J Steroid Biochem Molec Biol Vol 43, No 5, pp 469–477, 1992
Printed in Great Britain

0960-0760/92 $5 00 + 0 00

ANABOLIC STEROIDS: A REVIEW OF THEIR EFFECTS ON THE MUSCLES, OF THEIR POSSIBLE MECHANISMS OF ACTION AND OF THEIR USE IN ATHLETICS

F CELOTTI* and P NEGRI CESI
Department of Endocrinology, University of Milano, Via Balzaretti 9, 20133, Milano, Italy

Summary—Anabolic steroids are synthetic molecules developed in the hope of obtaining a complete separation of the androgenic and myotrophic (anabolic) actions of testosterone Such a goal has never been fully achieved However, some synthetic steroids present a partial dissociation between these two activities Since a single hormonal receptor apparently mediates the androgenic as well as the anabolic actions of testosterone, differences in patterns of androgen metabolization in the muscles and the sex accessory organs have been proposed as a possible cause of this phenomenon Undoubtedly, androgens are able to exert a trophic effect on skeletal and cardiac muscle fibres in subjects with low circulating levels of testosterone such as prepubertal or hypogonadal males and females, however, the widespread use of anabolic steroids in male athletes to increase their physical performances poses the question of whether these compounds are active in the presence of normal circulating levels of testosterone Most experimental animal studies indicate that anabolic steroids are ineffective in this situation Since the results of the experiments performed in humans are largely contradictory, it is still not clear whether anabolic steroids are able to improve athletic performances These and other relevant issues are reviewed

INTRODUCTION

Testosterone, the main testicular steroid hormone, exerts specific as well as trophic effects on a wide variety of central and peripheral androgen-dependent or -sensitive structures These include the sex accessory organs, the central nervous system, the anterior pituitary, the kidney, the liver, the muscles, etc Since the musculature contributes more than one third of the body mass, the myotrophic action of testosterone is specifically responsible for the retention of nitrogen, usually defined as the anabolic effect of the hormone

In adult animals testosterone exerts a trophic effect on skeletal and cardiac muscle fibres, since castration produces atrophy and testosterone administration hypertrophy of individual fibres without changing the number of myofibrils (see [1] for a review) However, rarely if ever, the trophic action of the exogenous hormone is more pronounced than that achieved by normal circulating levels of testosterone, this will be discussed later in more detail On the other hand, testosterone stimulates the mitotic activity in a myoblast culture system [2] and, when given to female rats before the 7th day of postnatal life, produces a significant increase in the number of fibres of the levator ani muscle, without affecting the cross-sectional area [3]; on the contrary, after the 7th day of life only an increase in the average cross-sectional area was observed [3] The developmental action of testosterone on this muscle is apparently a direct action of the hormone on the myofibrils, which already possess androgen receptors, and it is not mediated by the influence of testosterone on the spinal nucleus innervating these muscles, the sexual dimorphism of which is a consequence of the different number of myofibrils existing in the two sexes [4].

The response to androgens is different among the animal species and among the various muscle groups In the guinea pig, those from the shoulders, back and head show a greater sensitivity to the androgenic action than those of the chest and the hind legs [1]. Also in man, the muscles of the pectoral and shoulder region appear to possess a higher androgen sensitivity (see [5] for a review).

A particular mention should be made of the androgen-dependent, sexually dimorphic,

Proceedings of the XV Meeting of the International Study Group for Steroid Hormones, Rome, Italy, 28–30 November 1991
*To whom correspondence should be addressed

perineal muscles of the rat and of the guinea pig the levator ani, the bulbocavernosus and the ischiocavernosus which have been considered a model for testing the relative myotrophic–androgenic activity ratio of steroids since they possess a higher sensitivity to androgens than the other skeletal muscles This ratio, often called the myotrophic–androgenic index [6], has been usually evaluated in castrated immature male rats treated with different steroids as the ratio between the weight of the levator ani-bulbocavernosus complex (BCLA) and that of the ventral prostate and/or of the seminal vesicles [6–8]. However, the validity of the test has often been questioned, because the perineal muscles cannot be considered real extragenital organs [9] It will appear, in the discussion which follows, that the peculiar androgen sensitivity and sexual dimorphism of the perineal muscles is probably due to their receptorial and metabolic profile, which is intermediate between those present respectively in the skeletal muscles and in sex accessory organs

Although not well defined so far, the hypertrophic action of testosterone and other androgens on the muscle fibers is the consequence of an increase in protein synthesis [10] Boissonneault *et al* [11] have indeed described following gonadectomy in the rat, a progressive decrease of muscle weight and methionine incorporation, as well as of polyribosome translational efficiency, these effects can be reverted by the administration of testosterone propionate

Androgens also directly stimulate some biochemical parameters related to energy metabolism, like, for instance, the uptake and phosphorylation of glucose [12] and the synthesis of glycogen [13] In conclusion, there is no doubt that androgens exert a clear-cut effect on the muscles, which is apparent in females, in developing or hypogonadal animals, and appears to be mediated by the activation of androgenic receptors

ANABOLIC STEROIDS: BIOCHEMICAL STUDIES

Since the initial studies of Kochakian, which proposed the possibility to dissociate the anabolic from the androgenic effects of androgens, more than 600 molecules, the structure of which was mainly derived from that of testosterone, have been synthesized, particularly between the 50s and 60s, in the search for a compound exerting a pure anabolic action (see [6–8] for reviews) Such a compound has never been found, however, some synthetic steroids present a remarkable dissociation between the anabolic and the androgenic activities, at least on the basis of the myotrophic–androgenic index [6, 7] On the other hand, it must be underlined that all anabolic steroids, when used in adequate doses and for prolonged periods of time, lose the dissociation of these two pharmacodynamic activities, and can be used in the treatment of hypogonadism [5]

Which mechanism(s) might explain the partial dissociation of the anabolic and androgenic effects exerted by synthetic anabolic steroids?

