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Physiological basis behind ergogenic effects of anabolic androgens

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ABSTRACT

Anabolic androgenic steroids (AAS) are widely abused by the sporting community. Demonstrating performance enhancing effects of AAS in rigorous scientific studies is fraught with difficulty. In controlled studies, AAS have consistently been reported to increase muscle mass and strength. The clinical evidence that these anabolic effects are independent of, and additive to exercise are supported by preclinical studies suggesting that AAS and exercise affect muscle by overlapping, yet distinct mechanisms. AAS may also improve performance by their actions on other organ systems, such as the vasculature, and the erythropoietic and central nervous system, although this evidence is less strong. While most of the actions of AAS are thought to be mediated via classical androgen receptor-mediated genomic signalling, AAS may also produce rapid effects via non-genomic mechanisms.

1. Introduction

Despite their well-publicized adverse health effects (Basaria, 2010), anabolic androgenic steroids (AAS) are among the most commonly abused performance enhancing drugs among athletes. This reflects the assumption widely held by the sporting community and most of the general public that AAS improve physical performance. Certainly, authorities in the former German Democratic Republic believed this too, evidenced by a large-scale state-sponsored doping program in the 1980ies, and the involved scientists even used the data generated to obtain research higher degrees (Dickman, 1991). This period temporarily coincided with peak numbers of Olympic medals won by East German athletes.

However, the scientific evidence supporting the ergogenic (performance enhancing) effects of AAS remains scant. This is largely because it is all but impossible to definitively prove performance-enhancing effects by AAS by adequately designed randomised clinical trials (RCT) that replicate what athletes actually do in real life. It is unethical to conduct RCTs on illicit substances, or to randomise participants to vastly supraphysiological doses of androgens even if these are approved for clinical use. Available RCTs have generally not exceeded 600 mg of testosterone a week (approximately 5 times the conventional replacement dose) and have been short-term, while athletes may self-administer androgens up to 100- to even 1000-fold in excess of replacement doses, producing circulating testosterone levels two to three orders of magnitude above the healthy male reference range, and often for prolonged periods. The maximal anabolic dose of testosterone is not known, but almost certainly vastly exceeds 600 mg of testosterone a week, given that anabolic actions have been predicted to achieve a plateau only at doses approximately 2 log units higher that the minimal effective dose of testosterone (Storer et al., 2003). In addition, it is not feasible to conduct RCTs in elite athletes themselves that reliably control for important variables such as nutrition, exercise and covert use of performance enhancing drugs other than AAS.

The best currently available evidence clearly supports anabolic effects of androgens on skeletal muscle mass and strength in hypogonadal or eugonadal men irrespective of age. However, the extent to which this anabolic effect improves physical performance has been more difficult to assess. More limited evidence suggest that actions on the central nervous system, erythropoiesis and the vasculature may also contribute to the ergogenic effects of AAS (Fig. 1). In this brief review, we will focus our discussion on the evidence from key clinical studies in men. We will also highlight important findings from preclinical mechanistic studies.

The material presented is based on peer-reviewed journals indexed on the PubMed database from 1970 to November 2016, using, in multiple combinations, the following search terms “anabolic androgenic steroids, oxandrolone, stanozolol, nandrolone,

Abbreviations: AAS, Anabolic androgenic steroids.

