Anabolic Steroids

CYNTHIA M. KUHN

Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, North Carolina 27710

ABSTRACT

The term “anabolic steroids” refers to testosterone derivatives that are used either clinically or by athletes for their anabolic properties. However, scientists have questioned the anabolic effects of testosterone and its derivatives in normal men for decades. Most scientists concluded that anabolic steroids do not increase muscle size or strength in people with normal gonadal function and have discounted positive results as unduly influenced by positive expectations of athletes, inferior experimental design, or poor data analysis. There has been a tremendous disconnect between the conviction of athletes that these drugs are effective and the conviction of scientists that they aren’t. In part, this disconnect results from the completely different dose regimens used by scientists to document the correction of deficiency states and by athletes striving to optimize athletic performance. Recently, careful scientific study of suprapharmacologic doses in clinical settings – including aging, human immunodeficiency virus, and other disease states – supports the efficacy of these regimens. However, the mechanism by which these doses act remains unclear.

“Anabolism” is defined as any state in which nitrogen is differentially retained in lean body mass, either through stimulation of protein synthesis and/or decreased breakdown of protein anywhere in the body. Testosterone, the main gonadal steroid in males, has marked anabolic effects in addition to its effects on reproduction that are easily observed in developing boys and when hypogonadal men receive testosterone as replacement therapy. However, its efficacy in normal men, as during its use in athletes or in clinical situations in which men are eugonadal, has been debated. A growing literature suggests that use of suprapharmacologic doses can, indeed, be anabolic in certain situations; however, the clear identification of these situations and the mechanism by which anabolic effects occur are unclear. Furthermore, the pharmacology of “anabolism” is in its infancy: no drugs currently available are “purely” anabolic but all possess androgenic properties as well. The present review briefly recapitulates the historic literature about the androgenic/anabolic steroids and describes literature supporting the anabolic activity of these drugs in normal people, focusing on the use of suprapharmacologic doses by athletes and clinicians to achieve anabolic effects in normal humans. We will present the emerging literature that is beginning to explore more specific mechanisms that might mediate the effects of suprapharmacologic regimens. The terms anabolic/androgenic steroids will be used throughout to reflect the combined actions of all drugs that are currently available.

I. Use of Suprapharmacologic Doses of Anabolic/Androgenic Steroids (AAS)

People have been taking testosterone to restore “vitality” since the efficacy of some hormonal component of the testes was first described by Brown-Sequard in 1889. He reported the reversal of his own aging by self-injection of a testicular extract, thereby stimulated a flurry of experimentation into the putative anti-aging effects of testicular hormones long before the identity of testosterone was confirmed. The first use to improve athletic performance occurred shortly thereafter, in 1896. A contemporary of Brown-Sequard self-administered testicular extract, then measured his finger strength. Athletes have been using purified testosterone since it was first available (see a review of this early history in Yesalis *et al.*, 2000). The modern use of anabolic steroids in athletic competition dates from the Olympic competitions during the Cold War era. Russian athletes were putatively the first to use anabolic steroids to improve athletic performance in international competitions. Although the International Olympic Committee banned use of anabolic agents in 1964, the practice spread and probably reached its pinnacle in the athletic programs in Germany during the 1970s (Yesalis *et al.*, 2000).

Medical use of testicular extract began in the late 1800s. Clinical use of supraphysiological doses of AAS in eugonadal patients for anabolic benefit started in the 1940s. High-dose AAS regimens have been used to promote muscle deposition after burns, surgery, radiation therapy, and aging-related sarcopenia (muscle wasting). Recent uses include treating wasting in human immunodeficiency virus (HIV) and contraception (Bhasin *et al.*, 1996,1997; Amory and Bremner, 2000).

II. Anabolic Steroids

All steroids that are anabolic are derivatives of testosterone and are androgenic as well as anabolic, as they stimulate growth and function of male reproductive tract. Individual drugs vary in their balance of anabolic:androgen activity but none of the currently available drugs are purely anabolic. All the anabolic steroids currently used are derivatives of testosterone or are structural modifications of testosterone that influence its pharmacokinetics, bioavailability, or balance of androgenic to anabolic activity. These include testosterone itself, all of the derivatives that are used clinically, as well as numerous plant products that at least claim to possess anabolic actions.

The testosterone derivatives available in the United States comprise several groups: 1) endogenously produced androgens or their precursors, including testosterone and androstenedione; 2) synthetic derivatives of testosterone with altered metabolic or receptor-binding characteristics; and 3) various uncharacterized plant or animal materials. Testosterone actions represent the combination of several activities. First, it binds to the androgen receptor to exert its androgenic activity. Second, it is 5α reduced in some target tissues (including the male urogenital tract, skin, liver, and sebaceous glands) to dihydrotestosterone (DHT), which also acts on the androgen receptor. Finally, it can be aromatized to estradiol and exert estrogenic activities. The latter two actions are highly undesirable in anabolic drugs, 5α reduction because it decreases the ratio of anabolic:androgenic activity and aromatization because of the feminizing side effects.

Structural and pharmacokinetic properties have been reviewed extensively (Wilson, 1988,1996) and are abstracted briefly here (see Figures 1 and 2).

1. Testosterone as an injectable form, a transdermal patch, skin cream, and a micronized oral preparation

2. 17-β esters of testosterone:testosterone cypionate, propionate, enanthate, and undecanoate. Esterification at this site renders the steroid more fat soluble and delays absorption into the circulation. All but the undecanoate must be injected. Nandrolone 17-β esters also exist.

3. 17-α derivatives (methyltestosterone, methandrostenolone, norethandrolone, fluoxymesterone, danazol, oxandrolone, stanozol). These derivatives resist metabolism in the liver, so are orally active. This modification is associated with significant hepatic toxicities.

4. Modifications of the A, B, or C rings (mesterolone, nortestosterone, methenolone, fluoxymesterone, methandrostenolone, northandrolone, danazol, nandrolone, stanozol). These modifications achieve a number of goals, including a) slow metabolism; b) enhanced affinity for the androgen receptor (19-nortestosterone); c) resistance to aromatization to estradiol (fluoxymesterone, 19 nortestosterone); and d) decreased binding of metabolites to androgen receptor (5α-reduced metabolites of 19-nortestosterone, 7α-19- nortestosterone).

Structure:activity modifications that limit either conversion to DHT and/or to estradiol partially target specific testosterone derivatives to specific activities. Agents such as fluoxymesterone and 19-nortestosterone (nandrolone) that resist aromatization lack the feminizing side effects of testosterone. 19-nortestosterone possesses another characteristic that increases its anabolic activity because its

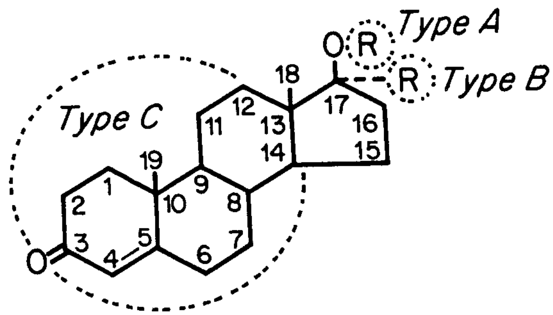

FIG. 1. Model testosterone structure. [Reprinted with permission from Wilson JD 1998 Androgen abuse by athletes. Endocr Rev 9:181–191. Copyright The Endocrine Society.]