The first question which can be asked is whether the androgenic receptors in the skeletal muscle differ from those found in classical androgen-dependent structures (e g prostate and seminal vesicles) Binding studies performed in several laboratories clearly indicate that the androgenic receptors in the skeletal or cardiac muscle possess the same binding affinity and biochemical characteristics of those present in the sex accessory organs [1, 14, 15] Moreover the binding affinities of muscle and prostate androgenic receptors for the anabolic steroids studied so far, do not show significant differences [16, 17] The identity of the two theoretical classes of receptors (anabolic vs androgenic) has been also indirectly confirmed by some *in vitro* studies [18], in which receptors isolated from the cytosol of rat prostatic glands can be easily translocated to nuclei of the cardiac muscle, where they bind to the chromatin Finally, recent immunocytochemical studies performed in rat, mouse and man with mono- and poly-clonal antibodies against the N-terminal domain of the androgen receptor, have indicated the immunological identity of the skeletal and cardiac muscle receptors with those of the prostate and of the brain [19]

However, at variance with these studies, Ruizeveld De Winter *et al* [20], utilizing different mono- and poly-clonal antibodies, always directed to the N-terminal domain of the androgen receptor, failed to identify a positive immunostaining in human skeletal muscle nuclei, while a low intensity nuclear androgenic receptor expression was found in myocardial biopsies from 2 male patients, but not in the corresponding specimens from 2 female patients It is possible that these negative findings might be due to the low level of receptors present in the muscle cells As a matter of fact, comparative binding studies performed in

the rat indicate that the number of binding sites/mg of protein are 60 times lower in the skeletal muscle than in the prostate, while in BCLA they are only 7 times less than in the prostate [14] Moreover the B_{max} values (an index of the number of binding sites) calculated for the cytosol of the human skeletal muscle are about 10-fold lower than those of normal or hyperplastic human prostate [21]

On the basis of the findings quoted above, it might be possible to conclude that the dissociation of the androgenic–anabolic properties of hormonal steroids cannot be due to the presence, in the muscles, of receptors different (or with different binding properties) from those present in the reproductive structures, it emerges, however, that the amounts of receptors present in the muscles are much lower than those found in the reproductive sex organs This finding may explain the relative low sensitivity of the skeletal muscles to androgens

The next question which can be asked is the following does the androgen metabolic pattern of the muscle explain the partial dissociation of the anabolic and androgenic effects?

It is well known that in the reproductive structures and in the brain testosterone does not act in its original molecular conformation, but it is locally transformed into active metabolites through the action of two different enzymes the 5α-reductase and the aromatase [22–24] The 5α-reductase converts testosterone into dihydrotestosterone (DHT), which can be further metabolized into 5α-androstan-3α,17β-diol (3α-diol) by a 3α-hydroxysteroid-dehydrogenase The conversion of testosterone to DHT is irreversible, while the conversion of DHT to 3α-diol is reversible in most of the tissues, with a notable exception the muscle [25] The aromatase catalyzes the irreversible transformation of testosterone into estrogenic molecules In male subjects, the 5α-reductive pathway is present in almost all the androgen-dependent structures [22–24], whereas the aromatase has been demonstrated and characterized only in the brain [23, 26], in the adipose tissue [27] and in the testes [28] Its presence in the prostate is still controversial [29, 30] The heart and skeletal muscle seem to possess a low activity of this enzymatic complex [31, 32]

Due to the multifactorial metabolic pattern described above, the androgenic signal can be amplified or modulated within the target cells through the interaction of the various testosterone metabolites with different receptors While the aromatization of androgens into estrogens produces compounds acting through the estrogenic receptor, the 5α-reduction of testosterone into DHT produces a compound possessing a binding affinity for the androgenic receptor 2 to 6 times higher than that of testosterone In this case the metabolic transformation is a mechanism of amplification of the androgenic signal, which is necessary to produce and maintain the normal development and trophism of peripheral androgen-dependent structures, as, for example, the prostate [33–35] Among the androgen-sensitive tissues, the muscle is one of the few structures in which the 5α-reductase is very low or absent Massa and Martini [36] have indeed found that, the *in vitro* formation of 5α-reduced steroids is virtually absent in the skeletal muscle and in the levator ani of the male rat The presence of a very low 5α-reductase activity in the skeletal muscle of the rat was subsequently confirmed by other authors [37, 38] In these studies, however, the enzymatic activity of the BCLA appears to be significantly higher than that present in the skeletal and cardiac muscles, even if it represents only 5% of that present in the prostate Therefore, as in the case of the receptor content, the testosterone metabolic pattern of BCLA also appears to be intermediate between that of the prostate and skeletal muscles

