An overview of the endocrinology of skeletal muscle

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Endocrine regulation of the balance between skeletal muscle anabolism and catabolism has been investigated extensively. Factors determining whether hormones exert anabolic or catabolic influences are multifaceted and often unclear. Testosterone, growth hormone, insulin and insulin-like growth factor-I have complex anabolic effects, some of which have only recently been elucidated, and are important regulators of muscle remodeling, whereas glucocorticoids have direct catabolic effects and induce muscle protein loss. The effects of estrogen are poorly understood and warrant further study. We review recent literature and evaluate the hormones driving skeletal muscle anabolism and catabolism, which ultimately dictate the endocrinology and metabolism of skeletal muscle in humans. Understanding hormonal regulation of skeletal muscle remodeling might facilitate development of improved hormone-mediated therapies for muscle wasting conditions.

Hormones are key regulators of human muscle metabolism in both health and disease. Despite the fact that human skeletal muscle tissue comprises ~40–45% of total body weight, and is one of the most metabolically active tissues in the body, its metabolic influence is often overlooked. Besides its obvious importance for human locomotion, the metabolic flexibility of muscle, in addition to its substrate storage capacity, make it an ideal hormonal target. Skeletal muscle serves as a seemingly endless repository of protein and free amino acids, in addition to providing precursors for glucose via gluconeogenesis. Human skeletal muscle protein undergoes continuous remodeling, which defines the delicate balance between synthesis and breakdown during growth, health, disease and aging. The net synthesis of protein or protein accretion occurs only when protein synthesis exceeds protein breakdown. Conversely, a net loss of protein occurs when protein breakdown exceeds protein synthesis, such as during a period of fasting or catabolic illness or injury. The homeostatic balance of muscle is affected by fasting [1,2], feeding [3,4], exercise [5,6], aging [7,8] and disease [9,10]. Hormones such as testosterone, growth hormone (GH), insulin, insulin-like growth factor-I (IGF-I) and glucocorticoids (GCs) have profound influences on human skeletal muscle and are important regulators of this remodeling process. Ultimately, hormones are responsible for modulating the swing towards positive or negative muscle protein balance, which can significantly alter the health status of an individual. Although many issues of hormone action remain unresolved with regard to skeletal muscle, we discuss here our current understanding of the actions of testosterone, GH–IGF-I, estrogen, insulin, myostatin and GCs on skeletal muscle anabolism and catabolism.

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Anabolic hormones

Anabolic hormones stimulate muscle growth in humans by increasing protein synthesis, by decreasing protein breakdown or both. How a specific hormone exerts its anabolic action on muscle depends on factors such as age, sex, duration of androgen exposure, amount of androgen administered (i.e. physiological versus supraphysiological doses) and clinical status (i.e. hypogonadal, GH-deficient, cancer or trauma). Our understanding of the in vivo actions of hormones both at the whole-body level and the level of the muscle has greatly advanced owing to the use of isotopic tracer technologies [11]. Furthermore, the identification of specific genes responsible for induction of protein synthesis in human and animal muscle has given scientists an excellent understanding of the basic process. However, hormonal regulation of muscle protein metabolism varies among species, and in some cases has directionally opposite protein metabolic effects on muscle.

Testosterone and skeletal muscle in men

Androgens are biologically diverse, targeting both reproductive and non-reproductive tissues, such as skeletal muscle. Much of the focus on androgens and testosterone has been aimed at hypogonadal men [12–18] or those suffering a particular muscle-wasting disease [19,20] or...
trauma [10,21] resulting in muscle loss. Furthermore, disease-driven muscle catabolism, such as that induced by AIDS, [22] correlates highly with circulating androgen levels. It is estimated that 50% of men above the age of 50 years are hypogonadal [23,24], although not all are symptomatic. The use of anabolic agents as replacement therapies for typical hypogonadism or circumstances of trauma-induced hypogonadism (e.g. burns or severe trauma) are clinically justified. In the case of severe trauma or burns, testicular steroid production is greatly decreased for several months after injury, despite normal levels of luteinizing hormone [25]. Regardless of the cause of the deficiency, positive outcomes from androgen therapy might include a decrease in muscle protein breakdown, an increase in muscle protein synthesis, enhanced skeletal muscle mass and increased muscle strength.

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Although the rationale for seeking androgen therapy varies among hypogonadal men, the primary goal in the older male is to improve or maintain muscle strength and functional capability [15,26]. Hypogonadal elderly men receiving testosterone replacement therapy show decreases in muscle protein breakdown [13] and increases in protein synthesis [14], lean body mass [12,13,16,18,27] and muscular strength [12–14,17,27]. To date, several testosterone replacement studies have shown a disproportionate response between increases in muscle strength and muscle mass, with muscle mass more often increasing without proportional increases in muscle strength [16–18,28]. Thus, there is a clear need for a large-scale, longterm testosterone replacement study in older men to determine the benefit to risk ratio of testosterone administration.