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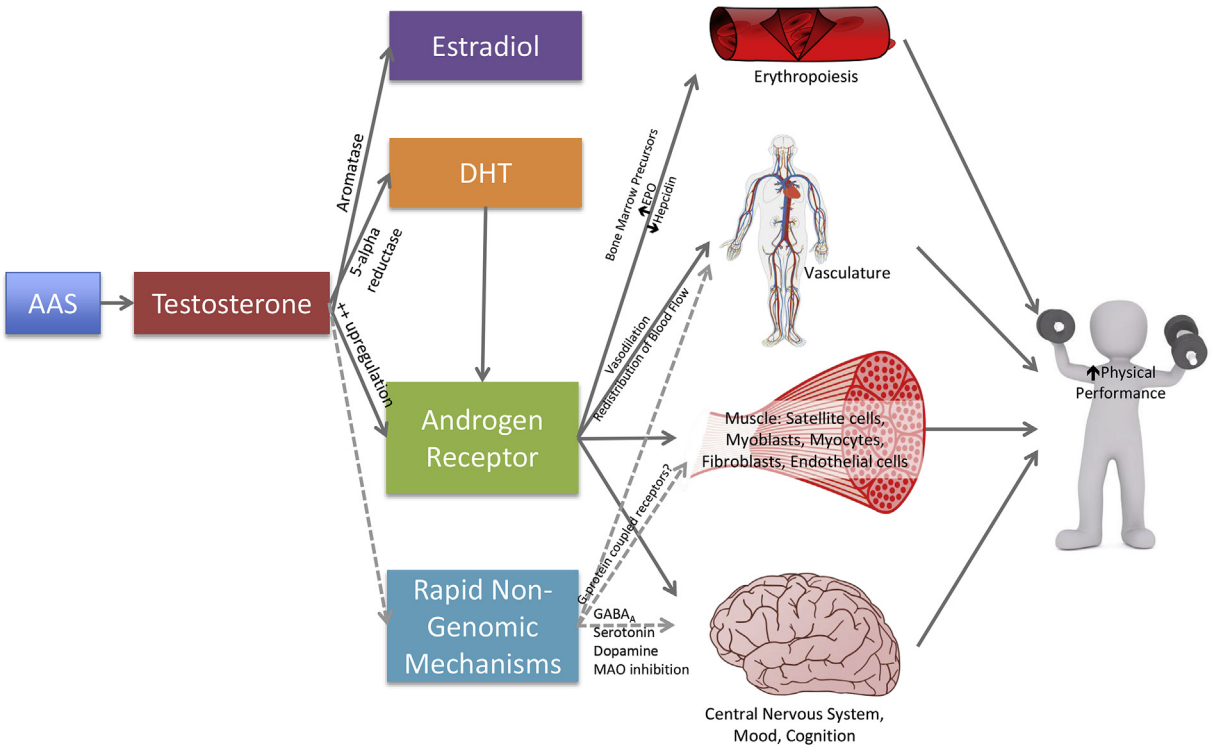

Fig. 1. Mechanisms of the ergogenic effects of AAS.
The effects of AAS on improving physical performance occur via metabolism to testosterone. Testosterone in turn has effects directly via the androgen receptor, non-genomic mechanisms as well as via aromatisation to estradiol and 5-alpha reduction to DHT.

trenbolone, physical performance, performance enhancing drugs, athlete, and testosterone", limited to English and studies in males. In addition, pertinent review articles were searched for additional publications, and relevant articles were selected.

2. Anabolic effects of AAS on muscle

2.1. Clinical studies

Following decades of controversy regarding anabolic effects of AAS, a 1996 landmark study by Bhasin et al. (1996). overcame many of the limitations of previous clinical trials. This carefully conducted RCT randomised healthy young eugonodal men to supraphysiologic testosterone enanthate (600 mg per week, about 6-times the replacement dose) or placebo for 10 weeks and standardized potentially confounding variables such as the amount of exercise and nutritional intake. While both testosterone treatment and weight-lifting exercise alone improved muscle mass and muscle strength (measured by bench press strength and squatting-exercise capacity) to a similar extent, importantly, effects were additive in the combined testosterone and exercise group. Thus, this study, for the first time, provided convincing proof that testosterone treatment enhances the effects of resistance exercise training, and that in turn resistance exercise enhances the anabolic effects of testosterone on muscle mass and strength (Bhasin et al., 1996). Additive effects of testosterone esters at modestly supraphysiological doses and resistance exercise on strength-based performance measures have since been confirmed in several RCTs of healthy active men that variously controlled for exercise regimens, food and protein intake, and living conditions (Storer et al., 2003; Giorgi et al., 1999; Rogerson et al., 2007). The additive effects of androgens and exercise are in part explained by the fact that both improve muscle strength by differential, non-overlapping mechanisms as further discussed below.

