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Review Article

The Mechanisms of Androgen Effects on Body Composition: Mesenchymal Pluripotent Cell as the Target of Androgen Action

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Testosterone supplementation increases muscle mass primarily by inducing muscle fiber hypertrophy; however, the mechanisms by which testosterone exerts its anabolic effects on the muscle are poorly understood. The prevalent view is that testosterone improves net muscle protein balance by stimulating muscle protein synthesis, decreasing muscle protein degradation, and improving the reutilization of amino acids. However, the muscle protein synthesis hypothesis does not adequately explain testosterone-induced changes in fat mass, myonuclear number, and satellite cell number. We postulate that testosterone promotes the commitment of pluripotent stem cells into the myogenic lineage and inhibits their differentiation into the adipogenic lineage. The hypothesis that the primary site of androgen action is the pluripotent stem cell provides a unifying explanation for the observed reciprocal effects of testosterone on muscle and fat mass.

AFTER nearly six decades of intense controversy (1), a consensus has emerged that androgens have direct anabolic effects on the mammalian skeletal muscle (2–17). Testosterone administration to androgen-deficient men is associated with an increase in lean body mass (2–6), mostly due to skeletal muscle accretion (4). In addition, testosterone administration leads to a reduction in whole body and regional fat mass (Table 1) (3–6). Testosterone effects on the muscle are linearly correlated with the administered dose and the prevalent circulating testosterone concentrations (7). Thus, administration of supraphysiological doses of testosterone to eugonadal men leads to further gains in muscle size and maximal voluntary strength (7,8). Testosterone-induced increase in muscle size is associated with hypertrophy of both type I and II fibers (9), and an increase in the number of myonuclei and satellite cells (10). Any proposal to explain the anabolic effects of testosterone should ideally reconcile all of these observed effects of testosterone administration on body composition and muscle morphology. Until recently, the dominant hypothesis had been that testosterone administration increases the synthesis rates of mixed skeletal muscle protein, including myosin heavy chain (MHC) (4,11–16). However, this hypothesis does not explain all of the observed effects of androgens on body composition; hence, the mechanisms by which testosterone induces skeletal muscle mass remain poorly understood. There are several additional vexing issues related to the effects of testosterone on the muscle that have not been fully explained. Are androgen effects on muscle and fat mass mediated through similar or different mechanisms? What cell type within the skeletal muscle is the primary target of androgen action—is it the muscle fiber, satellite cell, or yet another androgen-responsive cell? Are androgen effects on the muscle mediated through an androgen receptor-mediated pathway? What signal transduction pathways are involved in mediating androgen effects on the muscle? Is 5-alpha reduction of testosterone necessary for mediating testosterone effects on the muscle? What is the role of aromatization of testosterone in mediating androgen effects on body composition? What is the mechanistic basis of the tissue-specific differences in androgen responsiveness? This review attempts to address these issues, and is a summary of the data and thoughts generated in our laboratories over the past decade on the anabolic effects of testosterone on skeletal muscle.

Testosterone Induces Skeletal Muscle Fiber Hypertrophy

Administration of replacement doses of testosterone to healthy young (2–6) and older men with low testosterone levels (18–21) and HIV-infected men with low testosterone levels (17), and administration of supraphysiological doses to eugonadal men, increases muscle size (7,8). To evaluate whether testosterone-induced increase in muscle size is due to muscle fiber hypertrophy, we treated healthy young men with monthly injections of a long-acting gonadotropin-releasing hormone (GnRH) agonist to suppress endogenous testosterone secretion and weekly injections of 25, 50, 125, 300, or 600 mg testosterone enanthate (TE) for 20 weeks. Muscle biopsies were obtained from vastus lateralis muscle in eugonadal men before and after 20 weeks of combined treatment with GnRH agonist and testosterone (7,9). Muscle volume measured by magnetic resonance imaging increased in

