts brain sI concentration (Liang et al., 2013b), it is likely that smokers also have low brain sI concentrations, which could lead to the higher levels of A β reported in smokers (Durazzo et al., 2014a).

Nicotine itself seems unlikely to mediate the harmful effects of tobacco smoking on AD/ADRD risk because it does not enhance A β accumulation (Wallin et al., 2017). In fact, nicotine may help eliminate A β by increasing choroid plexus TTR secretion (Li et al., 2000) and the nicotine metabolite cotinine is both neuroprotective against A β and inhibits GSK3 β activity (Echeverria et al., 2011; Echeverria and Zeitlin, 2012). Yet, AD mice exposed chronically to cigarette smoke exhibit higher A β and tau-P burdens despite having high serum cotinine levels (Moreno-Gonzalez et al., 2013). Smoking also moderately elevates blood T levels in men (Muller et al., 2003; Svartberg and Jorde, 2007), which as noted above could reduce risk for developing AD/ADRD. These data suggest that any beneficial effects of tobacco smoking on AD/ADRD risk are outweighed by smoking's deleterious effects. Moreover, concurrent use of alcohol and nicotine exacerbates oxidative stress (Sandhya et al., 2016) and thus could amplify A β and tau-P increases.

8.3 Opioid Use Disorder

Because late-onset AD/ADRD diagnoses on average occur in the 8th decade of life (Villemagne et al., 2013; Barnes et al., 2015), the early mortality associated with opioid use disorder (Smyth et al., 2006; Degenhardt et al., 2011; Veldhuizen and Callaghan 2014; Gomes et al., 2018; Ma et al., in press) may explain why to date, a link between opioid use disorder and AD/ADRD has not been established (Veldhuizen and Callaghan 2014). Yet, as medication-assisted treatment for opioid use disorder becomes more widely available (Alderk17), early mortality rates in individuals with opioid use disorder are likely to decline (Ma et al., in press) and numbers of individuals with opioid use disorder living into their 8th decade likely will increase. Nonmedical opioid use, like supraphysiologic-dose AAS use, is initiated on average by the age of 23 and can rapidly progress to opioid use disorder (OUD) (Wu et al., 2011; Woodcock et al., 2015). Accordingly, reports from several groups that levels of AT8 antibody, a biomarker of tau-P, are elevated in postmortem brain in illicit opioid users, even in users under age 30 (Ramage et al., 2005; Anthony et al., 2010; Kovacs et al., 2015; Flanagan et al., 2018), as are levels of APP (Ramage et al., 2005), suggest that individuals with opioid use disorder are at increased risk for developing AD/ADRD.

Opioids increase oxidative stress in brain, blood, and body (Zhou et al., 2000; Qiusheng et al., 2005; Arana et al., 2006; Xu et al., 2006; Pereska et al., 2007; Pérez-Casanova et al., 2008; Doyle et al., 2009; Ndengele et al., 2009; Abdel-Zahar et al., 2010; Kovatsi et al., 2010a, 2010b; Cemek et al., 2011; Gutowicz et al., 2011; Sumathi et al., 2011; Deng et al., 2012; Ghazavi et al., 2013; Soykut et al., 2013; Fan et al., 2015; Motaghinejad et al., 2015;

Samarghandian et al., 2015; Yun et al., 2015, 2017; Lauro et al., 2016; Najafi et al., 2017; Mansouri et al., 2018) and thus could increase A β and tau-P syntheses and accumulations via multiple mechanisms described above. In neuronal culture, morphine upregulates GSK3 β activity (Masvekar et al., 2015), which could contribute to increased tau-P levels in opioid users. Opioids also suppress T levels in men (Mendelson et al., 1975; Bliesener et al., 2005; Hallinan et al., 2009; Duarte et al., 2013; Cepeda et al., 2015; Huang et al., 2016a; Raheem et al., 2017; Rubinstein and Carpenter, 2017; Yee et al., 2018) and E2 levels in women (Daniell, 2008). The prevalence of opioid-induced hypogonadism has been estimated at greater than 50%, prompting the recommendation that opioid users be screened for hypogonadism (Hsieh et al., 2018). In men, the medication-assisted treatment pharmacotherapy methadone is more likely than buprenorphine to blunt T levels (Bliesener et al., 2005; Hallinan et al., 2009; Yee et al., 2018), meaning that the type of medication-assisted treatment administered could affect risk for developing AD/ADRD. Hypogonadism, by increasing GSK3 β activity (Papasozomenos, 1997; Papasozomenos and Shanavas, 2002; Cardona-Gomez et al., 2004; Goodenough et al., 2005; Chen et al., 2013; Gu et al., 2014; Maurer et al., 2014; Duran et al., 2016), could contribute to the high brain GSK3 β and AT-8 levels found postmortem in opioid users (Ramage et al., 2005; Anthony et al., 2010; Kovacs et al., 2015; Flanagan et al., 2018). A potential analgesic benefit of correcting opioid-induced hypogonadism is illustrated in studies reporting that androgen supplementation given to males with pain reduces both hyperalgesia (Basaria et al., 2015) and opioid analgesic requirements (Raheem et al., 2017), suggesting that androgen normalization could reduce opioid analgesic requirements, risk for developing opioid use disorder, and perhaps risk for developing AD/ADRD.