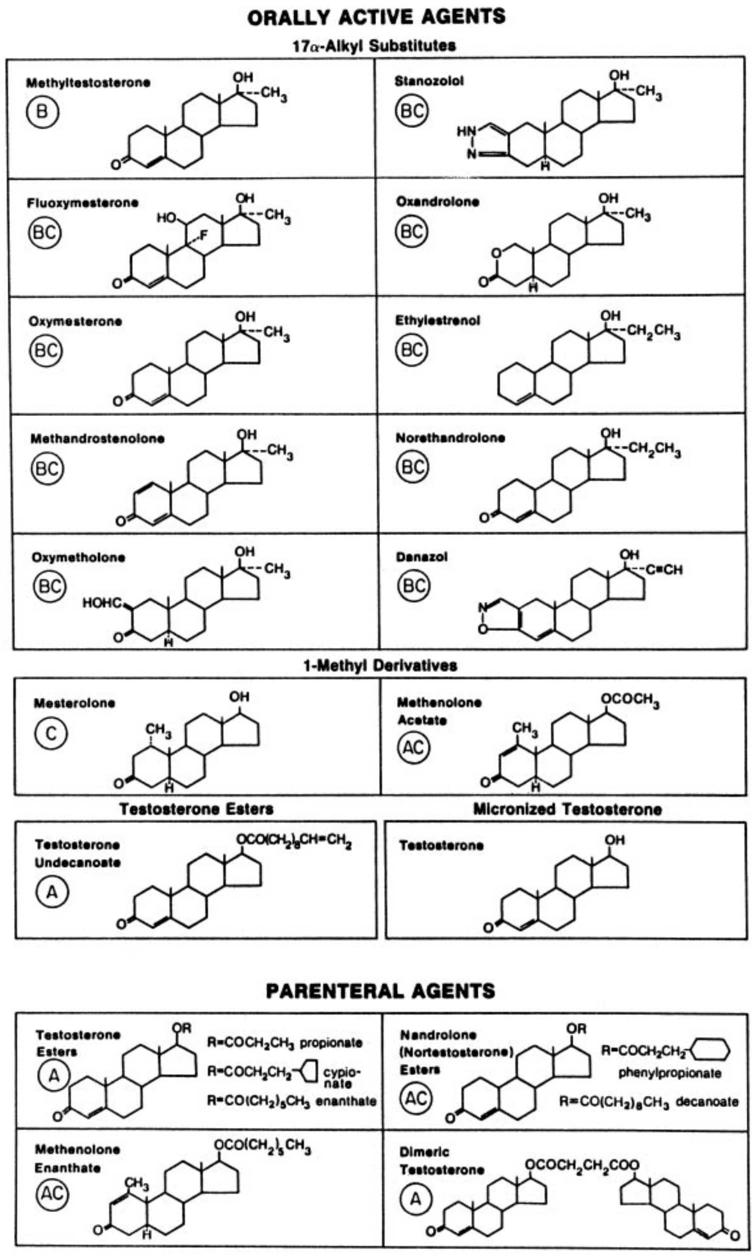

FIG. 2. Structures of several anabolic steroids. [Reprinted with permission from Wilson JD 1998 Androgen abuse by athletes. Endocr Rev 9:181–191. Copyright The Endocrine Society.]

5α-reduced metabolite has poor affinity for the androgen receptor. Similarly, alpha-methyl-19-nortestosterone is not a substrate for 5α reductase (Sundaram *et al.*, 1995).

Finally, a number of "natural products" that are purported to exhibit anabolic qualities are marketed freely in the United States due to the exemption of "natural products" from U.S. Food and Drug Administration regulation. Most of these are steroid precursors. Androstenedione and norandrostenedione are two widely marketed precursors. Marketers claim that they are converted into testosterone and nortestosterone (nandrolone). While a small percentage is, indeed, converted, the total amount produced is likely far below that which would have any anabolic activity in a eugonadal male. Finally, there are undefined mixtures with catchy names like "Horny Goat Weed" and "Testicular Extract" that are derived from both plant and animal materials and contain absolutely unknown ingredients.

All of the drugs listed above possess both anabolic and androgenic activities; none are absolutely selective. However, this ratio varies across a broad range. Table I shows the approximate anabolic:androgenic ratio of a number of clinically used AAS. The range is fairly narrow by clinical standards. All anabolic steroids are virilizing if administered for long enough at high enough doses.

These values are based on data collected in the 1950s and 1960s from bioassays of varying degrees of specificity and accuracy (see excellent historical review in Kochakian, 1976). Typically, the ability of a test drug to stimulate growth of a skeletal muscle and a reproductive target (prostate gland) was assessed. Two classic methods for establishing anabolic efficacy were the stimulation of growth of the levator ani muscle in the castrated rodent and stimulation of whole-body nitrogen retention in a castrated animal. Neither of these are ideal measures. The levator ani muscle may actually reflect androgenic efficacy of AAS because it can be viewed as part of the reproductive system. Its use as a bioassay for "anabolic" activity has been questioned. While the

TABLE I
Anabolic:Androgenic Ratio for Selected Anabolic Drugs

Anabolic/androgenic steroid	Anabolic:androgenic ratio
Testosterone, methyltestosterone	1
Methandrostenolone	2–5
Oxymetholone	9
Oxandrolone	10
Nandrolone	10
Stanozol	30

nitrogen-retention assay is better, it provides an extremely indirect measure of muscle deposition.

There has been virtually no investigation of the relative anabolic and androgenic properties of AAS since the mid-1970s and none using more modern tools to assess androgen receptor activity. One major goal of this chapter is to summarize recent developments in the molecular pharmacology of androgen receptors that are opening this area up for pharmaceutical development.

III. Androstenedione

In the summer of 1998, baseball player Mark McGwire revealed that he took regular androstenedione supplements during the season that he set a new home run record. The first scientific study of the anabolic efficacy of androstenedione appeared shortly thereafter (King *et al.*, 1999). This study showed that giving modest doses to untrained men who were started on an exercise program increased testosterone only transiently at the higher (i.e., 300-mg) dose but did not improve strength. However, it did increase plasma estradiol levels, a finding that was confirmed in a later study (Leder *et al.*, 2000). That is, this study recapitulated the large number of negative studies in the literature that documented that such combinations of training and AAS were no more effective than training alone. This study has been replicated in older men using a similar design (Broeder *et al.*, 2000). In this case, users took doses recommended by supplement manufacturers while they were engaged in resistance training. The results of both studies were similar: neither younger nor older subjects who received androstenedione showed greater increases in strength than those who received placebo, although circulating lipid profiles changed in the direction of greater cardiovascular risk (low-density to high-density lipoprotein/apolipoprotein A/apolipoprotein B) ratio. Since, at most, 10–15% of a dose is converted to testosterone, it is unlikely that regimens used by athletes will prove anabolic but the research has not been conducted. No published studies report effective anabolic activity of suprapharmacologic doses of androstenedione.

IV. Do Anabolic Steroids Increase Muscle Size and/or Strength in Eugonadal Men?

The anabolic effects of restoring normal physiologic levels of testosterone in hypogonadal men are uncontested. The rise in testosterone during puberty contributes to the increase in linear growth as well as muscle deposition at that time. Increased muscle deposition clearly results when hypogonadal men receive testosterone treatment (Kopera, 1985; Wilson, 1996; Bross *et al.*, 1999). AAS also can be anabolic in men who are hypogonadal as a result of disease such as HIV or after burns (Bhasin *et al.*, 1996,1999).

The anabolic effects of testosterone derivatives in women athletes are similarly explicable, as circulating testosterone levels of women are typically about 10% of those observed in men (Wilson, 1996). Therefore, raising female testosterone levels to those comparable to males provides supraphysiologic levels. Although there are very few published studies of muscle size and strength after AAS use in women, one report found elevations up to 30-fold of normal levels in women who were self-administering AAS (Malarkey *et al.*, 1991). There are virtually no controlled studies of AAS effects on women for obvious ethical reasons but dramatic evidence of these effects derives from the recently released results of the East German sports program of the 1970s and 1980s (Franke and Berendonk, 1997). Figure 3 shows shotput performance of a female German athlete, with the bars below indicating the periods of AAS administration. Unfortunately, women receiving AAS inevitably experience the androgenization associated with these drugs.

The benefit of anabolic steroid use for eugonadal men is far more controversial.