The anabolic effects of testosterone treatment on muscle mass and strength have consistently been reported across many RCTs in adult men. Skeletal muscle is one of the most testosterone responsive organs, and circulating testosterone concentrations are estimated to account for 40–67% of the gains in muscle mass observed in RCTs (Bhasin and Storer, 2009). Skeletal muscle mass remains responsive to testosterone treatment irrespective of endogenous testosterone levels, whether ranging from the castrate to clearly eugonadal levels. There is consistent RCT evidence that testosterone treatment increases muscle strength in both younger and older men and in those with frankly low, low-normal and eugonadal testosterone levels (Bhasin et al., 2005; Coviello et al., 2008; Srinivas-Shankar et al., 2010). Conversely, suppression of endogenous testosterone in healthy men reduces exercise-mediated gains in lean mass and muscle strength (Kvorning et al., 2006). Older men achieve similar incremental anabolic responses to graded doses of testosterone as do younger men: with supra-physiological doses, older men experience substantial, up to 50 kg, increases in leg press strength, albeit with a greater incidence of adverse effects compared to young men (Bhasin et al., 2005). However, testosterone treatment does not appear to affect muscle fatiguability or, in contrast to exercise, to improve the contractile quality of muscle as assessed by measuring specific tension (Storer et al., 2003). Moreover histology suggest that testosterone, in contrast to resistance exercise, has no effects on muscle fiber transition and fiber splitting (Sinha-Hikim et al., 2002). These differences in anabolic actions between resistance exercise and testosterone treatment provide a rational explanation for the synergistic effects of both interventions demonstrated in clinical studies (Bhasin et al., 1996).

Whether testosterone treatment targeted to achieve circulating testosterone levels in the mid normal healthy young reference range leads to clinically meaningful improvements in physical performance in older men remains unclear (Srinivas-Shankar et al.,

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2010; Travison et al., 2011). A 3-year RCT in men aged 65 years or older with a total testosterone <350 ng/dl demonstrated a modest 4% improvement in a timed physical performance test. Similarly, a recent 3-year RCT demonstrated significant, but modest improvements in stair-climbing power, chest press strength, and leg press power in testosterone treated men older than 60 years with baseline endogenous testosterone levels of 100–400 ng/dl or free testosterone <50 pg/ml (Storer et al., 2016a). In earlier studies, increases in muscle strength and power were proportional to the testosterone dose, but increasing testosterone dosing did not lead to progressive improvements in physical function (measured by walking speed, timed up and go test) in healthy older men (Storer et al., 2008). These uncertainties stem in part from the fact that for logistic reasons, most RCTs have used physical performance tests that only require submaximal effort. These tests may not detect performance improvements that may become evident during more physically demanding activities. Mobility limited, frail men may benefit more from the pro-anabolic effects of testosterone treatment than healthy men without functional impairments (Srinivas-Shankar et al., 2010; Travison et al., 2011). Indeed, the maintenance of some minimum level of circulating testosterone is clearly important in older men, given that a controlled study using a combination of computerized musculoskeletal modelling and three-dimensional gait analysis reported that androgen deprivation leads to decrements in lower-limb muscle function that are evident during walking, the most common and relevant activity of daily living for older adults (Cheung et al., 2016). Whether testosterone treatment improves physical performance in older men additive to structured exercise program has not been adequately studied.

2.2. Mechanisms

Androgens exert their anabolic actions on skeletal muscle in a variety of ways and at multiple sites, and several non-mutually exclusive mechanisms have been postulated. Testosterone promotes muscle protein accretion by improving net amino acid balance. Testosterone activates several anabolic pathways via IGF1-mediated stimulation of the Akt-mTOR pathway, activation of satellite cells and inhibition of myostatin activity (partly via follistatin) which are summarized in Fig. 2 (de Rooy et al., 2016). In skeletal muscle, testosterone treatment has been reported to increase fractional protein synthesis (Brodsky et al., 1996), to promote the efficiency of amino acid reuse (Ferrando et al., 2003) and possibly decrease protein breakdown, although not all studies are consistent. Nandrolone can maintain protein content and muscle weight through stimulation of protein synthesis with disuse (Camerino et al., 2015). Androgens may increase muscle mass both by promoting muscle hypertrophy and the formation of new muscle fibers (Kadi et al., 1999). In healthy young men, testosterone treatment leads to muscle fibre hypertrophy with greater myonuclear number per muscle fibre, and greater muscle fibre cross-sectional area of both type I and type II muscle fibers (Sinha-Hikim et al., 2002).

