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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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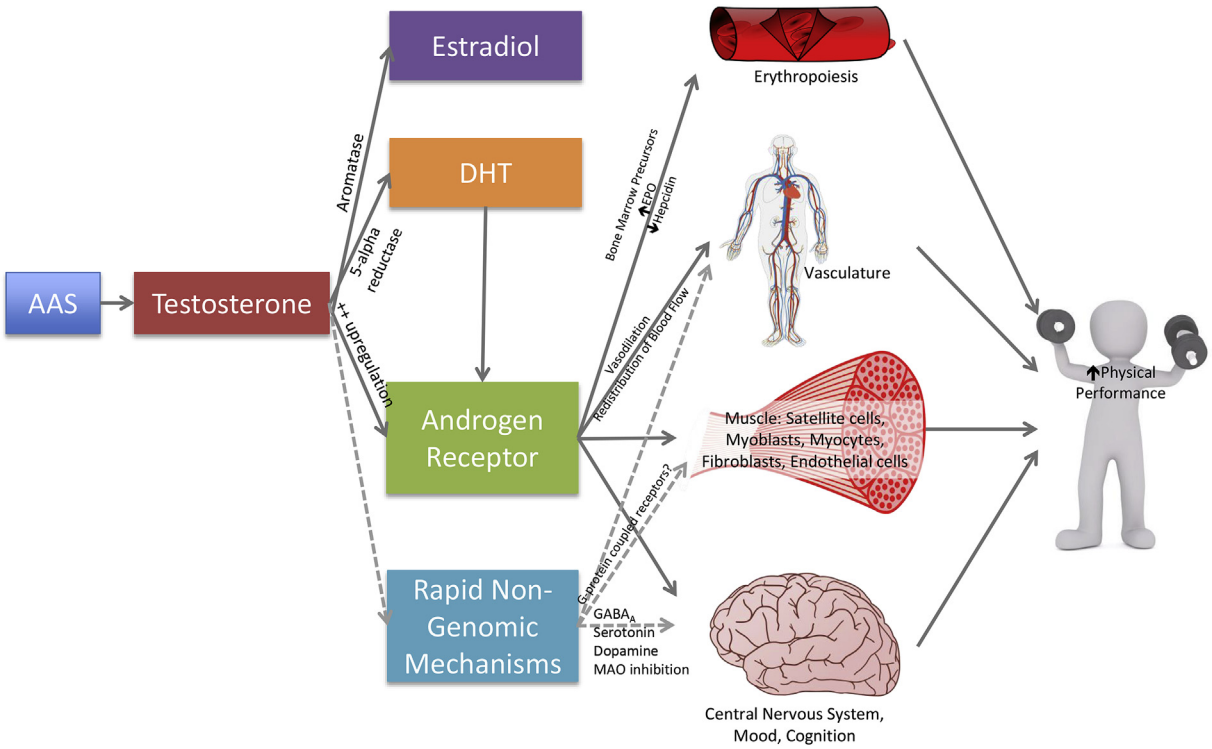

Fig. 1. Mechanisms of the ergogenic effects of AAS.
The effects of AAS on improving physical performance occur via metabolism to testosterone. Testosterone in turn has effects directly via the androgen receptor, non-genomic mechanisms as well as via aromatisation to estradiol and 5-alpha reduction to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