It is noteworthy that, in the muscles (both in the skeletal and heart muscles, and in the BCLA), there is a high activity of the enzyme 3α-hydroxysteroid-dehydrogenase [25, 36] converting DHT into 3α-diol, a compound which does not bind to the androgenic receptor [17] The enzyme is cytosolic, NADPH-dependent and is apparently unable to catalyze the back-conversion of 3α-diol to DHT, moreover, it possesses a higher activity in females and in castrated males [25] Consequently, in the muscles, intracellular DHT is low, not only because of the low 5α-reductase activity, but also because the 3α-hydroxysteroid-dehydrogenase further metabolizes this steroid to 3α-diol, which, as previously said, cannot revert back to DHT Moreover, 3α-hydroxysteroid-dehydrogenase helps to maintain low intracellular concentrations of DHT by inactivating the amounts of this steroid reaching the muscle cells from the circulation

Little is known on the role of aromatization in muscular function estrogen receptors have been identified in the rat and bovine muscles [39, 40], and a possible role of the

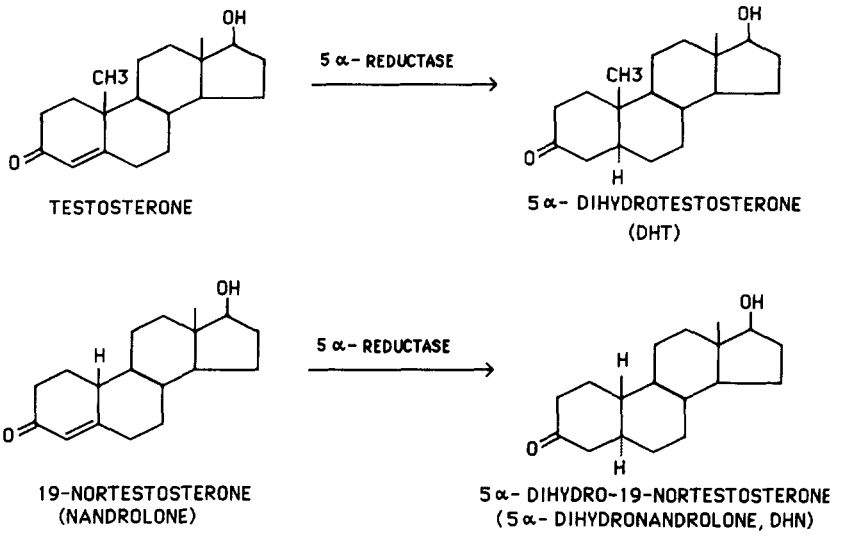

Fig 1 5α-Reductive metabolism of testosterone and of the anabolic steroid nandrolone

formation of estrogens in the control of glucose 6-phosphate dehydrogenase in the rat levator ani has been proposed [41] However, no clinically evident alterations of muscular function have been noted during prolonged treatments with antiestrogens or aromatase inhibitors [42, 43]

It is therefore likely that testosterone exerts its effects on muscle cells acting in its native molecular form This metabolic characteristic, which distinguishes the muscles from the other androgen-dependent or -sensitive tissues could help to explain the partial dissociation of the myotrophic from the androgenic actions in some anabolic steroids (see below)

Among the great number of anabolic molecules synthesized, 19-nortestosterone (nandrolone) is one of the first discovered, the most used and indeed the best studied When administered to castrated male rats, it appears to be 5 times more active in increasing levator ani than seminal vesicle weight [7] Nandrolone is as good a substrate for the 5α-reductase as testosterone [44] and the main metabolite of this reaction is 5α-dihydronandrolone (Fig 1) The relevant finding is that the 5α-reduction of nandrolone (at variance with what happens for testosterone) does not result in the amplification of the hormonal signal [45–47] Figure 2 shows the conversion of testosterone into DHT which is associated with an increase in the binding affinity of the reduced steroid to the androgen receptor, on the contrary, the 5α-reduction of nandrolone (a compound which itself binds to the prostatic androgenic receptor with an affinity higher than that of testosterone) produces a metabolite possessing a lower binding affinity than that of the parent compound These *in vitro* results might explain the different *in vivo* nuclear retentions of testosterone, nandrolone and their 5α-reduced metabolites in the prostate, in the skeletal and levator ani muscle of rats, after a continuous infusion of comparable amounts of testosterone or nandrolone (Fig 3) As hypothesized by Tooth and Zakar [45], it is possible that the simultaneous presence in the molecular structure of a 4-ene double bond and of a 19-methyl group results in a steric structure which presumably does not accurately fit the steroid binding domain of the receptor, once one of these chemical features is eliminated (by 5α-reduction or by the removal of the 19-methyl group), the molecule increases its binding affinity, however, when both these modifications are present, as in the case of 5α-dihydronandrolone, the affinity becomes low These *in vitro* and *in vivo* studies might

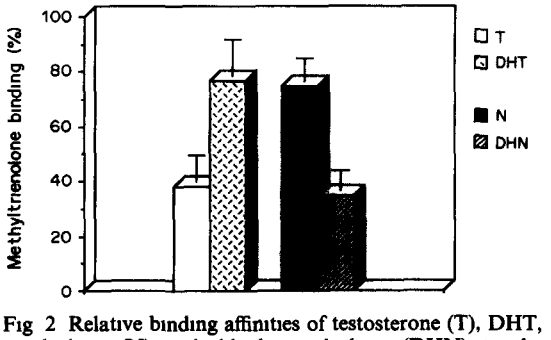

Fig 2 Relative binding affinities of testosterone (T), DHT, nandrolone (N) and dihydronandrolone (DHN) to the androgenic receptor of the rat prostate measured *in vitro* (Data from Ref [46])

explain the prevalent myotrophic effect of nandrolone the 5α-reduction of the drug, occurring in the prostate with high yields, leads to a compound which has a lower affinity and nuclear retention than DHT, and which therefore exerts a relatively low androgenic effect On the other hand, in the muscles, where the 5α-reductase is low, nandrolone possesses a higher affinity than testosterone for the androgenic receptor, leading to a relatively strong myotrophic action

