Endocrine aspects of anabolic steroids

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Understanding of the mechanism of androgen action has been enhanced by advances in knowledge on the molecular basis of activation of the androgen receptor and the importance of tissue conversion of circulating testosterone to dihydrotestosterone and estradiol. New evidence supports the view that supraphysiological doses of anabolic steroids do have a definite, positive effect on muscle size and muscle strength. However, the nature of the anabolic action of androgens on muscle is currently unclear and may involve mechanisms independent of the androgen receptor. The dose–response relationships of anabolic actions vs the potentially serious risks to health of androgenic-anabolic steroids (AAS) use are still unresolved. Most of the adverse effects of AAS are reversible but some are permanent, particularly in women and children. The reported incidence of acute life-threatening events associated with AAS abuse is low, but the actual risk may be underrecognized or underreported; the exact incidence is unknown. The long-term consequences and disease risks of AAS to the sports competitor remain to be properly evaluated.

INDEXING TERMS: androgen receptor • abused drugs • sports medicine

In the last 40 years, use of anabolic steroids has become much more widespread but has nevertheless remained covert and intermittent, involving an increasing number of agents. Consequently, clinical information concerning the effects of anabolic steroids has continued to be derived from isolated case reports. These uncontrolled anecdotal observations make it difficult to draw unequivocal conclusions. The virtual absence of long-term prospective data also makes judgments on safety rather uncertain. Here, I compare and contrast the principles and practice behind the abuse of androgenic-anabolic steroids (AAS) with the legitimate clinical therapeutic use of androgens, in order to discuss how the use of AAS by athletes fits into our current understanding of androgen physiology and the clinical practice of endocrinology.

PHYSIOLOGY OF ANDROGEN ACTION

Androgens are required life-long in males—from the heterogametic sexual differentiation in utero, through secondary sexual development during puberty (where they are the major determinants of extragenital sexual dimorphism), to the establishment and the maintenance of adult sexual function and fertility. Not only are the physiological functions of androgens spread out temporally, they also act on a large number of reproductive and nonreproductive target tissues, including bone, adipose tissue, skeletal muscle, brain, prostate, liver, and kidney (stimulating production of erythropoietin). It is therefore somewhat surprising that the extremely diverse biological actions of androgens are mediated by only one molecular species of androgen receptor with a singular mode of action, i.e., through transcriptional activation of androgen response elements in different target genes [1].

Some aspects of the tissue specificity of androgen action can be accounted for by the local conversion of testosterone to more-active or specific metabolites, including dihydrotestosterone (DHT) and estradiol. From the clinical syndromes of androgen [2] and estrogen resistance [3], and 5α-reductase [4] and aromatase deficiency [5], we can deduce that testosterone itself is adequate for in utero masculinization of the internal genitalia and postnatal skeletal muscle development as well as the activation of sexual behavior during adolescence and young adult life. DHT, on the other hand, is required for the fetal development of external genitalia, prostate and seminal vesicles, and adult secondary hair growth. Aromatization of testosterone to estradiol is necessary for sexual differentiation of the brain, bone mass accretion, and fusion of the epiphyses at the end of puberty. In other words, testosterone is a target hormone itself as well as a circulating prohormone for several target tissues that possess the converting enzymes 5α-reductase and aromatase. Hence not all actions of androgens are mediated through the androgen receptor.

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DOSE–RESPONSE RELATIONSHIPS OF ANDROGEN ACTION

The rationale of using anabolic steroids in competitive sports is based on the following considerations: (*a*) the clear differential in athletic performance between males and females, on average, the lean body mass being 30% higher in men than in women; (*b*) obvious anabolic effects resulting from the physiological increase in testosterone during pubertal development; (*c*) production of undoubted anabolic and ergogenic effects by physiological doses of testosterone in hypogonadal patients; (*d*) the assumption that use of supraphysiological doses of testosterone or more potent synthetic androgenic analogs would increase muscle bulk and improve performance in eugonadal adult men; and (*e*) the assumption that anabolic effects can be separated from virilizing effects by use of "pure anabolic" agents.