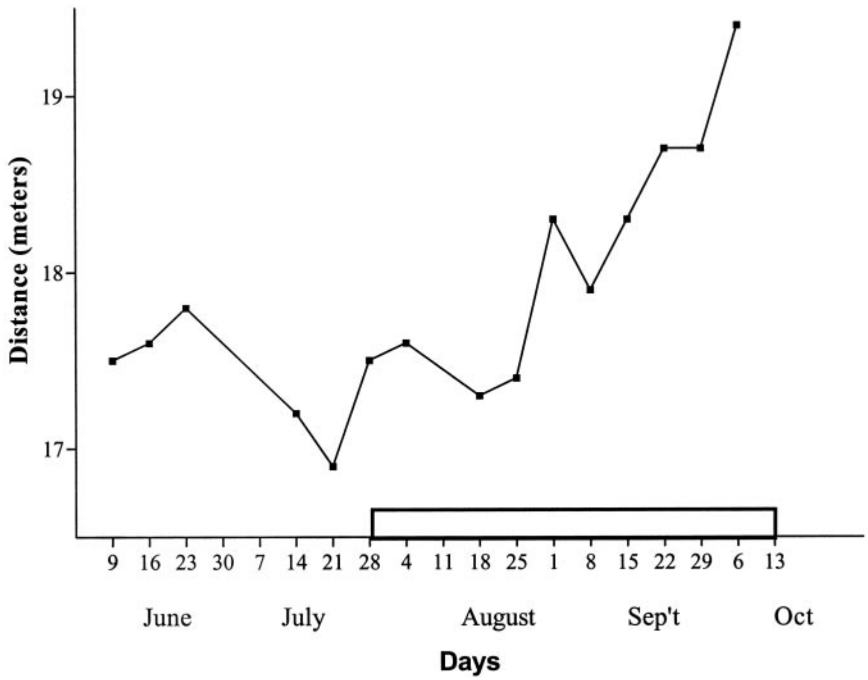

FIG. 3. Shot-put performance of woman athlete from East Germany. [Redrawn from Franke WW, Berendonk B 1997 Hormonal doping and androgenization of athletes: a secret program of the German Democratic Republic government. Clin Chem 43:1262–1279.]

For decades, scientists argued that anabolic steroids do not increase muscle mass or strength in normal men. This was based first on clinical experience that suggested that the nitrogen-retaining effects of testosterone treatment to normal men were modest and transient (Wilson, 1996). The controversy between those who state that anabolic steroids do not increase muscle mass or strength and those who believe in their effectiveness derives in part from which body of research is cited. Many critics properly cite many negative studies in which addition of testosterone or another AAS to a training regimen failed to improve performance (see reviews in Wilson, 1988; Elashoff *et al.*, 1991; O'Connor and Cicero, 1993; Friedl, 2000). They also critique the poor study design in studies conducted in athletes, including lack of placebo control, nonblinded study conditions, reliance on case studies or small study populations, lack of standardization of dose and training regimen, and the impact that expectation of benefit had on results.

These differences in study design might well play an important part in the different findings. First, nonfit people who are started on a training regimen generally experience such substantial benefit from the training regimen alone that it is difficult to show an additive benefit of AAS. The use of physiologic doses of AAS contributed to this problem. Little benefit of increasing testosterone within the physiologic range has been demonstrated in such studies. Furthermore, the dependent measure chosen to assess muscle strength is critical. Testosterone increases upper body mass differentially, so performance in tasks like weightlifting should improve more than lower-body tasks or tasks in which aerobic capacity rather than strength are assessed. As expected, the task in which increases have been reported most reliably are in the bench press (Friedl, 2000). Finally, the degree of improvement expected in such studies is generally small. Changes in performance of 1–5% are rarely statistically or clinically significant but they represent the margin of victory for elite athletes. Therefore, scientists, clinicians, and athletes all might interpret data from the same study quite differently.

Controversies about anabolic effects of AAS in animals have been similar but less intense. The same factors have entered into the outcome: gender of animals, conducting the study in trained vs. sedentary animals, dose regimen, and duration of exposure. AAS do effectively increase muscle size, protein content, and contractility in both male and female rats (Exner *et al.*, 1973; Menschikowski *et al.*, 1988; Lewis *et al.*, 1999), although negative findings have been reported (Bates *et al.*, 1987). Efficacy of AAS in trained animals has been established (Lubek *et al.*, 1984; Elashoff *et al.*, 1991; Lewis *et al.*, 1999), although different muscle beds respond differentially and slow twitch muscles improve more than fast twitch (Sachs and Leipheimer, 1988; Lewis *et al.*, 1999; Joumaa and Leoty, 2001).

V. Challenging the Conventional Wisdom: AAS Can Increase Muscle Size and Strength in Normal Men

Studies providing suprapharmacologic doses, using maximally trained athletes and testing performance in tasks like weightlifting, are mainly likely to show an effect of AAS. A recent study showing clear, statistically significant increases in muscle mass and strength after AAS administration in a proper placebo-controlled, blinded study may help put these controversies to rest. This complemented previous studies from the same laboratory demonstrating benefit in hypogonadal, HIV-infected men using the same strategy (Bhasin *et al.*, 1996,1999,2001; Strawford *et al.*, 1999).

Biochemical and anatomical studies show that AAS do significantly influence muscle morphology and biochemistry in humans. Body weight reliably increases after AAS use and part of the increase is in lean body mass, although part also reflects retention of water (see recent review in Friedl, 2000). Muscle biopsies in weightlifters reported that both the number of muscle fibers and average fiber size in the trapezius muscle were greater in AAS users than nonusers (Doumit *et al.*, 1996; Kadi *et al.*, 1999a). Controlled studies show that both the number of muscle fibers and the size of individual fibers increase with AAS treatment in animal models (Joubert and Tobin, 1989). Both of these processes depend upon activation of satellite cells within the muscle. Satellite cells contain androgen receptors (Doumit *et al.*, 1996). AAS action within these cells to stimulate proliferation may represent an important mechanism of AAS action. The specific genes that are regulated by androgens in the muscle are unknown. Muscle biopsies in AAS-using powerlifters, in comparison to drug-free powerlifters, showed increased expression of embryonic forms of myosin and the Leu-19 antigen that is expressed in developing myotubes and newly formed myonuclei. This finding supports the hypothesis that AAS trigger both hypertrophy and hyperplasia but does not elucidate the specific genes that are activated (Kadi *et al.*, 1999a,b,2000).

Increases in strength can also result not from hypertrophy or hyperplasia but from increased expression of specific elements of the contractile apparatus. Again, this has been little studied. However, a recent study (Joumaa and Leoty, 2001) began to address this phenomenon by evaluating potassium and caffeine-induced contractures. Both the magnitude of potassium-induced contractures and the rate of recovery were greater in slow-twitch muscles of animals that received training and nandrolone. The authors speculated that these results suggested changes in both the activation mechanism and recovery mechanisms that sequestrate calcium in the sarcoplasmic reticulum. Enhanced caffeine contractures could reflect enhanced calcium release from the sarcoplasmic reticulum or changes in the calcium sensitivity of the contractile proteins.

VI. Mechanism of Anabolic Effect in Eugonadal Men

A. ROLE OF SUPRAPHARMACOLOGIC DOSES

The mechanism by which AAS increase muscle size and strength is surprisingly confusing. Androgen receptors clearly mediate the increase in muscle size and protein synthesis in hypogonadal men and during puberty. In these situations, androgen increases net nitrogen balance, increases lean body mass, and increases the rate of muscle protein synthesis (see review by Wilson, 1996). However, it often is asserted that comparable effects are not observed in men with normal gonadal function because androgen receptors are saturated at physiologic levels of testosterone. If androgen effects are mediated by androgen receptors, which are saturated at physiologic levels of testosterone, then no additional benefit should result from providing more androgen.

Steroid regimens favored by athletes differ markedly from those used clinically to provide replacement for hypogonadal men. Athletes use suprapharmacologic doses and typically “stack” multiple drugs at total androgen doses that range from 10–100-fold above normal levels (Wilson, 1988). Typically, they take androgens in cycles of weeks, with drug holidays interspersed of weeks or months. Many athletes use “stacking” regimens that involve taking multiple agents simultaneously, and/or a pyramiding dose regimen in which doses are started low, increased, then tapered back down.

A small but expanding literature suggests that suprapharmacologic doses are effective in eugonadal men. The active hormone is probably testosterone, since 5α reductase is not present in muscle (Wilson and Gloyna, 1970). Two older studies (Griggs *et al.*, 1989; Forbes *et al.*, 1992) have been supplemented by several recent findings demonstrating increased lean body mass, muscle protein synthesis, and/or positive nitrogen balance in normal men after high doses of AAS (Bhasin *et al.*, 1996; Ferrando *et al.*, 1998; Sheffield-Moore *et al.*, 1999; Strawford *et al.*, 1999; see also review in Sheffield-Moore, 2000). The most important recent finding is the dose-response study showing that androgenic effects of testosterone saturate at fairly low doses, in contrast to measurable anabolic effects, which require considerably higher doses (Bhasin *et al.*, 1999).