Obviously, the mechanism of the anabolic action proposed for nandrolone cannot be generalized, since not all the anabolic steroids are good substrates for the 5α-reductase as, for example, methanedienone [48] Moreover, to the authors' knowledge, the metabolism of the anabolic steroids and the binding affinity of the metabolites to the androgenic receptor have been studied in detail only in the case of nandrolone However, it is interesting to note that some steroids with anabolic–androgenic activity *in vivo* do not bind *in vitro* to the androgenic receptor, as for example does oxymetholone and ethylestrenol [17] An indirect mechanism of action possibly via their biotransformation into active compounds should be postulated in these cases

ANABOLIC STEROIDS: EFFECTS IN ANIMALS

The classical therapeutic uses of androgens and of the anabolic steroids are linked to the correction of male hypogonadism, to the treatment of hereditary angioneurotic edema and to the stimulation of erythropoiesis and of bone mineralization [49] Unfortunately these drugs are also used by athletes in the hope of improving their muscular mass or their physical performance Androgens are undoubtedly able to

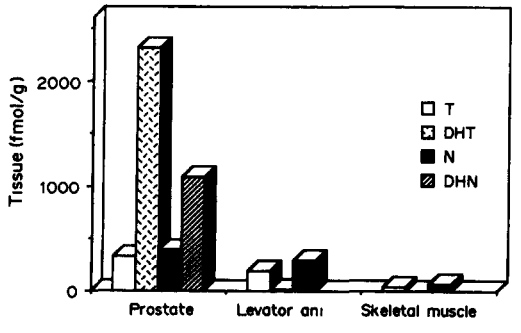

Fig 3 Nuclear retention of testosterone (T), DHT, nandrolone (N) and dihydronandrolone (DHN) in the prostate, levator ani and skeletal muscle of the rat after a continuous infusion of labelled T or N (Data from Ref [46])

Table 1 Negative experimental results in animals

Supraphysiological doses of androgens administered to rats do not produce additional muscle growth beyond that expected for physiological levels of testosterone [53]
The anabolic steroid stanzolol has no effect on the body weight, muscle growth and protein metabolism in normal well-fed male rats [54]
Testosterone administration does not alter the biochemical parameters related to energy metabolism in the rat gastrocnemius [55]
Testosterone implants do not produce synergistic effects on compensatory muscle hypertrophy (muscle weight and oxidative capacity) in normal male rats [50]

increase muscle mass in subjects with low circulating levels of testosterone such as prepubertal or hypogonadal males and females However, their actual effectiveness in producing synergistic effects with those of exercise has been challenged, since the castration of male rats [50] or chronic treatment with testosterone of female rats [51, 52] does not affect the compensatory hypertrophy of the plantaris muscle or its oxidative capability, after the removal of its synergistic muscles

Most of the results obtained in normal male animals (Table 1) substantiate the hypothesis that the administration of supraphysiological doses of androgens does not exert remarkable effects on the skeletal muscle Moreover, it is noteworthy that the number of androgenic receptors appears to be down-regulated by testosterone and other androgens, since castration of male rats and sheep produces an increase in receptor number without affecting their affinity [56, 57]

Anabolic steroids, however, appear to exert some positive effects in normal male animals on some aspects of protein and energetic metabolism of the muscles (Table 2)

ANABOLIC STEROIDS· EFFECTS IN HUMANS

In humans, most studies on the effects of anabolic steroids on muscle strength or mass have been performed in atheletes It is rather

Table 2 Positive experimental results in animals

Utilizing the ^{15}N-tracer technique it has been shown a positive influence of androgens and of androgens + training on protein synthesis in the rat [58]
Methanedione treatment in combination with physical exercise increases myofibrillar protein concentration [59]
Anabolic steroids can affect mitochondrial and sarcotubular enzymes in skeletal muscle of the male rats [60]
Anabolic steroids increase the activity of the enzyme carnitine palmitoyltransferase in mitochondrial outer membrane of fast-twitch muscles of male rats The enzyme plays an important role in regulating the flux of long-chain fatty acids to mitochondrial oxidative metabolism [61]

surprising that, after many years of use and abuse, it is still not clear whether anabolic steroids are able to improve athletic performances The difficulty in carrying out properly designed studies constitutes the reason for this uncertainty The number of controlled trials in which the administration of anabolic steroids was ineffective [62–72] is almost equal to those in which slight effects on muscle strength or mass have been shown [73–83]

Many experimental differences make it difficult to reach a unitary interpretation of the results (a) the studies usually include a limited number of subjects and they are not always blinded or blinding has been broken because of the side-effects of the drugs, (b) different steroids have been given in different doses (which are usually much lower than those utilized when the drugs are self-administered), (c) the lengths of the experimental periods are usually relatively short (3–4 weeks), particularly in placebo-controlled studies, (d) different training programs during and before the study, different assessment criteria, and different diets have been used, and (e) placebo effects or the increased aggressiveness reported by many steroid-users might have affected strength measurements

Despite the inconsistent results of the literature, some recent papers and reviews [84–88] maintain that significant improvements in athletic performances can be observed if the following criteria are met (1) steroid administration in previously trained athletes during intense training, (2) supplementation with high-protein, high-caloric diets, (3) utilization of very sensitive techniques of strength measurements (multiple-joint, single-repetition, maximal-weight techniques), and (4) administration of high doses of steroids for very prolonged observation times (for instance, significant effects appeared after 4 5 months of administration plus training in the study of Alen and Hakkinen [85])

This opinion is in substantial agreement with that of the American College of Sports Medicine which in the position stand [89] states that anabolic steroids can result in small but significant increases in strength in some but not all individuals

It is the view of the authors that, if an effect of the anabolic steroids on the muscle mass or physical performance in eugonadal male subjects exists, it is very small and still lacks a straightforward demonstration However, if we assume that such an effect exists, what are the possible mechanisms of action?