Unlike the severe losses in strength and muscle mass that accompany diseases such as AIDS, strength often decreases to a greater extent than muscle mass with aging [29,30]. Moreover, declines in functional capacity are probably exacerbated by lower levels of circulating testosterone. Direct support for this hypothesis comes from a 12-year longitudinal study showing that a reduction in muscle cross sectional area was a major contributor to the reduction in muscle strength seen with aging [31]. In fact, there is a positive correlation between levels of circulating testosterone and the capacity to improve strength in older adults involved in a resistance training program [32]. Furthermore, in individuals with restricted or impaired functional ability, the possibility of increasing muscle strength and lean body mass via the administration of therapeutic doses of androgen alone would be of considerable benefit.

**Testosterone and skeletal muscle in women**

Women, not unlike men, experience age-associated losses in skeletal muscle mass and strength [33]. Similar to men, levels of circulating testosterone in women decline considerably with age, with a decline of approximately one-half of all circulating testosterone taking place from age 20 to 40 [34]. Although testosterone therapy has been shown to be effective at improving well-being, mood and sexual function in premenopausal women [34], body mass index and levels of serum estrone, estradiol and 25-hydroxy vitamin D correlative better with skeletal muscle mass in women over the age of 65 [33]. Certainly, the demonstrated benefits of testosterone on libido, muscle, bone and cognition in men warrant further study of androgen therapy regimens in older women; namely, as a circulating precursor for local synthesis of estrogen in target tissues, where it acts in an ‘intracrine’ or paracrine fashion.

**GH–IGF-I and skeletal muscle**

The effect of GH on skeletal muscle is an area of uncertainty that has resulted in abuse of the hormone in the athletic community and as an anti-aging hormone. Since Rudman described the positive effects of recombinant GH (rhGH) in healthy older men [35], the hormone has received world-wide attention, and anecdotal stories of amazing responses to the hormone have been used for financial gain. In response to this, recent scientific reviews of GH and its effects on skeletal muscle have described relatively modest effects of the hormone on anabolism [36–38]. Although it is important for the scientific community to separate fact from popular account, the potential of the hormone should not be completely discarded in our attempts to stem its widespread abuse.

The most convincing evidence that GH can improve muscle strength and function can be found in the studies assessing the effects of rhGH in GH-deficient adults. Svensson and colleagues found that rhGH, when given to GH-deficient adults over five years, increased isometric and isotonic knee flexor and extensor strength, in addition to improving hand grip strength [39]. They also found that women had less of an improvement in strength than did men, and that proximal muscle groups are more responsive to GH than are distal muscle groups [39]. Although these positive effects on skeletal muscle are well documented, the length of time taken for the effects to become evident (years), as opposed to the more dramatic effects of androgens (weeks and months), have meant that the anabolic response of skeletal muscle to GH has been classified as minimal.

The efficacy of GH replacement is far less convincing in older men and women. Blackman and colleagues found that rhGH, when given to older men and women for 26 weeks, with or without sex steroids, increased lean body mass and decreased fat mass, but had little effect on muscle strength [40]. Only the combination of GH and testosterone in older men increased muscle strength and maximal oxygen capacity marginally, whereas there was no significant change in women receiving GH and estrogen [40]. Moreover, the adverse effects of GH on glucose metabolism resulted in the development of diabetes and glucose intolerance in several subjects [40]. The enhanced
insulin resistance is caused by GH stimulation of lipid substrate oxidation resulting in increased serum fatty acid concentrations [41]. In addition, GH did not further improve muscle strength when administered to children with burns undergoing a 12-week exercise training program, with and without GH administration [42]. Muscle strength was increased primarily by exercise [42].