2.2.1. Androgen receptor-mediated mechanisms

These effects appear largely mediated via the androgen receptor, and selective overexpression of the androgen receptor in myocytes is sufficient to increase muscle mass in mice male mice (Fernando et al., 2010). Testosterone and dihydrotestosterone (DHT) have been shown to induce muscle growth through promoting myogenic differentiation in mesenchymal $CD34^{+}$ pluripotent stem cells through an androgen receptor-mediated pathway (Singh et al., 2003). However, elegant clinical studies have demonstrated that DHT is not required for the anabolic actions of testosterone: healthy men had similar dose-dependent gains in fat free mass and muscle strength with testosterone treatment irrespective of whether they additionally received a 5alpha-reductase inhibitor or not (Bhasin et al., 2012). In muscle, endogenous androgen receptors are predominantly expressed by cells of the satellite lineage including satellite cells, myoblasts, and myocytes (Sinha-Hikim et al., 2004), and testosterone-induced muscle hypertrophy is associated with an increase in satellite cell number (Sinha-Hikim et al., 2003). Androgen receptors are also detected in cells present in the interstitium of muscle such as fibroblasts and endothelial cells. The possible contribution of androgen receptor signalling in these interstitial cells to the regulation of muscle mass is supported by the observation that DHT and the selective androgen receptor modulator enobosarm increased muscle mass in mice with a selective deletion of the androgen receptor in the satellite lineage (Dubois et al., 2015). In addition, dynamic changes in muscle androgen receptor content in response to AAS administration, and/or changing exercise routine may modulate the effects of androgenic ligands on skeletal muscle (Kadi et al., 2000). Upregulation of androgen receptors in response to AAS (Sheffield-Moore et al., 1999) may also explain why earlier assumptions that supra-physiogical testosterone doses should not provide added anabolic actions due to androgen receptor saturation at physiological doses have not been supported by the available evidence.

Androgen receptor dependent muscle growth is mediated by regulating a variety of downstream targets, and beta-catenin, transforming growth factor beta, Notch, c-Jun NH2-terminal kinase, p38 mitogen-activated protein kinase as well as the myostatin pathway have been implicated (Mendler et al., 2007; Brown et al., 2009; Lakshman et al., 2009). Interestingly however, a case study of an individual with partial androgen insensitivity syndrome due to a single amino acid mutation disrupting the DNA-binding domain of the androgen receptor reported that testosterone treatment resulted in a positive nitrogen balance similar to that in healthy adult men (Tincello et al., 1997). Hence it is possible that some of the anabolic effects of testosterone are independent of the androgen receptor, or mediated via androgen receptor-mediated signalling which does not require DNA binding.

Experiments in mice with tissue specific deletions of the androgen receptor raise the possibility that androgen receptor mediated signalling in organs other than muscle may contribute to maintenance of skeletal muscle mass. While global deletion of the androgen receptor in mice leads to 15–20% loss of muscle mass (MacLean et al., 2008), in muscle-specific androgen receptor knock out mice, the reduction in limb muscles is only 0–6% (Ophoff et al., 2009; Chambon et al., 2010). Potentially, neuronal androgen receptors may contribute to muscle regulation, consistent with studies in male rats reporting that testosterone treatment reduced neuromuscular transmission failure in the diaphragm muscle (Blanco et al., 1985), and that castration decreased the cross-sectional area of spinal motoneurons (Leslie et al., 1991).