In normal adult men, the concentration of testosterone in the blood is 3 to 10 times and that of DHT is 1 to 3 times the respective K_d for the androgenic receptor, in this situation, it is likely that the androgenic receptor system is almost completely saturated by the circulating steroids The androgen receptor is therefore probably not involved in the action of the anabolic steroids in these subjects It is then possible that anabolic steroids exert their action on several other parameters They might antagonize the increased protein breakdown during the muscular stress of athletic training (see below), they might increase fluid and electrolyte retention, producing an increase in body weight [5], they might induce a faster recovery after strenuous exercise as suggested by lower circulating lactate [90] and creatine kinase levels in anabolic users [91], or they might produce psychological effects (increased aggressiveness, euphoria and diminished fatigue) which might facilitate the training and help in competitive performances [5, 64]

Finally, it should be remembered that recent studies have identified rapid effects exerted by androgens on the skeletal [92] and heart muscle [93] These effects are still poorly characterized and may involve the action of androgens on membrane receptors present in motoneurons [92] or directly on the myocytes [93] In cultured cardiac myocytes, for example, testosterone may induce a transient accumulation of polyamines which apparently serve as intracellular messengers to regulate transmembrane calcium movements [93] The involvement of membrane effects of androgens in muscle physiology is purely speculative at this point The existence of an anticatabolic effect, proposed by many authors as the main mechanism of action of anabolic steroids, is rather controversial The field has been recently reviewed by Hickson *et al* [94] According to some authors, the muscle atrophy induced by corticosteroids may be retarded by anabolic steroids, however, other authors disagree Moreover, the binding studies performed *in vitro* and *in vivo* are also contradictory a very low binding affinity of anabolic agents to the glucocorticoid receptor has been shown in some studies, while others have underlined more significant cross-binding of anabolic steroids to the glucocorticoid receptor

In conclusion, it appears that the effectiveness and the possible mechanism(s) of action of anabolic steroids on the muscle of eugonadal

subjects are still open to discussion, unfortunately, it clearly appears from the literature that the continuous administration of high doses of anabolic steroids produces a large number of side-effects some of which are serious, irreversible and possibly life-threatening [5, 95–99]