Consistent with the possibility that heavy use of opioids influences risk for AD/ADRD is a report that dementia prevalence is elevated in prescription opioid users taking the highest cumulative opioid doses (Dublin et al., 2015). By contrast, a population-based study in Finland did not detect an association between past prescription opioid use and dementia (Taipale et al., 2017). However, since no studies to date have been designed to determine whether individuals with opioid use disorder are at increased risk for developing AD/ADRD, studies assessing a potential association are needed. Because supraphysiologic-dose AAS use may represent a gateway to opioid use in some individuals (Kanayama et al., 2018), it also will be important to determine whether polydrug use involving both of these substances increases risk for developing AD/ADRD.

8.4 Methamphetamine and Cocaine Use Disorders

Methamphetamine and cocaine use disorders also may modify risk for developing AD/ADRD by lowering sex-steroid hormone levels or by increasing oxidative stress levels or GSK3 β activity. Age of first regular use of methamphetamine and cocaine have been estimated to average 21 and 26 years old, respectively (Hser et al., 2008). Methamphetamine lowers plasma T levels in rats (Lin et al., 2014) and its use is associated with abnormal menstrual cycles in women (Shen et al., 2014). Methamphetamine increases systemic oxidative stress (Melo et al., 2010; Huang et al., 2013, 2018b; Walker et al., 2014; Najafi et al., 2017; Zhang et al., 2018) cardiac, retinal, and testicular oxidative stress (Lord et al., 2010; Melo et al., 2010; Lin et al., 2014), and brain oxidative stress (Mirecki et al., 2004;

Banerjee et al., 2010; Jang et al., 2017). Chronic methamphetamine reduces Nrf2 activity in lung (Bai et al., 2017). Methamphetamine upregulates GSK3 β expression in nucleus accumbens core, an effect linked to drug-induced sensitization (Xu et al., 2011). Methamphetamine also increases A β and tau levels in cultured vascular endothelial cells and in brain (Liu et al., 2017a), and in cultured neurons it upregulates GSK3 β and enhances tau hyperphosphorylation (Xu et al., 2018).

Chronic cocaine administration substantially reduces plasma T levels in young adult male rats (Berul and Harclerode, 1989; Budziszewska et al., 1996; Sarnyai et al., 1998; Chin et al., 2002; Alves et al., 2014) and in men (Wisniewski et al., 2007), although normal T levels were reported in cocaine-dependent subjects during inpatient detoxification (Mendelson et al., 1988). Cocaine increases oxidative stress in blood (Winhusen et al., 2013; Walker et al., 2014; Zaparte et al., 2015), heart (Devi and Chan, 1999; Isabelle et al., 2007; Fan et al., 2009; Pomierny-Chamioło et al., 2013; Frustaci et al., 2015), kidney (Pomierny-Chamioło et al., 2013; Kowalczyk-Pachel et al., 2016), liver (Pomierny-Chamioło et al., 2013), and in a number of brain areas (Dietrich et al., 2005; Muriach et al., 2010; Pomierny-Chamioło et al., 2013; Jang et al., 2015; López-Pedrajas et al., 2015; Vitcheva et al., 2015; Beiser et al., 2017), which could increase A β and tau-P levels by multiple mechanisms noted above. Chronic cocaine exposures upregulate total GSK (GSK3 α and β) activity in amygdala (Perrine et al., 2008) and nucleus accumbens core GSK3 β activity, an effect related to cocaine-induced locomotor sensitization (Xu et al., 2009). Higher tau-P levels are found in cortex, hippocampus, and striatum in rats administered cocaine for several days (Liu et al., 2003b).