2.2.2. Growth hormone and insulin-like growth factor-1 mediated mechanisms

Androgens are also thought to have complementary effects to stimulate secretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) which may contribute to skeletal muscle formation (Illig and Prader, 1970). Increased mRNA levels for myosin heavy chain, IGF-1 and the IGF-2 receptor have been reported in dialysis patients given oxymetholone, an oral AAS (Supasyndh et al., 2013). Furthermore, testosterone administration to elderly men for 1 month increased intramuscular (but not peripheral) IGF-1 mRNA expression with a concordant decrease in intramuscular IGF-binding protein 4, implying an increase in free IGF-1 in skeletal muscle (Urban et al., 1995). As IGF-1 can stimulate the differentiation of satellite cells into mature myocytes (Florini et al., 1991), the increased IGF-1 mRNA expression may have

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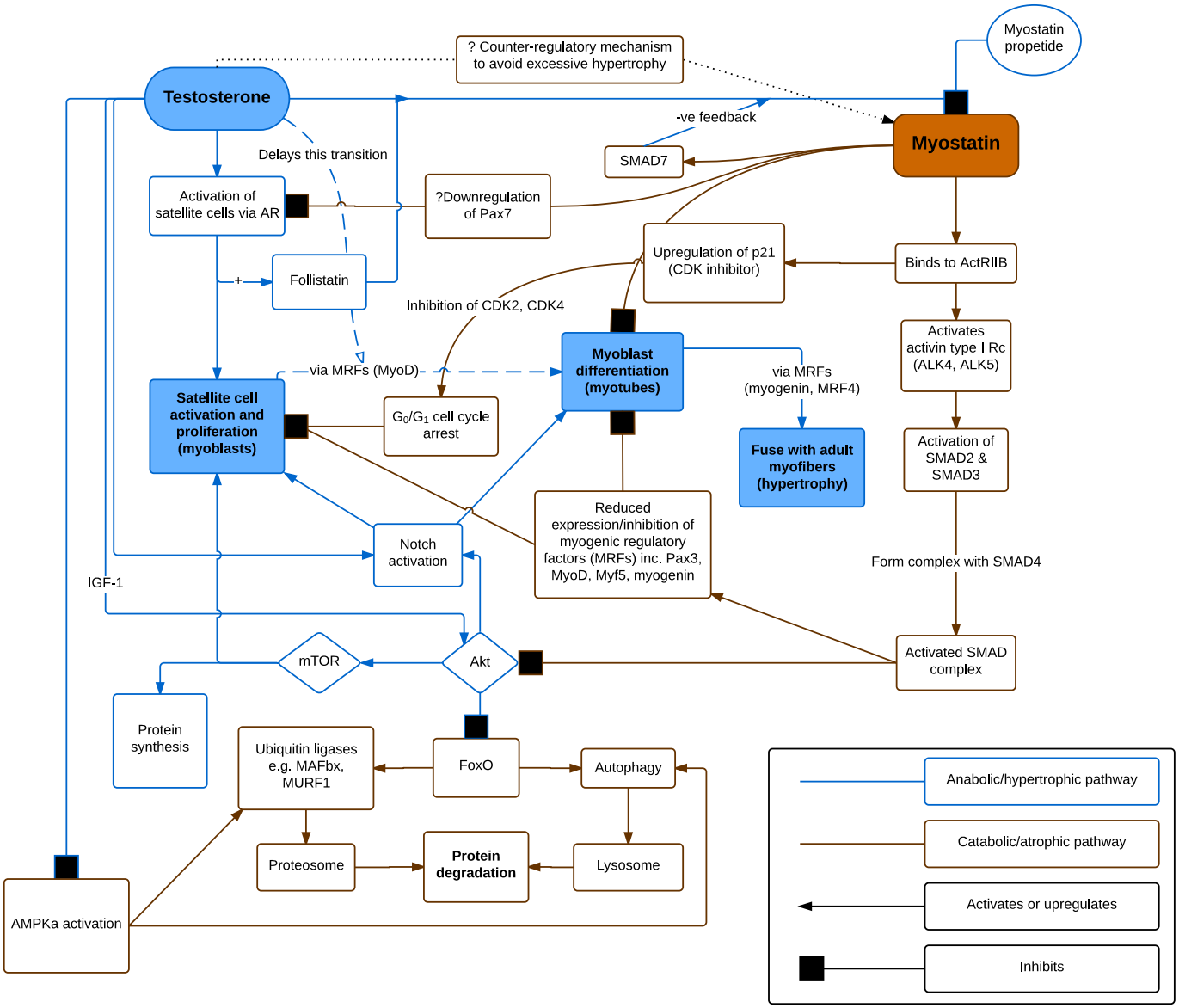