REFERENCES

1 Mooradian A D, Morley J E and Korenman S G Biological actions of androgens *Endocrine Rev* **8** (1987) 1–28
2 Powers M L and Florini J R A direct effect of testosterone on muscle cells in tissue culture *Endocrinology* **97** (1975) 1043–1047
3 Tobin C and Joubert Y Testosterone-induced development in the rat levator ani-muscle *Dev Biol* **146** (1991) 131–138
4 Fishman R B, Chism L, Firestone G L and Breedlove S M Evidence for androgen receptors in sexually dimorphic perineal muscles of neonatal male rats absence of androgen accumulation by the perineal motoneurones *J Neurobiol* **21** (1990) 694–704
5 Wilson J D Androgen abuse by athletes *Endocrine Rev* **9** (1988) 181–199
6 Kruskemper H L *Anabolic Steroids* Academic Press, New York (1969)
7 Vida J A *Androgens and Anabolic Agents Chemistry and Pharmacology* Academic Press, New York (1969)
8 Kopera H The history of anabolic steroids and a review of clinical experience with anabolic steroids *Acta Endocr* **110** (Suppl 271) (1985) 11–18
9 Hayes K J The so-called 'levator ani' of the rat *Acta Endocr* **48** (1965) 337–347
10 Breuer C B and Florini J R Effects of ammonium sulphate, growth hormone and testosterone propionate on ribonucleic acid polymerase and chromatin activities in rat skeletal muscle *Biochemistry* **5** (1966) 3857–3861
11 Boissonneault G, Gagnon J, Ho-Kim M A, Rogers P A and Tremblay R R Depressed translational activity in the androgen sensitive levator ani muscle of the rat *J Steroid Biochem* **32** (1989) 507–513
12 Max S R and Toop J Androgens enhance *in vivo* 2-deoxyglucose uptake by rat striated muscle *Endocrinology* **113** (1982) 119–126
13 Bergamini E Different mechanisms in testosterone action on glycogen metabolism in rat perineal and skeletal muscles *Endocrinology* **96** (1975) 77–84
14 Krieg M Characterization of the androgen receptors in the skeletal muscle of the rat *Steroids* **28** (1976) 261–274
15 Snochowski M, Dahlberg E and Gustafsson J-A Characterization and quantification of the androgen and glucocorticoid receptors in cytosol from rat skeletal muscle *Eur J Biochem* **111** (1980) 603–616
16 Dhalberg E, Snochowski M and Gustafsson J-A Regulation of the androgen and glucocorticoid receptors in rat and mouse skeletal muscle cytosol *Endocrinology* **108** (1981) 1431–1440
17 Saartok T, Dhalberg E and Gustafsson J-A Relative binding affinity of anabolic-androgenic steroids comparison of the binding to the androgen receptors in skeletal muscles and prostate, as well as to sex hormone-binding globulin *Endocrinology* **114** (1984) 2100–2106
18 Krieg M, Smith K and Elvers B Androgen receptor translocation from cytosol of rat heart muscles, bulbocavernous/levator ani muscle and prostate into heart muscle nuclei *J Steroid Biochem* **13** (1980) 577–587
19 Takeda H, Chodak G, Mutchnik S, Nakamoto T and Chang C Immunohistochemical localization of androgen receptors with mono- and polyclonal antibodies to androgen receptors *J Endocr* **126** (1990) 17–25
20 Ruizeveld De Winter J, Trapman J, Vermey M, Mulder E, Zegers N D and Van der Kwast T H Androgen receptor expression in human tissues an immunohistochemical study *J Histochem Cytochem* **39** (1991) 927–936
21 Snochowski M, Saartok T, Dhalberg E, Eriksson E and Gustafsson J-A Androgen and glucocorticoid receptors in human skeletal muscle cytosol *J Steroid Biochem* **14** (1981) 765–771
22 Wilson J D and Gloyna R E The intranuclear metabolism of testosterone in the accessory organs of reproduction *Recent Prog Horm Res* **26** (1970) 309–336
23 Martini L The 5α-reduction of testosterone in the neuroendocrine structures Biochemical and physiological implications *Endocrine Rev* **3** (1982) 1–25
24 Celotti F, Melcangi R C and Martini L The 5α-reductase in the brain molecular aspects and relation to brain function *Frontiers Neuroendocr* **13** (1992) 163–215
25 Smith K, Krieg M and Schwien S *In vitro* metabolism of 5α-dihydrotestosterone to 5α-androstane-3α,17β-diol in rat heart, diaphragm, skeletal muscle and bulbocavernous/levator ani enzyme characterization and quantification *J Steroid Biochem* **13** (1980) 917–924
26 Naftolin F, Ryan K J, Davies I J, Reddy V V, Flores F, Petro Z, Kuhn M, Whith R J, Takaoka Y and Wolin L The formation of estrogens by central neuroendocrine tissues *Recent Prog Horm Res* **31** (1975) 295–319
27 Simpsom E R, Merrill J C, Hollub A J, Graham-Lorence S and Mendelson C R Regulation of estrogen biosynthesis by human adipose cells *Endocrine Rev* **10** (1989) 136–148
28 Payne A H, Perkins L M, Georgiou M and Quinn P G Intratesticular site of aromatase activity and possible function of testicular estradiol *Steroids* **50** (1987) 435–448
29 Zoppi S, Negri-Cesi P, Lechuga M J and Motta M Effect of enzyme inhibitors and of LHRH analogs on androgen metabolism in the human prostate In *Progress in Endocrinology* (Edited by H Imura, K Shizume and S Yoshida) Excerpta Medica, Amsterdam, Vol 1 (1988) pp 293–299
30 Brodie A M H, Son C, King D A, Meyer K M and Inkster S E Lack of evidence for aromatase in human prostatic tissues effects of 4-hydroxyandrostenedione and other inhibitors on androgen metabolism *Cancer Res* **49** (1989) 6551–6555
31 Matsumine H, Hirato K, Yanaihara T, Tamada T and Yoshida M Aromatization by skeletal muscle *J Clin Endocr Metab* **63** (1986) 717–720
32 Sholl S A, Goy R W and Kim K L 5α-Reductase, aromatase, and androgen receptor levels in the monkey brain during fetal development *Endocrinology* **124** (1989) 627–634
33 George F W and Peterson K G 5α-Dihydrotestosterone formation is necessary for embryogenesis of the rat prostate *Endocrinology* **122** (1988) 1159–1164
34 Grino P B, Griffin J E and Wilson J D Testosterone at high concentration interacts with the human androgen receptor similarly to dihydrotestosterone *Endocrinology* **126** (1990) 1165–1172
35 Lubahn D B, Joseph D R, Sullivan P M, Willard H F, French F S and Wilson E M Cloning of human androgen receptor complementary DNA and localization to the X chromosome *Science* **240** (1988) 327–330
36 Massa R and Martini L Testosterone metabolism a necessary step for activity? *J Steroid Biochem* **5** (1974) 941–947