8.5 Cannabis Use Disorder

The main psychoactive component of cannabis, 9-tetrahydrocannabinol (THC), increases brain oxidative stress in a dose-related manner in rats (Wolff et al., 2015) and cannabis use disorder in humans is associated with excess systemic oxidative stress (Bayazit et al., 2017). However, the available evidence suggests that cannabinoids actually may reduce A β and tau-P accumulation. THC inactivates GSK3 β in several brain regions including hippocampus (Ozaita et al., 2007), which could increase Nrf2 activity and oxidative stress-buffering capacity while also attenuating tau hyperphosphorylation. Cannabinoid activation of CB2 receptors enhances A β turnover (Aso et al., 2016). Further, a cannabis constituent without psychoactive effects, cannabidiol (CBD), attenuates A β -induced GSK3 β activation and tau hyperphosphorylation in cultured PC12 cells (Esposito et al., 2006). Co-administration of THC and CBD more effectively attenuates AD-like phenotypes in a mouse AD model than administration of either compound alone (Aso et al., 2015). Accordingly, cannabinoids have been proposed as potential treatments for AD (Watt and Karl, 2017).

Collectively, the studies cited above demonstrate that the most common substance use disorders, with the apparent exception of cannabis, either have been linked to increased risk for developing AD/ADRD or, by triggering hypogonadism, excess oxidative stress, and/or GSK3 β activation, have the potential to increase risk for developing AD/ADRD. Use of these substances, which begins typically during adolescence or early adulthood, may constitute an early risk factor for AD/ADHD. Concurrent use of these substances by

supraphysiologic-dose AAS users may potentiate A β and tau-P accumulations and exacerbate risk for developing AD/ADRD. Figure 3 is a diagram representing the proposed role of supraphysiologic-dose AAS use in relation to other substance use disorders and biological mediators in the development of AD/ADRD.

9. Summary and Future Directions

The literature included in this review demonstrates that use of supraphysiologic doses of AAS to enhance muscularity and strength increases risk for developing a number of serious health consequences, including possibly AD/ADRD. By inducing androgen abnormalities and excess oxidative stress, supraphysiologic-dose AAS exposures may modify expression and/or function of many proteins involved in A β and tau-P syntheses and elimination in ways that likely accelerate A β and tau-P accumulation. Animal studies reporting that supraphysiologic doses of AAS given acutely (Ma and Liu, 2015) or over the short term (Wahjoepramono et al., 2008) rapidly increase A β levels suggest that the complex systems that regulate A β and tau-P levels may be impaired soon after the initiation of supraphysiologic-dose AAS use. Since human supraphysiologic-dose AAS use commences at a median age of about 23 (Pope et al., 2014b; Sagoe et al., 2014), A β burdens could begin to increase in such users by their third decade of life, two or more decades earlier than in the general population, in whom A β levels typically begin to increase in the 5th decade of life (Villemagne et al., 2013). Given that the balance between A β synthesis and elimination slightly favors elimination in middle age but transitions to accumulation with aging (Bateman et al., 2006; Patterson et al., 2015), lifestyle factors that enable premature A β accumulation, including several substance use disorders and possibly supraphysiologic-dose AAS use, have the potential to increase risk for developing AD/ADRD. To date, it remains to be determined whether supraphysiologic-dose AAS use increases A β and tau-P levels. Accordingly, we plan to conduct imaging studies to determine whether supraphysiologic-dose AAS users exhibit higher A β and tau-P burdens than age-matched individuals who do not use AAS.

The literature included in this review also spotlights how two relatively common physiologic abnormalities that occur as a consequence of normal aging in men and in women, namely, sex-steroid level declines and oxidative stress elevations, can increase A β and tau-P accumulations. Accordingly, early diagnosis and correction of sex-steroid and oxidative stress abnormalities, which may be important common biological sources of risk similar to genetic factors related to lipid metabolism (Sepulcre et al., 2018), could delay or prevent the development of AD/ADRD, especially in people with substance use disorders. Brain biomarkers such as scyllo-inositol, which complexes with A β (McLaurin et al., 2000; Li and Pomès 2013; Jin and Selkoe, 2015) and which can be measured noninvasively without using ionizing radiation (Griffith et al., 2007; Liang et al., 2013b; Sarma et al., 2014; Kaufman et al., 2015), could be assessed early on in posterior cingulate cortex, an A β propagation hub (Sepulcre et al., 2018), to detect early increases in A β levels and predict who might benefit most from early interventions. In this regard, posterior cingulate cortex sI MRS signal is low in middle-aged people with obstructive sleep apnea (Sarma et al., 2014), a condition that has been associated with increased brain A β burdens and that is suspected to enhance risk for developing AD/ADRD (Elias et al., 2018; Sharma et al., 2018).