Table 1. Summary of the Observed Effects of Testosterone on Body Composition

Effects on Fat-Free Compartment
Increase in fat-free and lean body mass (2–14)
Increase in bone mass (52)
Increase in nitrogen retention in castrated male mammals, eunuchoidal men, women, and prepubertal boys (25–28)
Changes in Muscle Histomorphology
Increase in cross-sectional areas of both types I and II skeletal muscle fibers (9)
Increase in the number of myonuclei (10)
Increase in the number of satellite cells (10)
Changes in Protein Dynamics
Increase in nonoxidative leucine disappearance rate (14)
Increase in fractional synthesis rates of mixed skeletal muscle protein (11–14)
No net increase in protein balance, although net protein balance becomes less negative in fasting state (15,16)
Decrease in protein degradation by the arteriovenous difference method (15)
Decrease in proteasome-mediated protein degradation (15)
Effects of Fat Compartment
Decrease in whole-body fat mass in hypogonadal men treated with replacement doses of testosterone (3–6)
Decrease in whole-body fat mass in eugonadal men with supraphysiological doses of testosterone and other androgens (7)
Decrease in intraabdominal fat mass in middle-aged men with low normal testosterone levels (25,26)
Increased lipolysis (26)
Regulation of lipoprotein lipase activity (52,53)
Decreased triglyceride assimilation in abdominal fat compartment (26)
Inhibits preadipocyte to adipocyte differentiation (52)

Note: Numbers in parentheses are reference numbers.

proportion to the administered dose and the prevalent testosterone concentrations. The cross-sectional areas of both type I and II fibers also increased in direct correlation with the testosterone dose and total and free testosterone concentrations during treatment (9) (Figure 1). The relative proportions of type I and type II fibers did not change significantly after treatment in any group. Thus, the increase in muscle volume in healthy eugonadal men treated with graded doses of testosterone is due to concentration-dependent hypertrophy of both type I and type II muscle fibers (9).

Testosterone Increases Number of Myonuclei and Satellite Cells in Skeletal Muscle of Healthy Young Men

We counted the number of myonuclei in biopsies of vastus lateralis obtained at baseline and after 20 weeks of treatment with a GnRH agonist and 125, 300, or 600 mg weekly dose of testosterone enanthate. Testosterone administration was associated with a significant increase in myonuclear number. Because myonuclei in muscle fibers are contributed by satellite cells, we considered the possibility that testosterone administration increases satellite cell number. Accordingly, we quantitated the number of satellite cells by direct counting and by spatial orientation methods. Testosterone administration was associated with a dose-dependent increase in percent satellite cell number, obtained by direct counting, and absolute satellite cell number obtained by spatial orientation in men treated with 300 mg and 600 mg doses (Figure 2) (10). The change in percent satellite cell number correlated with changes in total and free testosterone concentrations (10). Satellite cell and mitochondrial areas were significantly higher and the nuclear to cytoplasmic ratio lower after treatment with 300 mg and 600 mg doses (10). These data demonstrate that testosterone-induced muscle fiber hypertrophy is associated with an increase in satellite cell number, a proportionate increase in myonuclear number, and changes in satellite cell ultrastructure. These alterations in satellite cell number and ultrastructure and muscle morphology cannot be explained by the muscle protein synthesis hypothesis.

Testosterone Effects on Fat Mass

Testosterone is an important determinant of whole body and regional fat mass. Hypogonadal men have higher fat mass in comparison with eugonadal controls (3). Induction of androgen deficiency in healthy men by administration of a GnRH agonist leads to an increase in fat mass (14). In young, hypogonadal men, testosterone replacement therapy is associated with a decrease in fat mass (3–6). Long-term studies of testosterone supplementation of older men have also demonstrated a decrease in fat mass (18,19). Serum testosterone levels are lower in middle-aged men with visceral obesity than in age-matched controls (22,23). Serum testosterone levels correlate inversely with visceral fat area (22,23). Testosterone replacement of middle-aged men with visceral obesity has been reported to decrease intraabdominal fat mass and improve insulin sensitivity (24,25). In our dose–response studies, administration of graded doses of testosterone to men was associated with a dose-dependent decrease in fat mass (7). Loss of fat mass at higher doses was evenly distributed in the trunk and appendices and in the superficial and deep compartments. Until recently, testosterone effects on fat mass and metabolism have been assumed to be mediated by mechanisms that are distinct from those that mediate androgen effects on the muscle. Testosterone has been reported to inhibit lipid uptake and lipoprotein lipase activity in adipocytes, and stimulate lipolysis (21), in part by increasing the number of lipolytic beta-adrenergic receptors. In addition, testosterone inhibits the differentiation of preadipocytes to adipocytes. All of these hypotheses on the direct effects of testosterone on fat mass, although plausible, do not provide a unifying explanation for the reciprocal changes in muscle and fat mass.