37 Krieg M, Dennis M and Voigt K D Comparison between the binding of 19-nortestosterone, 5α-dihydrotestosterone and testosterone in rat prostate, and bulbocavernous/levator ani muscle *J Endocr* **70** (1976) 379–387
38 Bartsch W, Krieg M and Voigt K D Quantification of endogenous testosterone, 5α-dihydrotestosterone and 5α-androstane-3α,17β-diol in subcellular fractions of the prostate, bulbocavernous-levator ani muscle, skeletal muscle and heart muscle of the rat *J Steroid Biochem* **13** (1980) 259–264
39 Dube J T, Lesage R and Tremblay R R Androgen and estrogen binding in rat skeletal and perineal muscles *Can J Biochem* **54** (1976) 50–56
40 Sauerwein H and Meyer H H Androgen and estrogen receptors in bovine skeletal muscle relation to steroid-induced allometric muscle growth *J Anim Sci* **67** (1989) 206–212
41 Knudsen J F and Max S R Aromatization of androgens to estrogens mediates increased activity of glucose 6-phosphate dehydrogenase in rat levator ani muscle *Endocrinology* **106** (1980) 440–443
42 Mouridsen H, Palshoff T, Patterson J and Battersby L Tamoxifen in advanced breast cancer *Cancer Treat Rev* **5** (1978) 131–136
43 Santen R J, Worgul T J, Samojlik E, Interrante A, Boucher A E, Allan Lipton C R N P, Harvey H A, White D S, Emma Smart R N, Cox C and Wells S A A randomized trial comparing surgical adrenalectomy with aminogluthetimide plus hydrocortisone in women with advanced breast cancer *New Engl J Med* **305** (1981) 545–555
44 Tooth M and Zakar T Different binding of testosterone, 19-nortestosterone and their 5α-reduced derivatives to the androgen receptor of the rat seminal vesicle a step toward the understanding of the anabolic action of nortestosterone *Endokrinologie* **80** (1982) 163–172
45 Tooth M and Zakar T Relative binding affinities of testosterone, 19-nortestosterone and their 5α-reduced derivatives to the androgen receptor and to other androgen binding proteins a suggested role of 5α-reductive steroid metabolism in the dissociation of "myotropic" and "androgenic" activities of 19-nortestosterone *J Steroid Biochem* **17** (1982) 653–660
46 Bergink E W, Janssen P S L, Turpijn E W and Van der Vies J Comparison of the receptor binding properties of nandrolone and testosterone under *in vitro* and *in vivo* conditions *J Steroid Biochem* **22** (1985) 831–836
47 Bergink E W, Geelen J A A and Turpijn E W Metabolism and receptor binding of nandrolone and testosterone under *in vitro* and *in vivo* conditions *Acta Endocr* **110** (Suppl 271) (1985) 31–38
48 Steel R E, Didato F, Sawyer W K and Steinez G B Evidence that 5α-reduction of Δ4,3-ketosteroids may be more important for their androgenic than their luteinizing hormone-inhibiting activity *Endocrinology* **105** (1979) 1036–1040
49 Wilson J D and Griffin J E The use and misuse of androgens *Metabolism* **29** (1980) 1278–1295
50 Max S R and Rance N E No effect of sex steroids on compensatory muscle hypertrophy *J Appl Physiol* **56** (1984) 1589–1593
51 Kuhn F E and Max S R Testosterone and muscle hypertrophy in female rats *J Appl Physiol* **59** (1985) 24–27
52 Tsika R W, Herrick R E and Baldwin K M Effect of anabolic steroids on overloaded and overloaded suspended skeletal muscle *J Appl Physiol* **63** (1987) 2128–2133
53 Bartsch W, Krieg M and Voigt K D Regulation and compartmentalization of androgens in rat prostate and muscle *J Steroid Biochem* **19** (1983) 929–937
54 Bates P C, Chew L F and Millward D J Effects of the anabolic steroid stanozolol on growth and protein metabolism in the rat *J Endocr* **114** (1987) 373–381
55 Pastoris O, Dossena M, Fulle D, Taglietti M and Benzi G Action of testosterone on some biochemical parameters related to the energy metabolism of the skeletal muscle *Archs Int Pharmacodyn Ther* **263** (1983) 129–132
56 Rance N E and Max S R Modulation of the cytosolic androgen receptor in striated muscle by sex steroids *Endocrinology* **115** (1984) 862–866
57 Sinnett-Smith P A, Palmer C A and Butterly P J Androgen receptors in skeletal muscle cytosol from sheep treated with trenbolone acetate *Horm Metab Res* **19** (1987) 110–114
58 Menschikowski M, Jung K, Junghans P, Petzke K J and Albrecht V The influence of a steroid hormone and of physical exercise on protein metabolism in rats *Exp Clin Endocr* **92** (1988) 341–348
59 Morano I and Weicker H The influence of permanent physical stress and methandienone on the degradation of myofibrillar proteins of heart and soleus of Guinea pigs *Arzneim Forsch* **35** (1985) 501–503
60 Saborido A, Vila J, Molano F and Megias A Effect of anabolic steroids on mitochondria and sarcotubular system of skeletal muscle *J Appl Physiol* **70** (1991) 1038–1043
61 Guzman M, Saborido A, Castro J, Molano F and Megias A Treatment with anabolic steroids increases the activity of the mitochondrial outer carnitin palmitoyltransferase in rat liver and fast-twitch muscle *Biochem Pharmac* **41** (1991) 833–835
62 Fowler W M Jr, Gardner G W and Egstron G H Effect of anabolic steroid on physical performance of young men *J Appl Physiol* **20** (1965) 1038–1040
63 Casner S W Jr, Early R G and Carlson R B Anabolic steroid effects of body composition in normal young men *J Sports Med Phys Fit* **11** (1971) 98–103
64 Ariel G and Saville W Anabolic steroids the physiological effects of placebos *Med Sci Sports* **4** (1972) 124–126
65 Fahey T D and Brown C H The effects of an anabolic steroid on the strength, body composition, and endurance of college males when accompanied by a weight training program *Med Sci Sports* **5** (1973) 272–276
66 Stromme S G, Meen H D and Aakvaag A Effects of an androgenic-anabolic steroid on strength development and plasma testosterone levels in normal males *Med Sci Sports* **6** (1974) 203–208
67 Golding L A, Freydinger J E and Fishel S S Weight, size, and strength unchanged with steroids *Physician Sports Med* **2** (1974) 39–43
68 Johnson L C, Roundy E D, Allsen P E, Fisher A G and Silvester L J Effect of anabolic steroid treatment on endurance *Med Sci Sports* **7** (1975) 287–289
69 Hervey G R, Hutchinson I, Knibbs A V, Burkinshaw L, Jones P R M, Norgan N G and Levell M J "Anabolic" effects of methandienone in men undergoing athletic training *Lancet* **2** (1976) 699–702
70 Loughton S J and Ruhling R O Human strength and endurance responses to anabolic steroid and training *J Sports Med* **17** (1977) 285–296
71 Crist D M, Stackpole P J and Peake C T Effects of androgenic-anabolic steroids on neuromuscular power and body composition *J Appl Physiol* **54** (1983) 366–370
72 Ballarin E, Guglielmi C, Martinelli S, Casoni I, Borsetto C, Ziglio P G and Conconi F Unmodified performance in runners following anabolic steroid administration *Int J Sports Med* **7** (1986) 302–306