The potential benefits of therapeutic approaches that normalize androgen levels in men are manifold. Normalizing androgen levels attenuates CSF and plasma A β elevations (Ramsden et al., 2003; Rosario et al., 2006, 2010, 2012; Wahjoepramono et al., 2008; McAllister et al., 2010) and lowers tau-P levels (Papazosomenos, 1997; Papazosomenos and Shanavas, 2002; Rosario et al., 2010), likely by altering the activities of a number of regulatory proteins (Figure 2) including NEP (Yao et al., 2008; McAllister et al., 2010), AQP4 (Gu et al., 2003), PS-1 (Ghosh and Thakur, 2008), TTR (Reuter and Kennes, 1966; Gonçalves et al., 2008), IDE (Udrisar et al., 2005; McAllister et al., 2010), GSK3 β (Papazosomenos, 1997; Papazosomenos and Shanavas, 2002; Gu et al., 2014; Maurer et al., 2014; Duran et al., 2016), and PP2A (Yi et al., 2005, 2008; Ueda et al., 2018). Recent studies indicate that physiological concentrations of androgens upregulate microglial uptake and elimination of A β and reduce A β -induced inflammatory responses (Yao et al., 2017). Some of these molecular effects of androgens could underlie the improved spatial memory and cognition reported in hypogonadal men or male rodents administered supplemental androgens (Janowsky et al., 1994; Sandstrom et al., 2006; McAllister et al., 2010; Spritzer et al., 2011; McConnell et al., 2012; Hawley et al., 2013; Locklear and Krtizer, 2014). E2 normalization may exert comparable effects in hypogonadal women (Perianes-Cachero et al., 2015), perhaps in part by attenuating an age-related increase in GSK3 β activity reported in female mice (Krishnankutty et al., 2017) and by stimulating or preserving expression of PP2A (Yi et al., 2005, 2008; Ueda et al., 2018). T supplementation also increases Nrf2 protein expression and/or function after castration or with aging (Zhang et al., 2016; Bae et al., 2017; Cui et al., 2017) as does E2 supplementation, in part by inhibiting GSK3 β activity (Wu et al., 2014; Li et al., 2017). Yet, to date, pharmacotherapy with T or E2 as a cognitive preservation/enhancement strategy has been associated with marginal benefits, except in women taking E2 for greater than 10 years or in women who started taking E2 near the onset of menopause (Shao et al., 2012; Huang et al., 2016b; Imtiaz et al., 2017). However, these studies have involved subjects aged 55 or older, an age by when A β and tau-P proteins likely have been accumulating for a decade or more (Villemagne et al., 2013). Since buildup of A β or tau-P could limit cognitive benefits of T or E2 supplementation, these studies may not have detected the full impact of sex-steroid supplementation. Accordingly, it seems that future studies are warranted to assess whether earlier initiation of T or E2 supplementation improves or preserves cognition.

Like sex-steroid hormones, antioxidants exert pleiotropic beneficial effects on AD-related proteins and the potential benefits of attenuating oxidative stress are manifold. For example, the antioxidant N-acetylcysteine (NAC), which has been evaluated as a potential treatment for AD, substance use disorders, and other brain disorders (Uys et al., 2011; Deepmala et al., 2015; Hara et al., 2017; Womersley et al., in press), inhibits oxidative stress-induced PS-1 upregulation (Oda et al., 2010) and oxidative stress- and A β -induced NEP downregulation (Wang et al., 2010). An analog of NAC with greater brain bioavailability, N-acetylcysteine amide, normalizes oxidative stress-induced γ -secretase dysfunction and attenuates oxidative stress-induced A β 42/A β 40 ratio elevations (Arimon et al., 2015). Long-term dietary supplementation with an antioxidant mixture including NAC normalizes aging-induced oxidative stress, cortical β -secretase and NEP activity, and A β 42 levels, and also has been shown to improve spatial memory (Sinha et al., 2010, 2016). NAC attenuates excess