Fig. 2. Signalling pathways underlying the anabolic effects of testosterone.
Reproduced with permission from de Rooy et al, 2016 Testosterone activates several anabolic pathways via IGF1-mediated stimulation of the Akt-mTOR pathway, activation of satellite cells and inhibition of myostatin activity.

contributed to the increase in muscle protein synthesis seen in this cohort of elderly men receiving testosterone (Urban et al., 1995). However, while potentially contributing to anabolic effects, stimulation of the GH-IGF-1 axis appears not to be essential as testosterone treatment has anabolic effects even in men who are GH-deficient due to hypopituitarism (Brodsky et al., 1996).

3. Possible performance enhancing effects of AAS other than muscle anabolism

While the evidence for anabolic effects of AAS on muscle hypertrophy and strength based performance measures, as far as assessable within the ethical and logistic framework of scientific studies, is consistent, whether AAS improve other aspects of athletic performance is much less clear. For example, increased body mass (lean or otherwise) may be detrimental for marathon runners or triathletes. Yet, AAS are widely abused by the sporting community, even for disciplines where increased strength is of lesser importance, such as cycling or endurance athletics.

Very few RCTs have assessed the effects of androgen treatment in addition to exercise on non strength-based outcome measures. In one small double blinded 4-week RCT that assessed the effects of AAS on endurance performance in 24 healthy active young men additive to a structured training program, neither testosterone or androstenedione improved running velocity at anaerobic threshold more than exercise alone (Baume et al., 2006). Similarly, stanozol did not improve mile run time over placebo in college students engaged in a interval running program, despite increasing maximum oxygen intake (Johnson et al., 1975). In older mobility limited men, testosterone treatment for 6 months improved, compared to placebo, aerobic performance assessed as peak oxygen uptake and gas exchange lactate threshold during cycle ergometer exercise (Storer et al., 2016b), although this study did not include a structured exercise program. In rats, the AAS nandrolone enhanced submaximal running endurance (Georgieva and Boyadjiev, 2004; Van Zyl et al., 1995), but had no effect on running economy,

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maximum oxygen consumption, oxygen carrying capacity of the blood (Georgieva and Boyadjiev, 2004) or on muscle oxidative capacity (Van Zyl et al., 1995).

Another perception held by many athletes is that AAS promotes adaptation to strenuous exercise training and enhances recovery time, allowing an individual to train harder. Available clinical studies have only assessed indirect parameters associated with recovery time, and have been based on small convenience samples, comparing poorly matched groups of AAS users with nonusers. Some studies reported higher androgen/cortisol ratios and lower plasma lactate concentrations (Rozenek et al., 1990) or reduced creatinine kinase release (Boone et al., 1990) after acute bouts of exercise in AAS users compared with nonusers. In male rats, nandrolone decanoate has been reported to enhance the rate of muscle protein synthesis and muscle fatigue resistance during exercise recovery (Tamaki et al., 2001). Overall, the evidence is too limited to draw conclusions regarding the effects of AAS on recovery time or on sustaining intensive training periods. Similarly, despite rodent studies suggesting that AAS may aid in the healing of muscle contusion injury (Beiner et al., 1999), there are no clinical studies supporting the use of AAS to accelerate the recovery from sporting injury. In fact, AAS may lead to dysplasia of collagen fibrils, hence decreasing the tensile strength of tendon and thereby increase the risk of tendon rupture (Stannard and Bucknell, 1993).