Testosterone Effects on Protein Synthesis

Soon after the biochemical synthesis of testosterone, several groups investigated the anabolic effects of testosterone in animal models. During the 1930s, Kochakian (26) first described the nitrogen-retaining properties of urinary androgens in the castrated dog. He recorded similar effects of androgens in the castrated male rat and found that the androgen stimulation not only resulted in nitrogen retention but also increases in body weight (26–28). These studies suggested that androgen effects were dose related, with

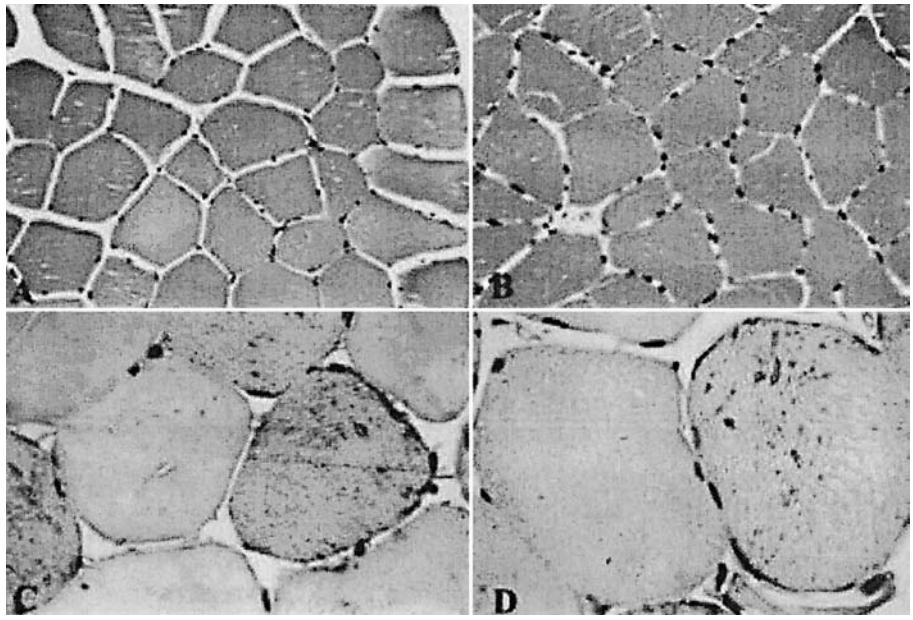

Figure 1. Testosterone induces skeletal muscle fiber hypertrophy. The figure shows cross-sections of muscle biopsies obtained before and after 20 weeks of treatment in one man treated with GnRH agonist and 600 mg testosterone enanthate weekly. The left panels represent baseline sections, and the right panels are sections obtained after 20 weeks of treatment. The magnification is 200-fold in **A** and **B**, and 1000-fold in **C** and **D** [reproduced with permission (9)].

higher nitrogen retention and weight gains observed with higher doses of androgens (26–28).

Shortly after the initial animal studies, Kenyon and colleagues (29) studied the effects of testosterone propionate in eunuchoidal men, and eugonadal men and women. During androgen treatment, urinary nitrogen excretion diminished, with the greatest magnitude of effects observed in eunuchoidal men. Kenyon concluded presciently that the ''protein estimated as retained by these subjects is not accounted for by increases in the bulk of genital tissues and represents deposit of new material elsewhere in the body'' (29). These observations, combined with the results of the animal studies (26–29), allowed the early recognition of the anabolic effects of androgens. It is notable that Kenyon and others were not able to demonstrate sustained increases in nitrogen retention with testosterone supplementation in eugonadal men, an observation that sparked considerable skepticism for the next 50 years about the anabolic effects of supraphysiological doses of androgens in eugonadal men.