B. ANDROGEN RECEPTOR IN AAS: EFFECTS ON EUGONADAL MEN

The finding that muscle hypertrophy associated with exercise is blocked by androgen antagonists (Inoue *et al.*, 1994) supports a primary role for androgen receptors in exercise-induced muscle hypertrophy. One androgen receptor has been cloned (see review by Lamb *et al.*, 2001) and while its expression varies quantitatively in muscle and reproductive tissues (Sar *et al.*, 1990; Kimura *et al.*, 1993), it is likely that this receptor mediates AAS effects in the muscle. The one study comparing the binding of a range of AAS to skeletal muscle and prostate reported, as expected, that little tissue specificity in binding affinity was observed across a broad range in binding affinities (Saartok *et al.*, 1984). Androgen receptors are present in skeletal muscle of every mammalian species (Sar *et al.*, 1990; Takeda *et al.*, 1990). Levels of expression differ from muscle bed to muscle bed in a manner consistent with reported AAS effects on muscle strength in different tasks. For example, human muscle beds differ from each other, with expression higher in the muscles of the neck and chest girdle, in comparison to the limbs (Kadi *et al.*, 2000).

Recent studies in multiple species show that androgen receptor can be upregulated by exposure to AAS (Bricout *et al.*, 1994; Doumit *et al.*, 1996; Sheffield-Moore *et al.*, 1999; Kadi *et al.*, 2000). The induction reported in humans (Sheffield-Moore *et al.*, 1999) suggests that suprapharmacologic concentrations might be effective because they increase the population of androgen receptors upon which they can act. These findings suggest at least one potential mechanism by which high doses could elicit different effects than physiologic doses.

In summary, two aspects of androgen receptor expression can influence the magnitude of anabolic effects: variations from muscle bed to muscle bed in androgen receptor expression and induction of androgen receptor expression after treatment with AAS. These are shown schematically in Figure 4.

Recent insights into the organization of the steroid hormone receptor:DNA complex suggest an alternative explanation for the varying anabolic:androgenic ratio of AAS. Steroid hormone receptors form a “tripartite” complex between ligand, receptor, and effector that can have varying actions (Katzenellenbogen *et al.*, 1996). When steroid hormones or their analogues bind to their receptor, they form a complex that binds to DNA. However, the receptor:DNA complex also binds a group of adaptor proteins that influence the transcriptional consequences of receptor binding to DNA. These proteins function as coactivators or co-repressors to enhance or prevent activation of transcription by the receptor (Torchia *et al.*, 1998). Each drug that binds steroid hormone receptor induces a particular “shape” in the drug:receptor complex that permits a unique pattern of adapter protein association. The adapter proteins that associate influence the consequence of drug:receptor binding on transcription (Darimont *et al.*, 1998). Selectivity can derive from the drug, the receptor, or the pattern of adaptor protein expression. This model has been exploited successfully in the development of tissue-selective estrogenic compounds. Different estrogenic compounds have specific actions, depending upon the coactivator and/or co-repressor environment (see McDonnell *et al.*, this volume).

A recent commentary (Negro-Vilar, 1999) suggests that a similar approach could be considered for androgens. Up to six different coactivators that are relatively specific for the androgen receptor have been described in the literature (Yeh and Chang, 1996; Fujimoto *et al.*, 1999; Kang *et al.*, 1999; Muller *et al.*,

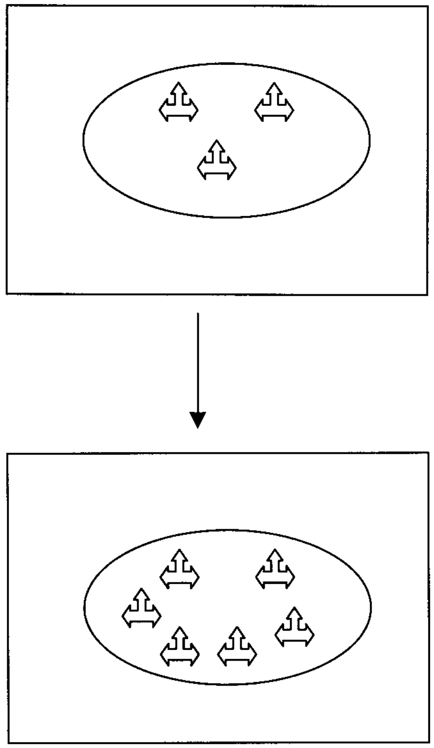

FIG. 4. Model cell containing nucleus with few (top) or more (bottom) androgen receptors. Top represents head and neck muscle relative to leg or normal individual compared to AAS-treated individual.

2000). Although tissue distribution is incompletely described, all are expressed in testis and prostate with widely varying levels of expression in other androgen target tissues. One, FHL2, is expressed highly in heart, slightly in prostate, but not elsewhere (Muller *et al.*, 2000). This coactivator is the first described that is expressed more highly in a nonreproductive tissue than in reproductive tissues. Its existence suggests that tissue-specific distribution of coactivators could theoretically contribute to the ability of different AAS agonists to vary in their ratio of actions in different tissues due to the different tissue distribution of coactivators or co-repressors. Information from a different source supports the possibility that different agonists do induce different conformations of the drug:receptor complex. An NH2-terminal and carboxyl-terminal interaction of the androgen receptor occurs in the presence of agonist binding (Langley *et al.*, 1995). In a co-transfection system, this interaction parallels agonist activity to a degree but weak agonists like medroxyprogesterone possess agonist activity in the absence of this interaction (Kemppainen *et al.*, 1999). However, the study of androgen receptor interactions of this type is in its infancy. It suggests that nonselective steroids like testosterone might occupy the androgen receptor in a way that produces a receptor conformation that permits binding of both general and tissue-selective co-activators (Figure 5). Model drugs with selective actions would results in a ligand:receptor conformation that permitted association only of one set of tissue-selective ligands (Figure 6).

C. ANTICATABOLIC EFFECTS OF ANDROGENS

There is also evidence to support a role for anticatabolic mechanisms in the anabolic effects of suprapharmacologic AAS regimens. A recent case report of two patients with a point mutation in the androgen receptor that rendered it inactive showed that a suprapharmacologic steroid regimen was anabolic in both individuals (Tincello *et al.*, 1997). Evidence from animal models also supports this possibility. These begin with binding studies that show that androgens can bind, albeit at low affinity, to glucocorticoid receptors (Danheive and Rousseau, 1986,1988). Such low-affinity binding would not be effective, unless extremely

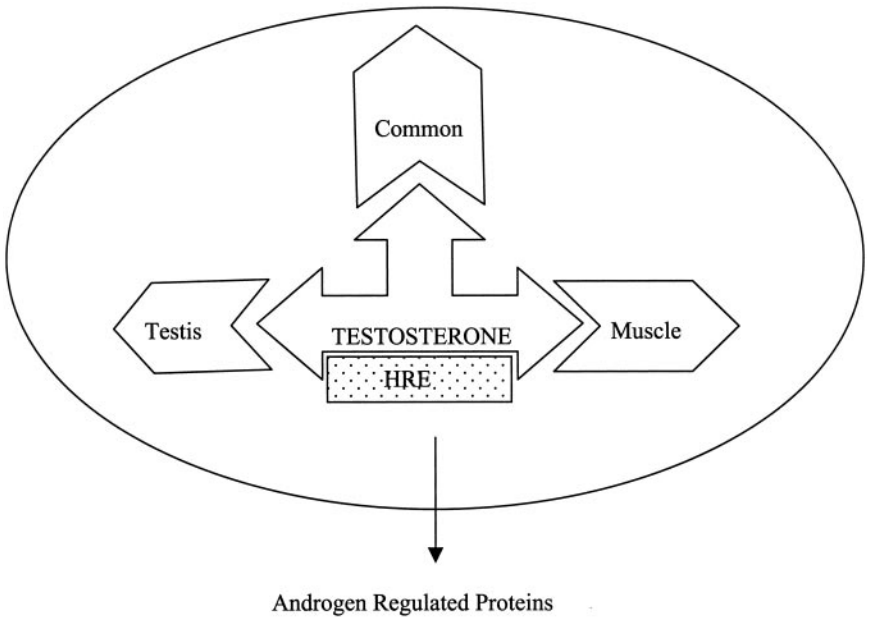

FIG. 5. Model of testosterone activation of androgen receptor (showing just one of the two ligand:receptor dimers that bind to DNA and activate transcription). HRE = hormone response element.