3.1. Vascular effects

In addition, there are purported effects of androgens on physical performance to increase oxygen delivery to the lungs and muscles through vasodilation and redistribution of blood flow. Testosterone has been shown to have acute vasodilatory effects on the pulmonary artery and vein in humans and animals (English et al., 2001; Rowell et al., 2009). Although not studied at supraphysiologic doses, short-term testosterone administration into coronary arteries has been shown to cause a rapid and direct increase in coronary artery dilatation and coronary blood flow (Webb et al., 1999). Hence, it is possible that testosterone may acutely improve cardiac output and in turn, physical performance. It should however be noted that other studies have shown no change in vascular reactivity (Ly et al., 2001; Zitzmann et al., 2002) and others have demonstrated the opposite effect with testosterone administration causing vasoconstriction (Schror et al., 1994). In animal studies testosterone has been reported to rapidly modulate vascular tone by regulation of calcium and potassium channels (Deenadayalu et al., 2001; Scragg et al., 2004) suggesting that at least some of these actions are non-genomic in nature.

There is some debate regarding whether testosterone administration can also increase capillary density within skeletal muscle. In addition to higher muscle mass, individuals who had admitted to AAS abuse for at least 5 years duration, had dose-dependent increases in capillary number per fibre and myonuclear number per fibre compared to individuals who had never used AAS (Yu et al., 2014). Prolonged androgen exposure over a number of years may be required to stimulate capillary growth, as shorter durations of administration (up to 20 weeks) have not demonstrated increases in skeletal muscle capillary density (Sinha-Hikim et al., 2002).

3.2. Haematological effects

During exercise, red blood cells transport oxygen to the tissues as substrate for working muscle and in turn, deliver metabolically produced carbon dioxide to the respiratory system for expiration. The greater the haemoglobin, the greater the capacity for gas diffusion and aerobic performance (Berglund and Hemmingson, 1987). Androgens have well established erythropoietic effects and testosterone treatment consistently increases haemoglobin and haematocrit in clinical trials (Calof et al., 2005). In one RCT of older men, testosterone treatment improved lower limb physical performance despite the absence of a detectable effect on lower extremity strength, leading the authors to speculate that the significant increase in haemoglobin observed in testosterone treated men and resultant increased oxygen carrying capacity may have contributed to the improved physical performance (Page et al., 2005). In a recent RCT of mobility limited men which demonstrated improvements in aerobic function with testosterone relative to placebo treated men, the authors discussed the possibility that this improvement could be accounted for by the observed haemoglobin increase with testosterone treatment (Storer et al., 2016b).

The exact mechanisms by which androgens regulate erythropoiesis have not been fully elucidated, but probably involve at least three different mechanisms. Androgens can stimulate red blood cell formation by firstly, stimulating the proliferation of bone marrow erythroid progenitor cells via the androgen receptor (Moriyama and Fisher, 1975), secondly via regulation of erythropoietin, and as reported more recently, by increasing iron utilization via suppression of the master iron regulatory protein hepcidin (Guo et al., 2013). In men, graded doses of testosterone led to a dose-dependent reduction of circulating hepcidin levels, and hepcidin levels were predictive of changes in haemoglobin (Bachman et al., 2010). Experimental work in mice showed that while testosterone increased erythropoietin levels, its hepcidin-suppressive effect was independent of its effects on erythropoietin or hypoxia-sensing mechanisms, and associated with increased incorporation of iron into erythrocytes (Guo et al., 2013). In testosterone-treated men, erythropoietin levels remain inappropriately elevated despite polycythemia, suggesting a erythropoietin set point recalibration, potentially via induction of hypoxia or disturbance in hypoxic sensing (Bachman et al., 2014).