The steep and linear dose–response relationship for both the virilizing and anabolic actions of testosterone, ranging from the concentrations in childhood and in females (<2 nmol/L) to the normal adult male physiological range (10–35 nmol/L), is indisputable (Fig. 1). Whether androgen responses can be stimulated by increasing doses of testosterone beyond the physiological range is at present unclear. There may also be significant differences in the dose–response characteristics between individual androgen-dependent actions and target tissues. Thus, although administration of AAS to women and children clearly stimulates hypertrophy and perhaps hyperplasia of skeletal muscle, whether these effects can be extrapolated beyond the physiological into the pharmacological range is not clear. Some sports competitors use extremely high doses of testosterone, producing plasma concentrations two or three orders of magnitude greater than that found in healthy men. At these nonphysiological concentrations of hormones, the receptors would already have been saturated and any biological response may well have reached a plateau, while at the same time atypical actions can be induced. It is therefore
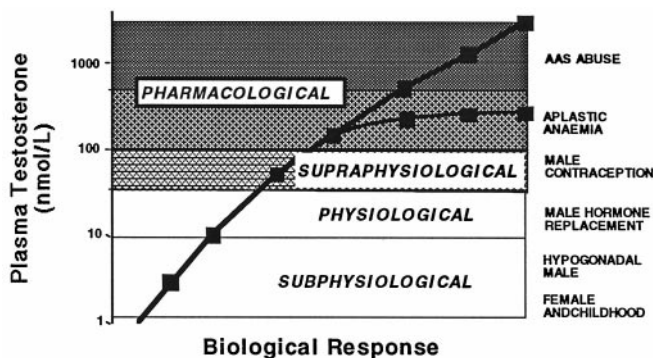

Fig. 1. Putative dose–response relation of biological responses to increasing concentrations of circulating testosterone characteristic of various clinical situations and therapeutic indications.

Testosterone concentrations encountered in AAS abuse are typically orders of magnitude higher than physiological concentrations, when some of the biological effects may have plateaued. However, the exact dose–response relations of individual androgen actions remain to be fully characterized.

important to know whether any actual or perceived gains of AAS administrations are countered by undesirable side effects.

DO AAS IMPROVE ATHLETIC PERFORMANCE?

Reviews and metaanalyses of literature addressing this question over the last 30 years have determined that many of the previous studies were flawed in their experimental design and, not surprisingly, results were equivocal [6, 7]. Some of the reported enhancement in performance may have been due to the effects of AAS in increasing aggression and competitiveness, differences in intensity of training or dietary intake, and important placebo effects. Studies generally did not mimic the dose and variety of drugs that athletes tend to use, a process known as "stacking," or the changes in doses during cycles of steroid administration, i.e., a pyramid program. The inherent polymorphism and individual variations in terms of innate ability and motivation tend to further blur any significant differences between controls and subjects. Practically, true double-blinding is difficult because clinical evidence of side effects such as greasiness of the skin and acne betray which groups—control or treated—the subjects belong to.

To overcome some of the pitfalls of previous investigations, a recent study [8] has been designed to control for the independent effects of testosterone, training, and diet while the dose of testosterone approached that commonly used in AAS abuse. The treated volunteers received 600 mg of testosterone enanthate intramuscularly weekly for 10 weeks. The 43 volunteers with some weightlifting experience were divided into one of four groups: placebo with no exercise, testosterone with no exercise, placebo plus exercise, and testosterone plus exercise. Muscle size, strength, and fat-free mass increased with testosterone without exercise, but exercise itself increased muscle strength. With testosterone administration and exercise together, all of these variables increased in an additive manner. This important study showed unequivocally for the first time that supraphysiological doses of androgens do have an anabolic effect on muscle mass and strength in eugonadal men, which can be further amplified by physical training.

HOW DO AAS WORK?

After puberty, the androgen receptor in striated muscle is down-regulated [9]; the androgen receptor in skeletal muscle is therefore virtually saturated with the physiological concentrations of testosterone present. Because there is little 5α-reductase activity in skeletal muscle [10], testosterone and possibly circulating DHT appear to be the key hormones for androgen action. In vitro studies have demonstrated that the dose–response relationship of testosterone on growth of skeletal muscle reaches a plateau once the physiological concentration is exceeded [11]. With supraphysiological doses of testosterone, the anabolic effects may therefore be evoked through a separate

mechanism independent of the androgen receptor, e.g., an anticatabolic effect based on an antiglucocorticoid action [12].