oxidative stress-induced PP2A inhibition (Chen et al., 2008; Raghuraman et al., 2009) and inhibits Zn^{2+} activation of GSK3 β and tau hyperphosphorylation (Kwon et al., 2015). NAC also converts TTR into its native state (Henze et al., 2013), which could increase its A β -complexing/elimination capacity. Yet, NAC is relatively ineffective at neutralizing key oxidative species including superoxide anion and H_2O_2 (Aruoma et al., 1989; Winterbourn and Metodiewa, 1999; Schneider et al., 2005), brain uptake of NAC is low because it is lipophilic, and NAC is actively extruded from brain (Clark et al., 2017). Thus, other antioxidants may be even more effective than NAC, such as activators of the master antioxidant transcription factor Nrf2, which as noted above is downregulated by abnormal sex-steroid levels, excess oxidative stress, high GSK3 β activity, and during aging (see section 6.3). Nrf2 activators broadly attenuate many different sources of oxidative stress including superoxide anion and H_2O_2 by increasing activities of hundreds of antioxidant and detoxifying proteins (Hybertson et al., 2011; Gorrini et al., 2013; Ma, 2013; Cuadrado et al., 2018). Given the wide range of oxidative stress biomarkers altered by AAS (Table 1), broad spectrum antioxidants such as Nrf2 activators may be especially beneficial in supraphysiologic-dose AAS users and in other groups at risk for developing AD/ADRD. This hypothesis is supported by the observations that genetic knockout of Nrf2 exacerbates A β and tau-P burdens and spatial cognition impairments in AD mice (Branca et al., 2017; Rojo et al., 2017) and by the finding that the nutraceutical Nrf2 activator sulforaphane decreases β -secretase and PS-1 expression, A β and tau-P burdens, and improves cognition in AD mice (Hou et al., 2018; Lee et al., 2018). In non-AD models, sulforaphane inhibits GSK3 β activity (Wang et al., 2016) and increases AQP4 expression (Zhao et al., 2005). In neuroblastoma cells, the Nrf2 activator dimethylfumarate reduces A β 42 levels and tau hyperphosphorylation (Campolo et al., 2018) and the Nrf2 activator carnosic acid increases ADAM10 (nonamyloidogenic APP processing) and IDE mRNA expression and reduces A β 42 protein levels (Meng et al., 2013). Thus, Nrf2 activators, through multiple mechanisms, could slow or prevent the development of AD/ADRD. By attenuating excess oxidative stress, antioxidants also may be able to enhance neural plasticity, which is impaired both in dementias and in addiction disorders (Kishida and Klann, 2007; Massaad and Klann, 2011; Uys et al., 2011, 2014; Hidalgo and Arias-Cavieres, 2016; Kumar et al., 2018a; Womersley et al., in press), and may reduce stimulant- or alcohol-seeking (Jang et al., 2015, 2017; Beiser et al., 2017; Quintanilla et al., 2018) or opioid tolerance or withdrawal symptoms (Abdel-Zaher et al., 2010).

GSK3 β inhibitors also have been evaluated in cell culture, animal, and human AD/ADRD models and several inhibitors exert promising effects. For example, in cultured cells or in transgenic mice, several different types of GSK3 β inhibitors including lithium (Li), inhibited A β 42 or tau-P accumulation, accelerated A β 42 clearance, upregulated LRP1 expression, and/or reduced spatial memory deficits (Ryder et al., 2003; Hu et al., 2009; Lin et al., 2016; Habib et al., 2017; Pan et al., 2018). In humans, low dose Li administered daily for 1 year significantly lowered CSF concentrations of tau-P, induced a trend level decline in CSF A β 42 concentration, and improved cognitive function in individuals with mild cognitive impairment (Forlenza et al., 2011). A subsequent 15-month Li microdosing study reported stabilization of cognitive function in individuals with AD (Nunes et al., 2013). Like antioxidants, GSK3 inhibitors also exert beneficial effects on substance use-related

behaviors including cocaine or methamphetamine hyperactivity or locomotor sensitization (Miller et al., 2009; Xu et al., 2009, 2011), cocaine cue memory reconsolidation (Shi et al., 2014), cannabis withdrawal signs (Rahimi et al., 2014), opioid-induced tolerance (Parkitna et al., 2006) or hyperalgesia (Yuan et al., 2013; Li et al., 2014), ketamine self-administration (Huang et al., 2015), and alcohol preference and withdrawal symptoms (van der Vaart et al., 2018). Accordingly, GSK3 inhibitors under development for substance use disorders also may have potential for reducing risk for developing AD/ADRD.