Induction of androgen deficiency by administration of a long-acting GnRH agonist in healthy young men is associated with decreased rates of ^{13}C-leucine appearance, a measure of proteolysis (14). Lowering of testosterone concentrations in this study (14) was also associated with a significant decrease in nonoxidative leucine disappearance, a marker for whole-body protein synthesis. Conversely, testosterone supplementation stimulates the synthesis of mixed skeletal muscle proteins (4,11–14). All of these studies of protein turnover have been performed in the fasting state in which the net balance between protein synthesis and breakdown is negative. Testosterone administration improves the muscle protein balance and reduces the loss of muscle protein during the fasting state (4,12–16). However, none of the studies have demonstrated a clear improvement in muscle protein balance into the positive territory, which would indicate net protein accretion. It is possible that during the fed state, testosterone administration leads to net protein accretion. Testosterone improves the efficiency of reutilization of amino acids in the muscle (16). The effects of testosterone administration on muscle protein breakdown have not been studied extensively. A recent study by Ferrando and colleagues (15) reported a significant decrease in muscle protein breakdown following testosterone supplementation in older men. In this study (15), the proteasome peptidase activity was decreased by testosterone administration, a finding consistent with the decrease in muscle protein degradation assessed by using labeled phenylalanine and measurements of arteriovenous differences. Thus, the net effect of testosterone administration is a greater net accretion of nitrogen because of the amelioration of protein loss during fasting, and by stimulation of protein anabolism with feeding (15).

Several observed effects of testosterone administration on body composition and muscle histomorphology are not easily explained by the muscle protein hypothesis. If muscle protein synthesis or degradation were the primary target of androgen action, then one would have to invoke a separate mechanism to explain the reduction in fat mass that occurs during androgen administration. Similarly, muscle protein hypothesis does not easily explain the observed increases in the number of myonuclei and satellite cells in the skeletal muscle during androgen treatment. Undoubtedly, muscle fiber hypertrophy could not occur without a net increase in protein accretion; however, it is likely that the increase in muscle protein synthesis is a secondary event in the cascade of molecular processes that culminate in muscle hypertrophy.

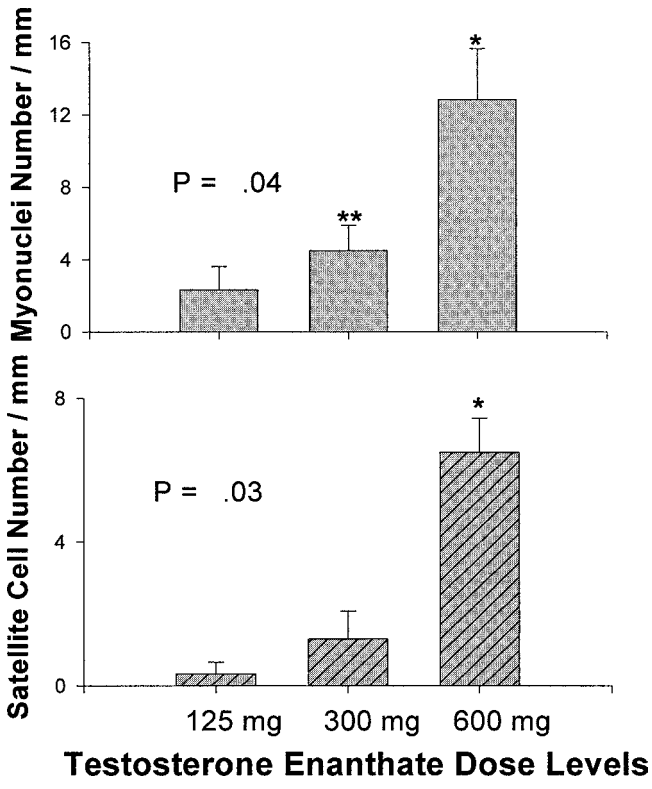

Figure 2. The effect of testosterone administration on myonuclear number and absolute satellite cell number. The number of myonuclei (upper panel) and satellite cells per millimeter of muscle fiber length (lower panel) were computed by spatial distribution. Change was calculated as the difference between post-treatment and baseline values. Values that were significantly different from zero are marked by asterisks. The weekly dose of testosterone enanthate is shown at the bottom. *$p = .04$ versus zero change; **$p = .03$ versus zero change [reproduced with permission (10)].

Are Anabolic Effects of Androgen on Muscle Mediated Through an Androgen Receptor-Mediated Pathway?