3.3. Effects on the central nervous system

Observational studies have reported that circulating testosterone levels rise pre-competition, increase following victory and decrease following loss, and endogenous testosterone levels have been associated with willingness to compete and motivation, increased risk taking, and enhanced visuo-spatial ability. Although many individual studies are observational in nature, a review of all available evidence suggests that (Wood and Stanton, 2012) high endogenous testosterone levels may confer psychological advantages in sport by effects on mood, behavior, and motivation (Wood and Stanton, 2012). Experimental studies suggest that androgens act on the central nervous system to affect mood and cognition in addition to motor function through a widespread network of intracellular androgen receptors, which are most abundant in the hypothalamus, hippocampus and amygdala (Fargo et al., 2008, 2009; Simerly et al., 1990). AAS can increase androgen receptor number in some brain areas similar to what occurs in muscle (Lynch and Story, 2000). In addition androgen receptor mediated genomic nuclear signalling, rapid androgenic effects may be produced by non-genomic extranuclear mechanisms in neurons (as well as skeletal and cardiac myocytes) possibly via G-protein coupled receptors on cell membranes to increase intracellular calcium concentrations (Wang et al., 2014; Vicencio et al., 2011). AAS may also modulate other receptors such as gamma-aminobutyric acid type A ($GABA_A$) to affect mood and behavior (Oberlander et al., 2012).

Clinical studies on the psychological and behavioral effects of AAS are few, however there have been two randomised controlled trials in men which demonstrate that testosterone administration does increase aggressive behavior (Kouri et al., 1995; Pope et al.,

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2000). Although individual response was highly variable, supraphysiologic doses of AAS also increased manic behavior (Pope et al., 2000). Most mechanistic data has come from animal studies. Animal studies have reported that behavioral effects of androgens can occur within minutes (Baum and Vreeburg, 1976). In the 1980s, East German scientists developed a nasal androgen spray in an attempt to acutely increase competitiveness and aggressive behavior (Dickman, 1991). AAS may enhance mood through an action similar to monoamine oxidase inhibitors and mesterolone has been shown in a double-blind trial to improve depressive symptoms (Vogel et al., 1985). Small studies have reported higher serotonin or dopamine levels in cerebrospinal fluid of AAS users (Hannan et al., 1991; Daly et al., 2001), although the relevance of such changes is not clear. A small 2-week double blind RCT of high-dose methyltoestosterone in healthy, AAS-naïve men reported mixed outcomes with one the one hand, improvements in energy and euphoria, yet increased irritability, mood swings and distractibility (Su et al., 1993). Androgens have also been show to play a role in neuroprotection and nerve regeneration, however adverse neurotoxicity has also been described with prolonged use (Fargo et al., 2009).

The majority of the literature on AAS and the central nervous system has focussed on adverse psychiatric effects including psychosis, depression, criminal aggressive behavior, dependency and addiction as well as long-term psychiatric effects resulting from presumed neurotoxicity. Several animal studies have shown that after prolonged exposure to AAS at high concentrations, anabolic steroids have been shown to cause neurotoxicity (Yang et al., 1985). There appear to be very variable and somewhat individualized effects of AAS on mood, behavior and cognition, which may well be related to dose and specific drug metabolism and pharmacokinetics. These dose related effects may explain the inconsistent results in the literature regarding possible neuroprotective and neurotoxic or psychiatric effects associated with AAS use.

4. Summary

Replicating real life AAS abuse patterns which involve vastly supraphysiologic multidrug regimens and other high risk behaviours in scientific studies is neither possible nor ethical. Therefore the scientific evidence validating the perceptions of the sporting community is relatively limited and are largely derived from clinical studies in non-athlete populations using modestly supraphysiologic androgen dosing, and from animal experiments. There are multiple potential mechanisms by which AAS may enhance physical performance with possibly synergistic effects on different organs and systems. While there is unequivocal evidence that AAS can increase muscle mass and strength in a dose dependent fashion, the evidence for performance enhancing effects via actions on the vasculature, erythropoiesis and the central nervous system is comparatively less well established. Indeed, there is considerable evidence that AAS effects on these same tissues cause toxicity (Basaria, 2010) that might be detrimental to optimal athletic performance. At the cellular level, while most data support the importance of classical androgen receptor signalling for mediating the performance enhancing effects of AAS, more rapid non-genomic mechanisms may also contribute.

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