By reducing the presence or severity of lifestyle and health conditions (including supraphysiologic-dose AAS use and other substance use disorders) and/or by initiating treatment that slows accumulation of A β and tau-P starting in middle age, when A β and tau-P protein burdens begin to build (or earlier in substance users), it may be possible to slow or prevent the development of AD/ADRD. Because so many proteins involved in regulating A β and tau-P accumulation are responsive to sex-steroid or oxidative stress levels or GSK3 β activity, the latter of which is modulated by sexsteroids and oxidative stress, the most effective interventions likely will include multi-targeting strategies that modulate these and downstream regulatory (e.g., Nrf2) pathways. Multi-targeting therapeutic strategies are increasingly being pursued because at least theoretically, they are likely to be comparably if not more effective than agents that selectively target any one protein involved in a pathophysiologic cascade (Cavalli et al., 2008; Agatonovic-Kustrin et al., 2018; Gameiro et al., 2017; Gong et al., 2018; Knez et al., 2018; Oset-Gasque et al., 2018; Reis et al., 2018). Multi-targeting strategies, by enhancing neural plasticity and learning and/or by reducing drug-seeking, drug-tolerance, or drug-withdrawal symptoms, also may improve treatment outcomes in people suffering from substance use disorders.

10. Conclusions

A number of lifestyle and health conditions – including smoking, excessive alcohol intake, hypertension, obesity, diabetes, depression, physical inactivity, and social isolation – have been identified as presumed causal factors for the development of AD/ADRD, and the co-occurrence of these and other causal factors may amplify risk for developing dementia (Song et al., 2014; Livingston et al., 2017). We propose that supraphysiologic-dose AAS use, which may induce hypogonadism and excess oxidative stress, also is a causal factor for AD/ADRD, particularly when occurring in adolescents and young adults, perhaps along with other substance use disorders. If this hypothesis proves correct, it follows that the public health burden of supraphysiologic-dose AAS use and other substance use disorders may be greater than previously recognized. It also follows that persistent AAS users may benefit from multi-targeting treatment strategies, as outlined above, that may slow accumulation of A β and tau-P and delay or prevent development of AD/ADRD.

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Highlights

- Supraphysiologic-dose anabolic-androgenic steroid (sAAS) use starts by the mid-20s
- sAAS use occurs primarily in men aiming to increase muscularity
- sAAS use causes health problems including hypogonadism & excess oxidative stress
- These effects may increase synthesis & decrease elimination of A β & tau-P proteins
- sAAS use may cause early A β & tau-P increases and may enhance risk for dementia

Figure 1:
Androgen Level Extremes During Supraphysiologic-dose AAS Cycling: Users Rarely Experience Physiologically-Normal (Eugonadal) Androgen Levels

Figure 2:

Effects of abnormal androgen levels and excess oxidative stress (OS) on beta amyloid ($A\beta$) and hyperphosphorylated tau (tau-P) protein syntheses & elimination. In the figure, blue paths represent non-amyloidogenic and tau-phosphorylating pathways, whereas red paths represent amyloidogenic and tau-phosphorylating pathways. Three key systems that are involved in the control of $A\beta$ and tau-P levels are affected by abnormal androgen levels (comprising both supraphysiologic and hypogonadal levels) and/or by excess OS. The **upper left box** illustrates the fate of amyloid precursor protein (APP), the precursor for $A\beta$. Under eugonadal conditions, APP is predominantly processed by the nonamyloidogenic α -secretase enzyme to form soluble $sAPP\alpha$, which inhibits $A\beta$ synthesis. Under supraphysiologic or subphysiologic androgen conditions, APP is processed to a greater extent by the amyloidogenic β -secretase enzyme to form $A\beta$. Excess OS tends to inhibit and activate the nonamyloidogenic and the amyloidogenic APP processing pathways, respectively. The **upper right box** illustrates GSK3 β /Nrf2/tau protein cycling. GSK3 β is inhibited by $sAPP\alpha$ and upregulated by $A\beta$, and so departures from eugonadism increase GSK3 β activity. This leads to increased phosphorylation of tau protein and accumulation of tau-P, together with increased phosphorylation and downregulation of Nrf2, the master antioxidant transcription factor, which reduces antioxidant defenses. As noted above, an oxidizing environment increases amyloidogenic processing. The **bottom box** shows a number of proteins and a small molecule (scyllo-inositol, sI) that normally catabolize $A\beta$ and/or facilitate its elimination. However, under supraphysiologic or subphysiologic