Androgen receptors are expressed in all the skeletal muscles that have been examined (30,31). The level of expression varies in different muscle groups (30). However, androgen receptors in most organ systems are nearly saturated at testosterone concentrations that are at or near the lower end of the normal male range (1). Indeed, many androgen-dependent functions in men are maintained at testosterone concentrations that are near the lower end of the male range (7). However, our dose–response studies in healthy young men have demonstrated that the anabolic effects of testosterone on the muscle are linearly related to testosterone dose and circulating concentrations over a range that extends at least a log unit higher than the lower end of the normative range in men (7). If androgen receptors are saturated at relatively low testosterone concentrations, then how can we explain the effects of higher, supraphysiologic doses of testosterone on the muscle? This apparent discordance led to considerable skepticism about the biological plausibility of direct anabolic effects of testosterone on the muscle. These observations also led to speculation that the anabolic effects of testosterone on the muscle might not be mediated through an androgen-dependent mechanism. It was hypothesized, with some support from experimental data, that testosterone's effects on the muscle might be mediated through an antiglucocorticoid effect (32–34). In animal models, glucocorticoids antagonize the anabolic effects of testosterone (32–34); conversely, testosterone administration can prevent glucocorticoid-induced muscle atrophy. Testosterone binds glucocorticoid receptor with low affinity (33), and it is not clear whether testosterone has additional postreceptor effects on the glucocorticoid pathway.

Administration of androgen receptor antagonists to men is associated with loss of muscle mass, suggesting that testosterone at the prevalent circulating concentrations is necessary for maintenance of skeletal muscle mass in men. These data also support the role of the androgen-receptor pathway in mediating androgen effects on the muscle. Androgen administration upregulates the expression of androgen receptor in the skeletal muscle (14). Therefore, it is possible that testosterone administration increases the responsiveness of the skeletal muscle to androgen action by upregulation of its own receptor.

Although there is agreement that androgen receptors are expressed in the mammalian skeletal muscle, the exact cell type or types that express androgen receptors have not been identified. Much of the previous work on androgen receptor localization has been performed by using homogenized extracts of skeletal muscles, which precludes cellular localization. However, Doumit and colleagues (35) have demonstrated, by immunoblotting and immunohistochemical staining, that porcine satellite cells express androgen receptor immunoreactive protein. Unpublished data (Sinha-Hikim and colleagues) suggest that additional cell types in the human skeletal muscle also express androgen receptor; the precise nature of these additional cells that express androgen receptor has not been elucidated.

Muscle Pluripotent Cell Differentiation As the Primary Target of Androgen Action

Muscle growth and regeneration during postnatal development and hypertrophy is dependent on the addition of myonuclei to muscle fibers (36–38). Because the nuclei within the muscle fibers are postmitotic, new myonuclei are contributed by the satellite cells (36–38). An increase in satellite cell number is an essential antecedent of an increase in myonuclear number and muscle fiber hypertrophy (36–38). Therefore, it is not surprising that testosterone supplementation increases satellite cell number in the levator ani of rats (39,40) and the skeletal muscle of men (10). The uncommitted pluripotent stem cells of mesodermal origin that are resident within the muscle serve as reservoirs for the generation of new satellite cells or myoblasts during muscle regeneration or hypertrophy (36–38), and of adipocytes in the muscle and adipose deposits throughout the body (41). To explain the reciprocal changes in fat and muscle mass, and the increase in satellite cell number during testosterone administration, we hypothesized that, in addition to direct effects on protein synthesis and satellite cell replication, testosterone promotes the commitment of pluripotent precursor cells into the myogenic lineage and inhibits their differentiation into the adipogenic lineage.

We tested this hypothesis by using pluripotent mesenchymal C3H10T1/2 cells (42) that, upon azacytidine treatment, are capable of differentiating into muscle, fat, cartilage, and bone cells; these cells have been employed widely as a model for studying the regulation of myogenic and adipogenic lineage determination (43). Commitment of C3H10T1/2 cells to myogenic lineage is associated with early activation of muscle-specific transcription factors such as MyoD, myogenin, and myf5, followed by the expression of desmin and MHC II in terminally differentiated cells. Similarly, peroxisomal proliferator-activated receptor-γ-2 (PPAR-γ-2) and CCAAT/enhancer binding protein α (C/EBPα) are key transcription factors necessary for adipogenic differentiation. We determined the effects of testosterone and dihydrotestosterone (DHT), two potent androgens, on the differentiation of these pluripotent cells into myogenic and adipogenic lineages (42).