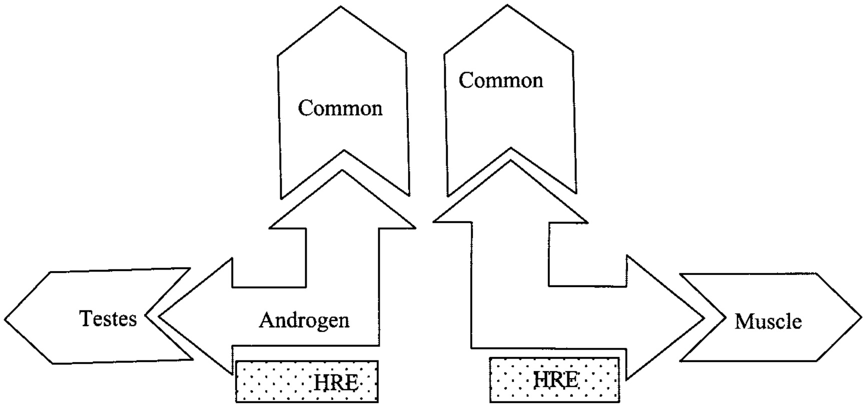

FIG. 6. Hypothetical ligand-occupied androgen receptor conformations that would allow an agonist to recruit coactivators in a tissue-specific way.

high doses of AAS were present. More directly, testosterone can block glucocorticoid-mediated induction of tyrosine amino transferase in liver just like the glucocorticoid antagonist RU486 (Danhaive and Rousseau 1986,1988). However, androgen blockade of glucocorticoid-induced muscle wasting is not observed consistently (see review by Hickson *et al.*, 1990). Furthermore, in healthy young men as well as in burn patients, the anabolic steroid oxandrolone has been shown to increase net protein synthesis without slowing protein degradation (Sheffield-Moore *et al.*, 1999; Hart *et al.*, 2001). Therefore, the specific contribution of glucocorticoid antagonism in AAS-induced anabolic effects has not been demonstrated unequivocally.

D. COMPLEMENTARY EFFECTS ON GROWTH HORMONE SECRETION AND INSULIN-LIKE GROWTH FACTOR-1 PRODUCTION

The growth hormone (GH)-insulin-like growth factor-1 (IGF-1) axis is thought to contribute to the anabolic effects of testosterone, both through androgen-induced stimulation of GH secretion and direct stimulation of hepatic production of IGF-1 (Rosenfeld *et al.*, 1994; Veldhuis and Iranmanesh, 1996). IGF-1 can stimulate skeletal muscle formation (Florini *et al.*, 1991). Increases in IGF mRNA have been reported in rats following nandrolone administration and increases in both IGF mRNA and circulating IGF-1 occur in men after testosterone treatment (Urban *et al.*, 1995; Gayan-Ramirez *et al.*, 2000) and decreases in mRNA occur when gonadal function is suppressed (Mauras *et al.*, 1998). However, none of these studies measured IGF-1 directly or established the relationship between IGF-1 and anabolic effects of the drugs.

E. COMPLEMENTARY EFFECTS OF TRAINING AND AAS

One of the challenges involved in understanding the effects of AAS in normal athletes is that many of the endpoints (e.g., muscle size, strength) are enhanced by training. Most studies of AAS action involve administration of AAS to sedentary animals, which presents a clear picture of what isolated AAS administration can achieve. Furthermore, comparing the benefits of beginning an exercise regimen and/or AAS in an unfit person provides a model for potential treatment of patient populations such as patients with HIV or the elderly. It does not replicate the environment in which AAS are most often used, which is in a highly trained athlete who is adding AAS to a rigorous exercise regimen. Clearly, exercise increases muscle mass on its own. The prospective, placebo-controlled testosterone trial in eugonadal men by Bhasin and colleagues (1996) that compared placebo, testosterone, exercise, or exercise plus testosterone showed clearly that effects of testosterone and resistance exercise were additive. Another recent study suggests a possible mechanism by which AAS use and exercise might complement each other. Resistance exercise itself increases androgen receptor mRNA and/or binding in both rodent and human muscle (Deschenes *et al.*, 1994; Bamman *et al.*, 2001). If androgen receptor number is induced in muscle by exercise, then more binding sites become available.

F. ROLE OF THE CENTRAL NERVOUS SYSTEM IN AAS EFFECTS ON STRENGTH

An increased sense of energy and wellbeing is one of the earliest and most frequently documented effects in hypogonadal men. It has been suggested that effects within the central nervous system (CNS) contribute to AAS effects on strength because AAS users feel more energetic and therefore train harder. Case reports, cross-sectional studies, and prospective, longitudinal studies show that AAS use by athletes can be accompanied by increased feelings of energy, aggressiveness, and elevated mood (Bahrke and Yesalis, 1996; Rubinow and Schmidt, 1996; Pope *et al.*, 2000). Effects of AAS typically focus on negative reports of psychotic symptoms and criminal aggressive behavior (Pope *et al.*, 1988,2000; Uzych, 1992; Porcerelli and Sandler, 1998). However, two studies of high-dose androgen administration to normal volunteers reported increases in euphoria, energy, and sexual arousal, as well as several negative mood characteristics, including irritability, mood swings, violent feelings, and hostility (Hannan *et al.*, 1991; Su *et al.*, 1993). However, administration of supraphysiologic levels of testosterone did not change aggression as assessed with the Multi-Dimensional Anger Inventory in normal, eugonadal men (Tricker *et al.*, 1996). These few laboratory studies do not provide definitive answers to this question because they utilize controlled dosing of testosterone (although in the supraphysiologic range), employ a variety of methods for measuring aggression/

hostility, and use as subjects eugonadal men in laboratory settings rather than athletes in highly competitive settings who are self-administering even-higher doses of steroids. However, the frequency of case reports of extreme behaviors and positive findings in controlled studies suggest that AAS might influence strength through effects on behavior.

The mechanism by which the psychological effects of androgens occur is unknown. A study of cerebrospinal fluid (CSF) monoamine levels in a controlled study of high-dose methyltestosterone administration reported that levels of the serotonin metabolite 5HIAA were higher and levels of the norepinephrine metabolite MHPG were lower after methyltestosterone treatment. 5HIAA levels correlated negatively in subjects who experienced more negative mood symptoms (e.g., irritability, hostility) and higher 5HIAA in subjects who experienced increased mood symptoms such as euphoria (Daly *et al.*, 2001). The latter findings are consistent with a broad literature supporting an association between low serotonin and aggression/irritability/hostility (Lucki, 1998; Oquendo and Mann, 2000). Another study showed increases in aggression that correlated with changes in CSF dopamine metabolites (Hannan *et al.*, 1991).

Testosterone influences brain function by three mechanisms. It contributes to the differentiation of brain areas that regulate regulation of reproductive hormone secretion, sexual behavior, as well nonreproductive behaviors, including aggression (reviewed by Rubinow and Schmidt, 1996). While these organizational effects establish the anatomical basis for sex-specific behavior patterns, they do not contribute to the acute effects of AAS. Androgens also influence many neural functions through both classical genomic effects and rapid membrane effects. Androgen receptors are distributed (Simerly *et al.*, 1990; Pelletier, 2000) and likely have similar distributions in humans. AAS administration – at least in animal models – can increase androgen receptor number in some brain areas, just as it does in muscle (Lynch and Story, 2000). Effects on many neurotransmitter-specific proteins, including serotonin receptors, choline acetyltransferase, the rate-limiting synthetic enzyme for acetylcholine, and monoamine oxidase have been described (see review in Rubinow and Schmidt, 1996). These likely reflect changes in transcriptional activity but effects of suprapharmacologic doses are virtually unexplored.

Rapid membrane effects also may contribute to behavioral effects of AAS. Suprapharmacologic doses of AAS influence GABA receptor function acutely, over a timeframe that likely reflects rapid membrane rather than genomic effects. In some brain areas and model systems, AAS decrease GABA receptor function, while in others it increases it (Masonis and McCarthy, 1996; Jorge-Rivera *et al.*, 2000). Rapid changes in GABA function theoretically could contribute to disinhibition of behavior and changes in arousal like those reported in AAS users. A single recent report (Schlussman *et al.*, 2000) showed nandrolone caused increases in corticotropin (ACTH) and corticosterone secretion acutely as well as protracted effects that were the reverse 24 hours later. This finding indicates that AAS influences at least one neuronal system related to stress and arousal exhibits through what may be both rapid and genomic effects.