androgen conditions, the A β -neutralizing effects of these proteins are attenuated. Excess OS also attenuates the function of many of these proteins and of sI. The proteins and small molecules within each of these 3 systems interact such that when concurrently present, abnormal androgen levels and excess OS likely potentiate A β and tau-P production and accumulation – as displayed in the red paths in the figure. These effects, if induced at an early age as a consequence of nonmedical AAS (or other drug) use, could lead to premature accumulation of A β and tau-P and increased risk for developing AD/ADRD. **Legend:** **A β :** beta-amyloid protein; **AD/ADRD:** Alzheimer's Disease and its Related Dementias; **APP:** amyloid precursor protein; **AQP4:** Aquaporin 4 protein; **GSK3 β :** Glycogen synthase kinase 3 β ; **HCY:** Homocysteine; **IDE:** Insulin degrading enzyme; **LRP1:** Low-density lipoprotein receptor-related protein1 and its soluble form (sLRP1); **NEP:** Neprilysin; **Nrf2:** Nuclear factor (erythroid-derived 2)-like 2; **OS:** Oxidative stress; **-P:** Phosphorylated protein; **PP2A:** Protein Phosphatase 2A; **PS-1/2:** Presenilins 1,2; **sAPP α :** Soluble APP α ; **sI:** scyllo-inositol; **tau:** Tau protein; **TTR:** Transthyretin (prealbumin); **Zn²⁺:** Zinc ion.

Figure 3:

Model for supraphysiologic AAS use, other substance use disorders, and biological mediators in the causation of Alzheimer's Disease and its Related Dementias. AAS use and other substance use disorders, which develop by young adulthood, induce premature hypogonadism and/or excess oxidative stress, effects that are associated with increased A β and tau-P burdens in later life. Accordingly, substance use disorders may constitute early, modifiable causal factors for the development of AD/ADRD. Treatments that optimize sex steroid hormone levels, that reduce excess oxidative stress, or that inhibit GSK3 β activity may exert powerful multi-targeting benefits on key mediators in the causal pathway to AD/ADRD. **Legend:** AAS: supraphysiologic-dose anabolicandrogenic steroid abuse; A β : beta-amyloid protein; AD/ADRD: Alzheimer's Disease and its Related Dementias; GSK3 β : Glycogen synthase kinase 3 β ; Meth: methamphetamine; Nrf2: Nuclear factor (erythroid-derived 2)-like 2.

Table 1.

Supraphysiologic doses of commonly-used AAS administered to animals induce widespread oxidative stress, as evidenced by oxidative small molecule, DNA, mRNA, protein, and lipid modifications and antioxidant enzyme expression changes

Study/AAS/Dose	Model	Route/Duration	Tissue	Oxidative Stress Abnormalities
¹ Nandrolone/20 mg kg ⁻¹	Rats	SC, Single Depot/4 Weeks	Blood	↑TBARS
² Nandrolone/10 mg kg ⁻¹	Rabbits	IM, Twice Weekly/6 Months	Blood	↑TBARS
³ Stanozolol/2 or 5 mg kg ⁻¹	Rats	IM, Weekly/8 Weeks	Erythrocyte	↑GPx
⁴ Testosterone/ 500 nM	TM3 Leydig Cell culture	Culture Application, 1 Hour	Leydig Cell	↑ROS ↑Lipid Peroxides
⁵ Testosterone/5 mg kg ⁻¹	Rats	IM, Every 48 Hours/2 Weeks	Testicular	↑TBARS, ↑AGEs, ↓TAC
⁶ Nandrolone/10 mg kg ⁻¹	Rats	IM, Weekly/8 Weeks	Testicular	↑MDA, ↑8-OHdG, ↓GSH, ↓iSOD
⁷ Nandrolone/5 mg kg ⁻¹	Rats	IM, Twice Weekly/8 Weeks	Prostate	↑NOX1, ↑Nrf2
⁸ Boldenone or Stanozolol/ 1.25 or 5 mg kg ⁻¹	Rats	IM, Weekly/12 Weeks for Low Dose or 4 Weeks for High Dose	Testicular	↑ROS, ↑MDA
⁹ Oxymetholone or Methyltestosterone/100 uM	Rat 1° hepatocyte culture	Culture Application, 2–4 Hours	Hepatocyte	↓GSH
¹⁰ Stanozolol/2 mg kg ⁻¹	Rats	PO, 5 Days Each Week/8 Weeks	Liver	↑TBARS, ↑GSH, ↑SOD, ↑CAT, ↑GPx
¹¹ Nandrolone/10 mg kg ⁻¹	Rats	IM, Weekly/8 Weeks	Liver; Kidney	↑NOX1, ↓SOD, ↓CAT, ↓Thiols; ↑Carbonyls
¹² Nandrolone/3.75 or 10 mg kg ⁻¹	Mice	IM, Twice Weekly/7 Weeks	Kidney	↑MDA, ↓GPx, ↓GR
¹³ Sustanon/10 mg kg ⁻¹	Rats	IM, Weekly/8 Weeks	Liver	↑SOD, ↑GPx, ↑GR
¹⁴ Boldenone or Stanozolol/ 1.25 or 5 mg kg ⁻¹	Rats	IM, Weekly/12 Weeks for Low Dose or 4 Weeks for High Dose	Liver and Kidney	↑ROS, ↑TBARS, ↓GSH
¹⁵ Testosterone/8 or 80 mg kg ⁻¹	Rats	IM, Weekly/6 Weeks	Liver	↑MDA, ↓SOD, ↓CAT, ↓GPx, ↓GR
¹⁶ Nandrolone/10 mg kg ⁻¹	Rats	IM, Thrice Weekly/6 Weeks	Kidney	↑8-OHdG
^{16a} Stanozolol/20 mg kg ⁻¹	LDLr ^{-/-} mice	SC, Weekly/8 Weeks	Liver	↑TBARS, ↑AOPP
¹⁷ Stanozolol/2 mg kg ⁻¹	Rats	PO, 5 Days Each Week/8 Weeks	Muscle	↑SOD
¹⁸ Stanozolol/5 mg kg ⁻¹	Rats	SC, 5 Days Each Week/6 Weeks	Heart	↑SOD, ↑CAT
¹¹ Nandrolone/10 mg kg ⁻¹	Rats	IM, Weekly/8 Weeks	Heart	↑NOX1
¹⁹ Nandrolone/10 mg kg ⁻¹	Rats	IM, Thrice Weekly/6 Weeks	Heart	↑Oxidized LDL, ↑NOX1, ↑8-OHdG, ↑HCY
²⁰ Stanozolol/5 mg kg ⁻¹	Rats	SC, 5 Days Each Week/4 Weeks	Heart	↑Carbonylation