Coincubation of C3H10T1/2 cells with testosterone and DHT was associated with higher number of MyoD+ myogenic cells and MHC+ myotubes (Figure 3) (42). MyoD and MHC mRNA and protein levels that are markers of myogenic differentiation increased dose dependently in response to testosterone and DHT treatment. Both testosterone and DHT decreased the number of adipocytes; correspondingly, these androgens down-regulated the expression of PPAR-γ-2 mRNA and PPAR-γ-2 and C/EBPα proteins that are markers of adipogenic differentiation (Figure 3). Androgen receptor mRNA and protein expression was low at baseline, but increased after testosterone or DHT treatment. Significant effects of testosterone on myogenesis and adipogenesis were observed at concentrations that bracket its physiological concentrations in the plasma of healthy young men; higher concentrations were associated with greater stimulation of myogenesis than physiological concentrations. The effects of testosterone and DHT on myogenesis and adipogenesis were blocked by bicalutamide. Hence, testosterone and DHT regulate lineage determination in mesenchymal pluripotent cells by promoting their commitment to myogenic lineage and inhibiting their differentiation into adipogenic lineage through an androgen receptor-mediated pathway.

The observation that differentiation of pluripotent cells is androgen dependent provides a unifying explanation for the reciprocal effects of androgens on muscle and fat mass in men (42). These data do not exclude the possibility that testosterone might act at one or more additional steps in the myogenic and/or adipogenic pathways (Figure 4). It is possible that androgens might have additional effects on muscle protein synthesis, satellite cell replication, myoblast fusion, myogenic progression to fully differentiated fibers, and one or more steps in the adipogenic differentiation pathway (Figure 4). For instance, testosterone has been reported to increase satellite cell replication in vitro and in vivo in the levator ani muscle of the rat (39,40). However, the reciprocal effects of androgens on myogenic and adipogenic differentiation suggest that these hormones likely act at sites that are proximal to both the myogenic and adipogenic differentiation pathways, and involve mechanisms for lineage determination in mesenchymal precursor cells. The molecular mechanisms by which androgens regulate lineage commitment are unknown. Previous studies have suggested that the Wnt signaling pathway plays an important role in lineage determination in pluripotent stem cells (44). Further studies are needed to determine the role of Wnt and other signaling pathways in mediating androgen action on pluripotent stem cell differentiation.

Biologic Basis of Tissue-Specific Differences in Androgen Responsiveness

Studies in male rats and healthy men have demonstrated that different androgen-sensitive organ systems have different testosterone dose–response relationships. Thus, most measures of sexual function in men and serum prostate-specific antigen levels are normalized at testosterone doses that are at the lower end of the normal male range. In contrast, the anabolic effects on the skeletal muscle require higher doses and concentrations of testosterone, and are linearly related to testosterone concentrations in a range that is clearly supraphysiological. It is generally believed, but has not been unequivocally demonstrated in controlled trials, that different skeletal muscles differ significantly in their anabolic response to androgen administration. It is particularly intriguing that levator ani, which has many morphological features of a skeletal muscle, undergoes marked changes in its mass after castration and testosterone supplementation. The magnitude of the change in levator ani muscle mass after castration and androgen administration is substantially greater than that observed in any other muscle group. The change in levator ani muscle mass has been widely used as a bioassay of androgenic activity. Androgen receptor protein is expressed at a higher level in the levator ani muscle than in other skeletal muscles of the rodent. The mechanistic basis of these tissue-specific differences in androgen responsiveness is not known; the difference in androgen receptor density in different muscle groups has been invoked. It is more likely that differences in the expression and recruitment of tissue-specific coactivators and corepressors account for the observed tissue-specific dose–response relationships. Only a single androgen receptor type has been demonstrated in all the tissues that have been studied, and we do not know whether there are androgen receptor subtypes that might explain tissue-specific differences in androgen responsiveness.

Role of 5-alpha Reduction of Testosterone in Muscle

We do not know whether conversion of testosterone to DHT is required for mediating the androgen effects on the muscle. The enzyme steroid 5-alpha-reductase that converts testosterone to DHT is expressed at low concentrations within the muscle (45). Men with benign prostatic hypertrophy who are treated with a 5-alpha reductase inhibitor do not experience muscle loss. Similarly, individuals with congenital 5-alpha-reductase deficiency have normal muscle development at puberty (46). These data suggest that 5-alpha reduction of testosterone is not obligatory for mediating its effects on the muscle. However, there are significant constraints in the interpretation of data from both of these models. For instance, all the known patients of