Unfortunately, the question remains: do the behavioral effects of AAS influence training intensity and, therefore, muscle strength? Furthermore, although speculations abound that AAS improve neuromuscular function, this hypothesis has not been tested either.

The issue of AAS "dependence" reflects another widely publicized notion based on a small amount of data. Although not directly related to anabolic effects of AAS, a brief discussion is provided because this issue features prominently in discussion of AAS effects on behavior. Several studies report incidence of steroid "dependence" as reflected by psychological symptoms, including depressed mood, fatigue, anorexia, insomnia, restlessness, muscle and joint pain, depression, and desire to take more AAS when athletes stop using (Uzych, 1992; Bahrke and Yesalis, 1996). These reports – and the public perception that AAS use represented a public health crisis – led to the labeling of AAS as "addictive" drugs that were then scheduled by the Drug Enforcement Agency.

There are no clear data supporting the "addictiveness" of AAS use. This may reflect a lack of information or the fact that these drugs are not "addictive" in a neurobiologic sense. "Addictive drugs" must 1) be self-administered by humans and animals, 2) produce positive subjective effects, and 3) produce tolerance and dependence, manifested as a withdrawal syndrome when use stops. Other addictive drugs elicit positive subjective effects by activating the "reward" system in the brain, adaptation of which is thought to produce the gradual dysregulation of drug use (Wise, 1998). In a classical sense, anabolic steroids do not activate the reward system. They are not self-administered by animals and people cannot discriminate an injection of testosterone from placebo (see review in Lukas, 1996). It is impossible to conduct double-blind, placebo-controlled studies of long-term testosterone treatment on mood because users can usually recognize the active drug from the side effects. However, few AAS users fulfill psychiatric criteria for drug dependence (Lukas, 1996).

Nevertheless, some AAS users report positive feelings when they are taking drug and changes in mood when they stop (Su *et al.*, 1993; Lukas 1996). How does one reconcile the clinical reports with the laboratory studies? Genomic effects of AAS are delayed rather than immediate, so they would not be detected in any of the standard models of drug taking. It is possible that AAS do affect reward systems in the brain but in a delayed manner, as would be expected from a gonadal steroid, and so these effects have not been detected. Occasional reports of AAS effects on aspects of dopaminergic transmission, including upregulation of D1 receptors and increases in dopamine turnover, suggest that further exploration of this possibility is warranted (Thiblin *et al.*, 1999; Kindlundh *et al.*, 2001).

VI. Other Consequences of Suprapharmacologic AAS Regimens

Androgen receptors are distributed throughout the body. Androgens affect behavior, cardiovascular function, reproduction, and other endocrine functions. Since anabolic actions are not easily dissociated pharmacologically from the other actions of testosterone derivatives, anabolic steroid use by athletes and patients inevitably is accompanied by unwanted side effects that result from the many actions of androgens in the body. During a typical high-dose paradigm, additional AAS effects occur, including 1) feedback inhibition of reproductive function, including decreased production of testosterone and sperm; 2) acne, due to stimulation of sebaceous glands in the skin; and 3) male-pattern hair distribution (Wilson, 1988). In addition, multiple effects on the cardiovascular system occur, including increased blood pressure, change in the ratio of blood lipids (decrease in HDL:LDL ratio), increased blood clotting, increased production of red blood cells, and left ventricular hypertrophy and subsequent decreased left ventricular function (Sullivan *et al.*, 1998). Extended discussion of potential mechanisms for these effects is beyond the scope of this review. However, the regular occurrence of these additional effects contradicts the common argument that AAS cannot be anabolic because androgen receptors are completely saturated at physiologic levels of androgen. The impact of these other systemic effects on the anabolic effects of AAS is unknown. Although increased production of red blood cells should theoretically improve oxygen-carrying capacity of the blood, and so the ability to do sustained work, these effects have not been documented in eugonadal men.

One final note about the use of AAS for their anabolic properties: when used in women, they produce a consistent pattern of virilizing side effects that are predictable, severe, and, in some cases, irreversible. The first published study (Strauss *et al.*, 1985) reported physical changes in the majority of a small group of AAS-using female athletes, including deepening of the voice, clitoral hypertrophy, menstrual irregularities, decreased body fat, and increased facial hair. Behavioral changes included increased libido, aggressiveness, and appetite. About half reported additional changes, including acne, breast size, and body hair distribution. A more recent study (Malarkey *et al.*, 1991) reported a 39% fall in HDL lipoprotein. All of these effects were reported more recently (Gruber and Pope, 2000) in a study involving a larger group. Some of these effects (e.g., deepening of the voice, clitoral hypertrophy) represent irreversible virilization, while others (e.g., reproductive effects, acne, blood lipids) are reversible. The consistency of these findings argues strongly that clinical trials for AAS use for anabolic purposes, as in burn patients, be conducted with great caution because there is no clinically available AAS that lacks androgenizing effects in women.

VII. Conclusions

Studies in AAS-using human subjects as well as experimental model systems have refuted the decades-old assertion that suprapharmacologic dose regimens of AAS are not anabolic in normal men or are only anabolic due to the impact of their CNS effects on motivation to train. The physiopathology of suprapharmacologic doses of AAS is clearly demonstrated and predicted by the beneficial effects on the same systems when AAS are used in hypogonadal men. However, there has been surprisingly little work on the mechanism by which these suprapharmacologic doses exert their actions or on pharmacologic strategies to distinguish beneficial (anabolic) effects from pathologic side effects on brain and heart. The recent demonstration of clinical benefits of suprapharmacologic regimens (Bhasin *et al.*, 1996,1997,1999,2001) suggests that such developments could be clinically beneficial. A recent review proposed the potential value of exploring the possible tissue specificity of protein regulators of androgen receptor function, comparable to those which have been exploited so successfully in the development of selective estrogen receptor modulators (Negro-Vilar, 1999).

REFERENCES

Amory JK, Bremner WJ 2000 Newer agents for hormonal contraception in the male. Trends Endocrinol Metab 11:61–66

Bahrke MS, Yesalis CE 1996 Psychological and behavioral effects of endogenous testosterone and anabolic-androgenic steroids. Sports Med 22:367–390

Bamman MM, Shipp JR, Jiang J, Gower BA, Hunter GR, Goodman A, McLafferty CL, Urban RJ 2001 Mechanical load increases muscle IGF-1 and androgen receptor mRNA concentrations in humans. Am J Physiol 280:E383–E390

Bates PCL, Chew LF, Millward DJ 1987 Effects of the anabolic steroid stanozol on growth and protein metabolism in the rat. J Endocrinol 114:373–381

Bhasin SW, Storer TW, Berman N, Callegari C, Clevenger B, Phillips J, Bunnell TJ, Rricker R, Shirazi A, Casaburi R 1996 The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 335:1–7

Bhasin S, Storer TW, Berman N, Yarashski K, Cleveneger B, Casaburi R 1997 A replacement dose of testosterone increases fat-free mass and muscle size in hypogonadal men. J Clin Endocrinol Metab 82:407–413

Bhasin S, Storer TW, Javanbakht M, Berman N, Yarasheski KE, Phillips J, Dike M, Sinha-Hikim I, Shen R, Hays RD, Beall G 1999 Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. J Am Med Assn 283:763–770

Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N, Yarasheski KE, Magliano L, Dzekov C, Dzekov J, Bross R, Phillips J, Sinha-Hikim I, Sher R, Storer TW 2002 Testosterone dose response relationship in healthy young men. Am J Physiol, in press

Bricout V, Germain P, Serrurier B, Guezennec C 1994 Changes in testosterone muscle receptors: effects of an androgen treatment on physically-trained rat. Cell Mol Biol 40:291–294

Broeder CE, Quindry J, Brittingham K, Panton L, Thomson J, Appakondu S, Breul K, Byrd R, Douglas J, Earnest C, Mitchell C, Olson M, Roy T, Yarlagadda C 2000 The Andro project: physiological and hormonal influences of androstenedione supplementation in men 35 to 65 years old participating in a high-intensity resistance training program. Arch Intern Med 160:3093–3104

Bross R, Javanbakht M, Bhasin S 1999 Anabolic interventions for aging-associated sarcopenia. J Clin Endocrinol Metab 84:3420–3430

Daly RC, Su TP, Schmidt PJ, Pickar D, Murphy DL, Rubinow DR 2001 Cerebrospinal fluid and behavioral changes after methyltestosterone administration: preliminary findings. Arch Gen Psych 58:172–177