73 Johnson L C and O'Shea J P Anabolic steroid effects on strength development *Science* **164** (1969) 957–960

74 O'Shea J P The effects of an anabolic steroid on dynamic strength levels of weightlifters *Nutr Rep Int* **4** (1971) 363–370

75 Johnson L C, Fisher G, Silvester L J and Hofheins C C Anabolic steroid effects on strength, body weight, oxygen uptake and spermatogenesis upon mature males *Med Sci Sports* **4** (1972) 43–45

76 Ward P The effects of an anabolic steroid on strength and lean body mass *Med Sci Sports* **5** (1973) 277–282

77 Ariel G The effect of anabolic steroid upon skeletal muscle contractile force *J Sports Med* **13** (1973) 187–190

78 Ariel G Residual effect of an anabolic steroid upon isotonic muscular force *J Sports Med* **14** (1974) 103–111

79 Freed D L J, Banks A J, Longson D and Burley D M Anabolic steroids in athletics crossover double-blind trial on weightlifters *Br Med J* **2** (1975) 471–473

80 Win-May M and Mya-Tu M The effect of anabolic steroids on physical fitness *J Sports Med* **15** (1975) 266–271

81 Hervey G R, Knibbs A V, Burkinshaw L, Morgan D B, Jones P R M, Chettle D R and Vartsky D Effects of methandienone on the performance and body composition of men undergoing athletic training *Clin Sci* **60** (1981) 457–461

82 Lamb D R Anabolic steroids in athletics How well do they work and how dangerous are they? *Am J Sports Med* **12** (1984) 31–38

83 Alen M and Hakkinen K Androgenic effects on serum hormones and maximal force development in strength athletes *J Sports Med* **27** (1987) 38–46

84 Hauput H A and Rovere G D Anabolic steroids a review of literature *Am J Sport Med* **12** (1984) 469–484

85 Alen M and Hakkinen K J Androgenic steroid effects on serum hormones and on maximal force development in strength athletes *J Sports Med* **27** (1987) 38–46

86 Holden S C, Calvo R D and Sterling J C Anabolic steroids in athletics *Texas Med* **86** (1990) 32–36

87 Kleiner S M Performance-enhancing aids in sport health consequences and nutritional alternatives *J Am Coll Nutr* **10** (1991) 163–176

88 Strauss R H and Yesalis C E Anabolic steroids in the athlete *A Rev Med* **42** (1991) 449–457

89 American College of Sports Medicine position stand on the use of anabolic-androgenic steroids in sports *Med Sci Sports Exerc* **19** (1987) 534–539

90 Rozenek R, Rahe C H, Kohl H H, Marple D N, Wilson G D and Stone M H Physiological responses to resistance-exercise in athletes self-administering anabolic steroids *J Sports Med Phys Fit* **30** (1990) 354–360

91 Boone J B, Lambert C P, Flynn M G, Michaud T J, Rodriguez-Zayas J A and Andres F F Resistance exercise effects on plasma cortisol, testosterone and creatinine kinase activity in anabolic-androgenic steroid users *Int J Sports Med* **11** (1990) 293–297

92 Sachs B D and Leipheimer R E Rapid effects of testosterone on striated muscle activity in rats *Neuroendocrinology* **48** (1988) 453–458

93 Koening H, Fan C-C, Goldstone A D, Lu C Y and Trout J J Polyamines mediate androgenic stimulation of calcium fluxes and membrane transport in rat heart myocytes *Circ Res* **64** (1989) 415–426

94 Hickson R C, Czerwinski S M, Faltudo M T and Young A P Glucocorticoid antagonism by exercise and androgenic-anabolic steroids *Med Sci Sports Exerc* **22** (1990) 331–340

95 Hickson R C, Ball K L and Falduto M T Adverse effects of anabolic steroids *Med Toxic Averse Drug Exp* **4** (1989) 254–271

96 Lenders J W M, Demacker P N M, Vos J A, Jansen P L M, Hoitsma A J, van 't Laar A and Thien T Deleterious effects of anabolic steroids on serum lipoproteins, blood pressure, and liver function in amateur body builders *Int J Sports Med* **9** (1988) 19–23

97 Laseter J T and Russel J A Anabolic steroid-induced tendon pathology a review of the literature *Med Sci Sports Exerc* **23** (1991) 1–3

98 Brower K J, Eliopulos G A, Blow F C, Catlin D H and Beresford T P Evidence for physical and psychological dependence on anabolic androgenic steroids in eight weight lifters *Am J Psychiat* **147** (1990) 510–512

99 Johnson F L The association of oral androgenic-anabolic steroids and life-threatening disease *Med Sci Sports* **7** (1975) 284–286