Some indirect evidence supports an anticatabolic effect of androgens. AAS can displace glucocorticoids bound to the glucocorticoid receptor. Antagonists of glucocorticoid action can prevent the muscle atrophy that follows orchidectomy, and urinary free cortisol increases with administration of large doses of AAS. Clinical evidence can be derived from patients who have the androgen insensitivity syndrome as a result of inactivating mutations in the androgen receptor gene. In a recent case study [13], a patient with androgen insensitivity syndrome resulting from a single amino acid substitution (Arg-608 to Lys) in the DNA-binding domain of the androgen receptor received pharmacological doses of testosterone enanthate (5 mg/kg per day for 10 days). Although there were no treatment effects that suppressed gonadotropin and sex-hormone-binding globulin or sebum excretion, testosterone administration resulted in a positive nitrogen balance of 3 g/24 h, similar to that in healthy adult men. Hence, these data indirectly support the hypothesis that the effect of supraphysiological doses of testosterone on muscle is probably mediated through an antiglucocorticoid action independent of the androgen receptor.

ADVERSE EFFECTS OF AAS
Even though different mechanisms may mediate the action of AAS, the unwanted androgenic effects cannot be completely dissociated from the anabolic effects [14]. The adverse effects of AAS abuse depend on the age and sex of the individual, the duration and total dose of exposure, and the type of steroid used [15]. These effects may be differentiated into androgenic (Table 1) or toxic effects (Table 2). Whereas the former are amplifications of the physiological effects of androgens, the latter can be regarded as the more serious consequences encountered mainly with prolonged usage of pharmacological doses of AAS.

The unwanted consequences of AAS abuse are most damaging in females and adolescents: irreversible virilization and stunting of linear growth, respectively. Suppression of the hypothalamic–pituitary–gonadal axis that

Table 1. Adverse effects of AAS abuse: androgenic.

Virilization—women, some irreversible
  Acne
  Hirsutism
  Alopecia
Premature epiphyseal closure—stunted final height
Gynecomastia
Decreased testicular volume
Infertility—reversible
Increased sexual interest
Decreased HDL-cholesterol
Increased prostatic disease risk

Table 2. Adverse effects of AAS abuse: toxic.

Cardiovascular	Psychological
Cardiomyopathy	Aggression increased
Acute myocardial infarct	Dysphoria—rage
Cerebral vascular accident	Psychosis
Pulmonary embolism	Addiction
Liver	Withdrawal effects—depression
Cholestatic jaundice	Needle sharing
Peliosis hepatis	Hepatitis
Tumors	HIV infection

results in disturbances in menstrual function and infertility is, in contrast, reversible. Stimulation of the sebaceous glands appears to be dose-related: Increasing testosterone beyond the physiological range in normal men results in further increases in the sebum excretion rate. Consequently AAS users tend to suffer from severe acne.

One of the more serious problems associated with anabolic steroid abuse is the invariable decrease in circulating HDL-cholesterol because of the action of androgens in suppressing hepatic endothelial lipase activity. This may have long-term consequences in increasing the risk to ischemic heart disease, but is probably unrelated to the cardiomyopathy, cerebral vascular accident, or pulmonary embolism associated with AAS use—which may be independent effects of androgens on the vasculature and hemostasis. Possible adverse effects on the prostate gland arising from prolonged administration of anabolic steroids have not been fully elucidated, the data consisting of isolated and infrequent case reports. Data from male contraceptive trials, where volunteers have received testosterone enanthate 200 mg weekly for up to 18 months, showed no change in plasma concentrations in prostate-specific antigen, and the prostatic transverse diameter increased by only 14% [16]. The serious hepatic abnormalities are virtually always associated with the orally active 17α-alkylated androgens such as methyltestosterone, methandrostenolone, oxandrolone, and stanozolol. Users of anabolic steroids have exhibited changes in behavior ranging from increased aggression to the so-called "roid rage" and psychosis [17]. Some evidence suggests that androgen users become addicted and suffer withdrawal symptoms [17]. Withdrawal effects are probably also related to the slow recovery of endogenous production of testosterone after cessation of exogenous use.

Although individual case reports are extant in the literature, the exact incidence of serious or fatal adverse effects is unknown. It therefore remains difficult to assess accurately just how dangerous the use of AAS is. Intuitively, one can deduce that there is probably substantial underreporting of AAS use. Nevertheless, the overall incidence of serious and fatal complications is probably low. These isolated cases of pathology may represent idiosyncratic responses of susceptible individuals to the pharmacological doses used in AAS abusers; as a rule, however, the reported effects cannot be extrapolated to indicate a systematic generic/class effect of androgens—

with the important exception of the 17α-alkylated compounds, the most harmful of the anabolic agents. It is sometimes claimed that the intermittent style of using anabolic steroids probably ameliorates the long-term side effects and that using anabolic steroids may not be as dangerous to well-being or as addictive as the use of other forms of recreational drugs. In the absence of any supporting data, however, such assertions should not be generally accepted at present.

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