Danhaive PA, Rousseau GG 1986 Binding of glucocorticoid antagonists to androgen and glucocorticoid hormone receptors in rat skeletal muscle. J Steroid Biochem 24:481–487

Danhaive PA, Rousseau GG 1988 Evidence for sex-dependent anabolic response to androgenic steroids mediated by muscle glucocorticoid receptors in the rat. J Steroid Biochem 29:575–581

Darimont BD, Wagner RL, Apriletti JW, Stallcup MR, Kushner PJ, Baxter JD, Fletterick RJ, Yamamoto KR 1998 Structure and specificity of nuclear receptor-coactivator interactions. Genes Dev 12:3343–3356

Deschenes M, Maresh C, Armstrong L, Covault J, Kraemer W, Crivello J 1994 Endurance and resistance exercise induce muscle fiber type specific responses in androgen binding capacity. J Ster Biochem Mol Biol 50:175–179

Doumit ME, Cook DR, Merkel RA 1996 Testosterone up-regulates androgen receptors and decreases differentiation of porcine myogenic satellite cells *in vitro*. Endocrinology 137:1385–1394

Elashoff JD, Jacknow AD, Shain SG, Braunstein GD 1991 Effects of metabolic-androgenic steroids on muscular strength. Ann Intern Med 115:387–393

Exner GU, Staudte HW, Pette D 1973 Isometric training of rats: effects on fast and slow muscle and modification by an anabolic hormone (nandrolone decanoate). II. Male rats. Pfluger's Arch 345:15–22

Ferrando AA, Sheffield-Moore M, Wolf SE, Herndon DN, Wolfe RR 2000 Tetosterone normalization in severe burns ameliorates muscle catabolism. FASEB J 14(4):A797

Florini JR, Ewton DZ, Roof SL 1991 IGF-1 stimulates terminal myogenic differentiation by induction of myogenin gene expression. Mol Endocrinol 5:718–724

Forbes GB, Porta CR, Herr BE, Griggs MRC 1992 Sequence of changes in body composition induced by testosterone and reversal of changes after drug is stopped. J Am Med Assn 267:397–399

Franke WW, Berendonk B 1997 Hormonal doping and androgenization of athletes: a secret program of the German Democratic Republic government. Clin Chem 43:1262–1279

Friedl KE 2000 Effect of anabolic steroid use on body composition and physical performance. In: Yesalis CE, ed. Anabolic Steroids in Sport and Exercise. Champaign, IL: Human Kinetics; 139–174

Fujimoto N, Yeh S, Kang HY, Inui S, Chang HC, Mizokami A, Chang C 1999 Cloning and charadcterization of androgen receptor co-activator, RA55, in human prostate. J Biol Chem 274:8316–8321

Gayan-Ramirez G, Rollier H, Vanderhoydonc F, Verhoeven G, Gosselink R, Decramer M 2000 Nandrolone decanoate does not enhance training effects but increases IGF-1 mRNA in rat diaphragm. J Appl Physiol 88:26–34

Griggs RC, Kingston W, Jozefowicz RF, Herr BE, Forbest G, Halliday D 1989 Effect of testosterone on muscle mass and muscle protein synthesis. J Appl Physiol 66:498–503

Gruber AJ, Pope HG 2000 Psychiatric and medical effects of anabolic-androgenic steroid use in women. Psychother Psychosom 69:19–26

Hannan CJ, Friedl KE, Zold A, Kettler TM, Plymate SR 1991 Psychological and serum homovanillic acid changes in men administered androgenic steroids. Psychoneuroendocrinology 16:335–343

Hart DW, Wolf SE, Ramzy PI, Chinkes DL, Beauford RB, Ferrando AA, Wolfe RR, Herndon DN 2001 Anabolic effects of oxandrolone after severe burn. Ann Surg 233:556–564

Hickson RC, Czerwinski SM, Falduto MT, Young AP 1990 Glucocorticoid antagonism by exercise and androgenic-anabolic steroids. Med Sci Sports Med 22:331–340

Inoue K, Yamasaki S, Fushiki T, Okada Y, Sugimoto E 1994 Androgen receptor antagonist suppresses exercise-induced hypertrophy of skeletal muscle. Eur J Appl Physiol 69:88–91

Jorge-Rivera JC, McIntyre KL, Henderson LP 2000 Anabolic steroids induce region- and subunit-specific rapid modulation of GABA-A receptor mediated currents in the rat forebrain. J Neurophysiol 83:3299–3309

Joubert Y, Tobin C 1989 Satellite cell proliferation and increase in the number of myonuclei induced by testosterone in the levator ani muscle of the adult female rat. Dev Biol 131:550–557

Joumaa WH, Leoty C 2001 Differential effects of nandrolone decanoate in fast and slow rat skeletal muscle. Med Sci Sports Exerc 33:397–403

Kadi F, Eriksson A, Holmner S, Butler-Browne G, Thornell LE 1999a Cellular adaptation of the trapezius muscle in strength trained athletes. Histochem Cell Biol 111:189–195

Kadi F, Eriksson A, Holmner S, Thornell LE 1999b Effects of anabolic steroids on the muscle cells of strength-trained athletes. Med Sci Sports Exerc 31:1528–1534

Kadi F, Bonnerud P, Eriksson A, Thornell LE 2000 The expression of androgen receptors in human neck and limb muscles: effects of training and self-administration of androgenic-anabolic steroids. Histochem Cell Biol 113:25–29

Kang HY, Yeh S, Fujimoto N, Chang C 1999 Cloning and characterization of human prostate coactivator ARA54, a novel protein that associates with the androgen receptor. J Biol Chem 274:8570–8576

Katzenellenbogen JA, O'Malley BW, Katzenellenbogen BS 1996 Tripartite steroid hormone receptor pharmacology: interaction with multiple effector sites as a basis for the cell- and promoter-specific action of these hormones. Mol Endocrinol 10:119–131

Kemppainen JA, Langley E, Wong C, Bobseine K, Kelce WR, Wilson EM 1999 Distinguishing androgen receptor agonists and antagonists: distinct mechanisms of activation by medroxyprogesterone acetate and dihydrotestosterone. Mol Endocrinol 13:440–454

Kimura N, Mizokami MA, Oonuma T, Sasano H, Nagura H 1993 Immunocytochemical localization of androgen receptor with polyclonal antibody in paraffin-embedded human tissues. J Histochem Cytochem 41:671–678

Kindlundh AM, Lindblom J, Bergstromg L, Wikberg JE, Nyberg F 2001 The anabolic-androgenic steroid nandrolone decanoate affects the density of dopamine receptors in the male rat brain. Eur J Neurosci 13:291–296

King DS, Sharp RL, Vukovich MD 1999 Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men: a randomized controlled trial. J Am Med Assn 281:2020–2028

Kochakian CD 1976 Anabolic-Androgenic Steroids. New York: Springer-Verlag

Kopera H 1985 The history of anabolic steroids and a review of clinical experience with anabolic steroids. Acta Endocrinol (suppl)271:11–18

Lamb DJ, Weigel NL, Marcelli M 2001 Androgen receptors and their biology. Vitam Horm 62:199–230

Langley E, Zhou ZX, Wilson EM 1995 Evidence for an anti-parallel orientation of the ligand-activated human androgen receptor dimmer. J Biol Chem 270:29983–29990

Leder BZ, Longcope C, Catlin DH, Ahrens B, Shoenfeld DA, Finkelstein JS 2000 Oral androstenedione administration and serum testosterone concentrations in young men. Clin Invest J Am Med Assn 283:779–782

Lewis MI, Fournier M, Yeh AY, Micevych PE, Sieck PM 1999 Alterations in diaphragm contractility after nandrolone administration: an analysis of potential mechanisms. J Appl Physiol 86:985–992

Lubek BM 1984 Contractile responses of rat lateral gastrocnemius and soleus to dianabol (17 beta-hydroxy-17-methyl-1,4androstadien-3-one) and exercise. Steroids 44:485–495

Lucki I 1998 The spectrum of behaviors influenced by serotonin. Biol Psychol 44:151–162

Lukas SE 1996 CNS effects and abuse liability of anabolic-androgenic steroids. Annu Rev Pharmacol Toxicol 36:333–357

Lynch CS, Story AJ 2000 Dihydrotestosterone and estrogen regulation of rat brain androgen receptor immunoreactivity. Physiol Behav 69:445–453