Study/AAS/Dose	Model	Route/Duration	Tissue	Oxidative Stress Abnormalities
²¹ Testosterone/100 nM	Neuronal N27 Cells *	Culture Application, 48 Hours	Neuronal	↑Peroxides ↓Thiols
²² Nandrolone/10 mg kg ⁻¹	Rats	IM, Weekly/8 Weeks	PF Cortex & Hippocampus	↑MDA, ↓GPx
²³ Nandrolone/15 mg kg ⁻¹	Rats	SC, Every 3 rd Day/30 Days	Brain	↑MDA, ↓Nrf2, ↓CAT
²⁴ Stanozolol/10 mg kg ⁻¹	Rats	IM, Weekly/12 Weeks	Brain	↑GPx
²⁵ Nandrolone/1.875 mg kg ⁻¹	Rats	IM, Twice Weekly/8 Weeks	PF Cortex, Striatal, Hipp., & Cb	↑MDA
²⁶ Boldenone or Stanozolol/ 1.25 or 5 mg kg ⁻¹	Rats	IM, Weekly/12 Weeks for Low Dose or 4 Weeks for High Dose	Cortical & Hipp.	↑ROS, ↑MDA, ↓GSH
²⁷ Testosterone/20 mg kg ⁻¹	Rats	SC, Weekly/6 Weeks	Hipp.	↑TBARS, ↓SOD

* Sex of cells not specified.

AAS: anabolic-androgenic steroid; AGEs: advanced glycation endproducts; AOPP: Advanced oxidation protein products; CAT: catalase; Cb: cerebellum; GPx: glutathione peroxidase; GR: glutathione reductase; GSH: glutathione; HCY: homocysteine; Hipp.: hippocampus; IM: intramuscular; LDL: low density lipoprotein; LDLr^{-/-}: Low density lipid receptor deficient; MDA: malondialdehyde; NOX1: NADPH Oxidase; Nrf2: Nuclear factor (erythroid-derived 2)-like 2; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; PF: prefrontal; PO: oral; ROS: reactive oxygen species; SC: subcutaneous; SOD: superoxide dismutase; TAC: total antioxidant capacity; TBARS: thiobarbituric acid reacting substances.

Cited Studies:

- ¹Nikolic et al. 2016
- ²Vasilaki et al. 2016
- ³Tahernejad et al. 2017
- ⁴Hwang et al. 2011
- ⁵Tóthová et al. 2013
- ⁶Ahmed, 2015
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- ¹⁴Dornelles et al. 2017
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¹⁸Barbosa Dos Santos et al. 2013

¹⁹Tofighi et al. 2017

²⁰Kara et al. 2018

²¹Cunningham et al. 2009

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²³Ahmed and El-Awdan, 2015

²⁴Camiletti-Moirón et al. 2015

²⁵Turillazzi et al. 2016

²⁶Bueno et al. 2017a

²⁷Joksimovi et al. 2017

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