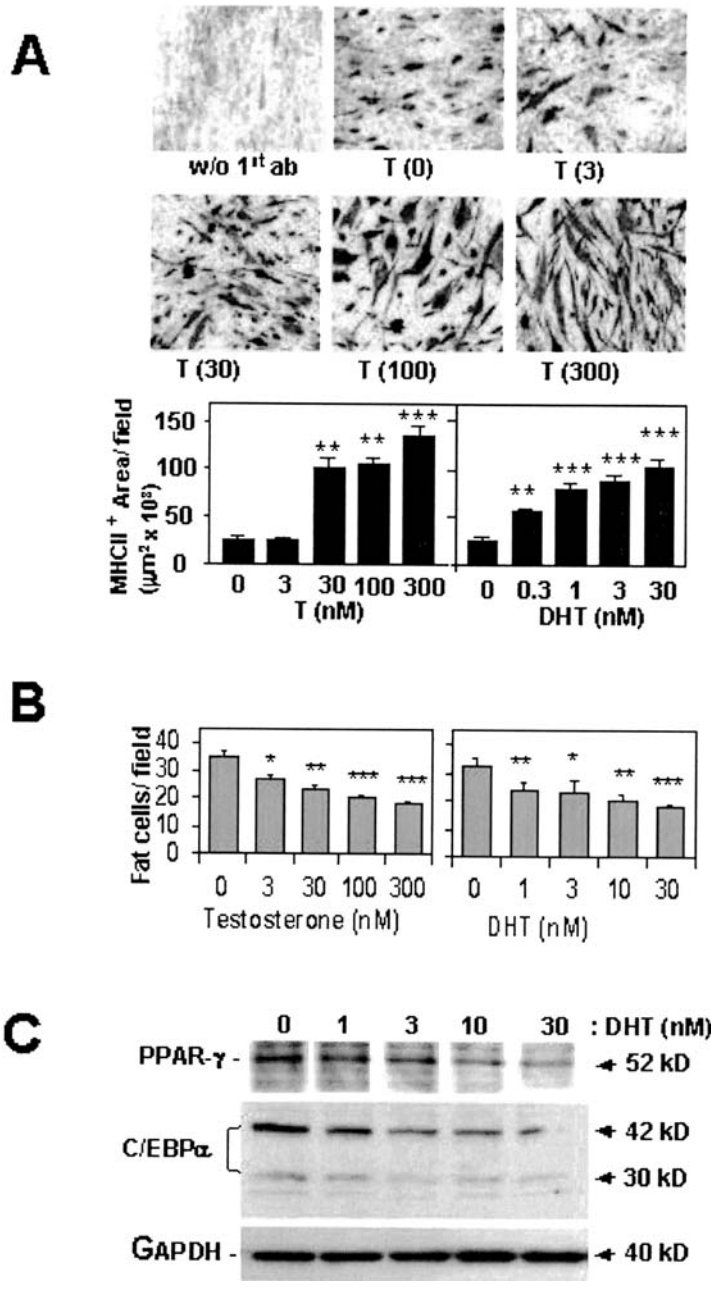

Figure 3. Effects of testosterone supplementation on myogenic and adipogenic differentiation in C3H10T1/2 pluripotent cells [adapted with permission (42)]. **A**, C3H 10T1/2 cells in culture were treated with graded concentrations (0, 3, 30, 100, and 300 nM) of testosterone (T). The area of myosin heavy chain type II (MHCII) positive myotubes was measured by image analysis, as shown in the bar diagram. The negative control did not contain the first antibody (without first Ab). The data are mean ± *SEM* (standard error of mean). *P* values versus control, $^{**}p < .01$; $^{***}p < .001$). Magnification is ×100. **B**, Effects of testosterone and dihydrotestosterone (DHT) on the number of fat cells in C3H10T1/2 cells treated with graded concentrations of testosterone or DHT. The average number of adipocytes was calculated for each ×100 high-power field. P values versus control wells, $^{*}p = .02$; $^{**}p < .004$; $^{***}p < .001$). **C**, Effects of graded concentrations of DHT on PPAR-γ-2 and C/EBPα protein expression. GAPDH served as a control. PPAR-γ-2 = peroxisomal proliferator-activated receptor-γ-2; C/EBPα = CCAAT/enhancer binding protein α; GAPDH = glyceraldehyde-3-phosphate dehydrogenase.