Malarkey WB, Strauss RH, Leizman DJ, Liggett M, Demers LM 1991 Endocrine effects in female weight lifters who self-administer testosterone and anabolic steroids. Am J Obstet Gynecol 165:1385–1390

Masonis AE, McCarthy MP 1996 Effects of the androgenic/anabolic steroid stanozol on GABA A receptor function: GABA-stimulated ^{36}Cl(-) influx and [^{35}S] TBPS binding. J Pharmacol Exp Ther 279:186–193

Mauras N, Hayes V, Welch S, Rini A, Helgeson K, Dokler M, Veldhuis JD, Urban RJ 1998 Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity. J Clin Endocrinol Metab 83:1886–1892

McDonnell DP, Connor CE, Wijayaratne A, Chang CY, Norris JD 2002 Definition of the molecular and cellular mechanisms underlying the tissue selective agonist/antagonist activities of selective estrogen receptor modulators (SERMs). Rec Progr Horm Res 57:295–316

Menschikowski M, Jung K, Junghans P, Petzke KJ, Albrecht V 1988 The influence of a steroid hormone and physical exercise on protein metabolism in rats. Exp Clin Endocrinol 92:341–348

Muller JM, Isele U, Metzger E, Rempel A, Moser M, Pschere A, Breyer T, Holubarsch C, Buettner R, Schule R 2000 FHL2, a novel tissue-specific coactivator of the androgen receptor. EMBO J 19:359–369

Negro-Vilar A 1999 Selective androgen receptor modulators (SARMs): a novel approach to androgen therapy for the new millennium. J Clin Endocrinol Metab 84:3459–3462

O'Connor LH, Cicero TJ 1993 Anabolic steroids: misuse or abuse. In Chulkin JS, ed. Hormonally Induced Changes in Mind and Brain. New York: Academic Press; 129–156

Oquendo MA, Mann JJ 2000 The biology of impulsivity and suicidality. Psychiat Clin N Am 23:11–25

Pelletier G 2000 Localization of androgen and estrogen receptors in rat and primate tissues. Histol Histopathol 15:1261–1270

Pope HG, Katz DL 1988 Affective and psychotic symptoms associated with anabolic steroid use. Am J Psychiat 145:487–490

Pope HG, Kouri EM, Hudson JI 2000 Effects of supraphysiological doses of testosterone on mood and aggression in normal men: a randomized controlled trial. Arch Gen Psychol 57:133–140

Porcerelli JF, Sandler BA 1998 Anabolic:androgenic steroid abuse and psychopathology. Psychiat Clin N Am 21:829–832

Rosenfeld RG, Rosenbloom AL, Guevara-Aguirre J 1994 Growth hormone (GH) insensitivity due to primary GH receptor deficiency. Endocr Rev 15:369–390

Rubinow DR, Schmidt PJ 1996 Androgens, brain and behavior. Am J Psychiat 153:974–984

Saartok T, Dahlberg E, Gustafsson JA 1984 Relative binding affinity of anabolic-androgenic steroids: comparison of the binding to the androgen receptors in skeletal muscle and in prostate, as well as to sex hormone-binding globulin. Endocrinology 114:2100–2106

Sachs BD, Leipheimer RE 1988 Rapid effect of testosterone on striated muscle activity in rats. Neuroendocrinology 48:453–458

Sar M, Lubahn DB, French FS, Wilson EM 1990 Immunohistochemical localization of the androgen receptor in rat and human tissues. Endocrinology 127:3180–3186

Schlussman SD, Zhou Y, Johansson P, Kiuru A, Ho A, Nyberg F, Kreek MJ 2000 Effects of the androgenic anabolic steroid, nandrolone decanoate, on adrenocorticotropin hormone, corticosterone and proopiomelanocortin, corticotropin releasing factor (CRF) and CRF receptor1 mRNA levels in the hypothalamus, pituitary and amygdala of the rat. Neurosci Lett 284:190–194

Sheffield-Moore M 2000 Androgens and the control of skeletal muscle protein synthesis. Ann Med 32:181–186

Sheffield-Moore M, Urban RJ, Wolf SE, Jiang J, Catlin DH, Herndon DN, Wolfe RR, Ferrando AA 1999 Short-term oxandrolone administration stimulates net muscle protein synthesis in young men. J Clin Endocrinol Metab 84:2705–2711

Simerly RB, Chang C, Muaramatsu M, Swanson LW 1990 Distribution of androgen and estrogen receptor mRNA-containing cells in the rat brain: an *in situ* hybridization study. J Compar Neurol 294:76–95

Strawford A, Barbieri T, Van Loan M, Parks E, Catlin D, Barton N, Neese R, Christiansen M, King J, Hellerstein MK 1999 Resistance exercise and supraphysiologic androgen therapy in eugonadal men with HIV-related weight loss: a randomized controlled trial. J Am Med Assn 281:1282–1290

Strauss RH, Liggett MT, Lanese RR 1985 Anabolic steroid use and perceived effects in ten weight-trained women athletes. J Am Med Assn 253:2871–2873

Su TP, Pagliaro M, Schmidt PJ, Pickar D, Wolkowitz O, Rubinow DR 1993 Neuropsychiatric effects of anabolic steroids in male normal volunteers. J Am Med Assn 269:2760–2764

Sullivan ML, Martinez CM, Gennis P, Gallagher EJ 1998 The cardiac toxicity of anabolic steroids. Progr Cardiovasc Dis 41:1–15

Sundaram K, Kumar N, Monder C, Bardin CW 1995 Different patterns of metabolism determine the relative anabolic activity of 19-norandrogens. J Steroid Biochem Mol Biol 53:253–257

Takeda H, Chodak G, Mutchnik S, Nakamoto T, Chang C 1990 Immunohistochemical localization of androgen receptors with mono- and polyclonal antibodies to androgen receptor. J Endocrinol 126:17–25

Thiblin I, Finn A, Ross SB, Stenfors C 1999 Increased dopaminergic and 5-hydroxytryptaminergic activities in male rat brain following long-term treatment with anabolic androgenic steroids. Br J Pharmacol 126:1301–1306

Tincello DG, Saunders PTK, Hodgins MB, Simpson NB, Edwards CRW, Hargreave TB, Wu FCW 1997 Correlation of clinical, endocrine and molecular abnormalities with *in vivo* responses to high-dose testosterone in patients with partial androgen insensitivity syndrome. Clin Endocrinol 46:497–506

Torchia J, Glass C, Rosenfeld MG 1998 Co-activators and co-repressors in the integration of transcriptional responses. Curr Opin Cell Biol 10:373–383

Tricker R, Casaburi R, Storer TW, Clevenger B, Berman N, Shirazi A, Bhasin S 1996 The effects of supraphysiological doses of testosterone on angry behavior in healthy eugonadal men – a clinical research center study. J Clin Endocrinol Metab 81:3754–3758

Urban RJ, Bodenburg C, Gilkison C, Foxworth J, Coggan AR, Wolfe RR, Ferrando A 1995 Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. Am J Physiol 269:E820–E826

Uzych L 1992 Anabolic-androgenic steroids and psychiatric-related effects: a review. Can J Psychiat 37:23–28

Veldhuis JD, Iranmanesh A 1996 Physiological regulation of the human growth hormone (GH)-insulin-like-growth factor type I (IGF-1) axis: predominant impact of age, obesity, gonadal function and sleep. Sleep 19(10 suppl):S221–S224

Wilson JD 1988 Androgen abuse by athletes. Endocr Rev 9:181–191

Wilson JD 1996 Androgens. In Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Goodman Gilman A, eds. Goodman Gilman's Experimental Basis of Therapeutics. New York: McGraw-Hill; 1441–1457

Wilson JD, Gloyna E 1970 The intranuclear metabolism of testosterone in the accessory organs of male reproduction. Rec Progr Horm Res 26:309–336

Wise RA 1998 Drug activation of brain reward pathways. Drug Alcoh Depend 51:13–22

Yeh S, Chang C 1996 Cloning and characterization of a specific coactivator, ARA70, for the androgen receptor in human prostate cells. Proc Natl Acad Sci USA 93:5517–5521

Yesalis CE, Courson SP, Wright JE 2000 History of anabolic steroid use in sport and exercise. In: Yesalis CE, ed. Anabolic Steroids in Sport and Exercise. Champaign, IL: Human Kinetics; 51–71