5-alpha reductase deficiency have had mutations of type 2 isoform of 5-alpha reductase. The affected individuals have serum DHT levels that are lower than age-matched controls, but are not zero. We do not know whether the low circulating DHT levels are derived from the activity of type 1 5-alpha reductase isoform or the result of low levels of 5-alpha reductase activity of the mutant type 2 isoform. Similarly, finasteride is an inhibitor of only the type 2 isoform. Furthermore, in the doses used clinically, it inhibits the type 2 isoform incompletely so that the circulating levels of DHT in finasteride-treated men are decreased but are still significantly above zero. Therefore, it remains unclear whether conversion of testosterone to DHT is obligatory for mediating androgen effects on the muscle. This issue is of

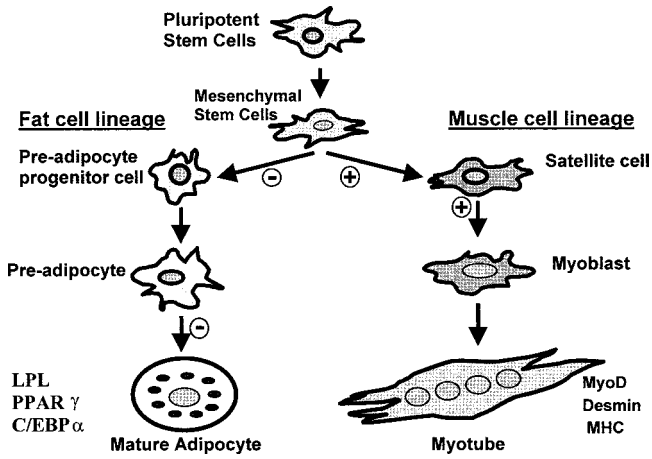

Figure 4. A schematic representation of the hypothetical sites in pluripotent stem cell differentiation at which testosterone might act to affect body composition. Testosterone has been shown to stimulate mesenchymal pluripotent cell commitment into the myogenic lineage and inhibit the differentiation of these cells into the adipogenic lineage. In addition, testosterone has been reported to stimulate satellite cell replication and inhibit the differentiation of preadipocytes into adipocytes. Thus, testosterone action at multiple sites in this cascade might serve to amplify androgen effects on myogenesis and adipogenesis. Testosterone supplementation also stimulates muscle protein synthesis and inhibits muscle protein degradation; these actions could also contribute to muscle fiber hypertrophy. MHC = myosin heavy chain; LPL = lipoprotein lipase; PPAR-γ-2 = peroxisomal proliferator-activated receptor-γ-2; C/EBPα = CCAAT/enhancer binding protein α.

considerable clinical and therapeutic importance because if 5-alpha reduction were not obligatory for mediating the anabolic effects of testosterone, then the development of selective androgen receptor modulators that do not undergo 5-alpha reduction, or administration of testosterone along with an effective 5-alpha reductase inhibitor, would be therapeutically attractive.

Role of CYP19aromatase in Mediating Testosterone Effects on Muscle

The mice that are null for the P450-linked CYParomatase gene (47) have a higher fat mass and lower muscle mass than their wild-type controls. As they grow older, the aromatase knock-out mice accumulate a greater amount of intraabdominal fat than wild-type controls (47).

After menopause, women tend to gain weight and experience an increase in body mass index (48) mostly due to fat mass accumulation (49,50); this weight gain is attenuated in women who receive estrogen replacement therapy (49,50). These data contradict widely held notion that hormone replacement therapy is associated with significant weight gain. Taken together, the collective body of experimental data suggests that aromatization of testosterone might also be important in mediating androgen effects on body composition. Further studies are needed to determine the important role of estrogens in regulation of body composition.

Synopsis

The hypothesis that androgens regulate body composition by modulating lineage determination in mesenchymal pluripotent cells provides a unifying explanation that reconciles the observed effects of testosterone administration on muscle and fat mass and satellite cell number in men. Additional downstream effects of testosterone in the myogenic and adipogenic cascades may provide a mechanism for amplifying androgen effects. The signaling pathways by which androgens determine cell fate and the molecular basis of the tissue-specific differences in androgen responsiveness are not known. The potential importance of these changes to the treatment of sarcopenia and body fat changes associated with aging in both men and women represents an extremely important area for future research (54–56).

Acknowledgment

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