Despite this minimal response of muscle to GH, it could still be an important contributor to muscle anabolism, because it does stimulate IGF-I synthesis in muscle [43,44]. In young men made hypogonadal by administration of a gonadotropin-releasing hormone (GnRH) agonist, rhGH, increased concentrations of IGF1 mRNA in muscle biopsy samples obtained from the vastus lateralis [43]. In older men, administration of rhGH for one month also increased IGF1 mRNA concentrations in vastus lateralis muscle biopsy samples [44]. IGF1 expression is associated with skeletal muscle hypertrophy, as best demonstrated by animal studies where the IGF1 gene is selectively overexpressed in skeletal muscle [45]. Moreover, one mechanism by which IGF-I causes skeletal muscle hypertrophy might be through the stimulation of satellite cell replication; that is, by accelerating the progression of cell division [46]. There are many different triggers for local IGF1 expression, including androgens [13,47], mechanical load [48] and exercise [49]. Chronic inflammation, as indicated by interleukin-6 synthesis, is thought to cause loss of physical function by inhibiting local IGF1 skeletal muscle expression [50]. As an added complexity, multiple splice variants of IGF-I are found in skeletal muscle in response to different stimuli. Goldspink has described an alternative splice variant of IGF-I named mechano growth factor (MGF) that is produced in response to muscular activity [51]. Following heavy resistance exercise in young and older men, the expression of mRNA encoding MGF was increased in the young men, but an IGF-1 isoform (IGF-IEa), which is similar to hepatic endocrine IGF-I but synthesized in muscle, is not altered during the exercise bout [49]. Moreover, older men did not increase MGF synthesis in response to the exercise bout [49]. The increase in IGF1 mRNA expression in skeletal muscle is probably driven by increased transcription of the IGF1 gene [52]. Therefore, as more is understood about the mechanisms controlling the expression of IGF1 in skeletal muscle and the mechanisms whereby IGF-I stimulates muscle hypertrophy, improved paradigms of rhGH administration or protocols using GH in combination with other agents could still make GH an important anabolic hormone for skeletal muscle function.

Insulin and skeletal muscle
Aside from its role in the regulation of glucose and fatty acid metabolism, insulin is also an important regulator of skeletal muscle protein metabolism. Although its exact mechanism of action has been widely debated, insulin is clearly a potent anabolic stimulus for muscle protein metabolism, both when given alone [53,54] and in combination with amino acids [55]. Conversely, conditions of insulin deficiency are characterized by a reduction in skeletal muscle protein synthesis, with diminished mammalian target of rapamycin-mediated signaling and eukaryotic initiation factor 2B activity probably responsible for the reduction in synthetic rates of muscle protein [56]. The importance of amino acid availability has been established from studies demonstrating that the combination of insulin and amino acids is more beneficial than either stimulus alone [57,58]. Furthermore, the effectiveness of insulin as an anabolic agent for skeletal muscle protein is highly dependent upon, and correlated with, the rate of appearance of amino acids in the intracellular compartment. In circumstances where intracellular amino acid availability has been reduced, such as during insulin infusion following exercise, protein synthesis is unaffected by insulin [59]. Future studies with insulin should focus on establishing the molecular pathway(s) responsible for its action on skeletal muscle, in addition to the role of insulin resistance in muscle protein metabolism.

Estrogen and skeletal muscle
The effect of estrogen on skeletal muscle function has received minimal mechanistic scientific investigation. Expression of the estrogen receptor α has been demonstrated in skeletal muscle, so estrogen might have effects in this tissue [60]. The studies assessing muscle strength and hormone replacement therapy (HRT) have been equivocal. Some show an improvement in strength, whereas others do not, as recently reviewed [61]. The most recent studies indicate that estrogen has no significant effects on muscle mass and strength in postmenopausal women. Kenny and colleagues found that postmenopausal women taking HRT showed no improvement in age-associated sarcopenia [62]. Similarly, Blackman and colleagues found no improvement in muscle strength in postmenopausal women receiving estrogen by patch for 26 weeks [40]. Given the current concerns over the use of estrogen, particularly in postmenopausal women, and the mostly negative studies regarding the effects of estrogen on muscle strength, this area of investigation will probably not be as actively pursued in the near future. Nevertheless, given that there is only a limited understanding of the mechanisms of estrogen actions in skeletal muscle, it should not be excluded from further study.

Role of local estrogen biosynthesis in men and women
In recent years, it has become apparent that circulating androgenic steroids play an important role in the physiology of women and men, and the well-being of the elderly [63]. Considerable emphasis has been placed on the regulation of extragonadal estrogen biosynthesis, in particular that which occurs in adipose, bone and brain tissue. In postmenopausal women, the mesenchymal cells of the adipose tissue are the primary source of estrogen [63], and thus, the extent of a woman's adiposity determines the degree of estrogenization. This in turn affords some protection against diseases such as osteoporosis and, by contrast, increases the risk of breast cancer. In men, it is estimated that the testes account for no more than 15% of circulating estrogens; thus, local biosynthesis of estrogens has considerable physiological significance throughout life. In particular, estrogen production in bone plays as vital a role in the maintenance of bone mineralization,
and hence the prevention of osteoporosis, in men as it does in women [64]. Moreover, it has been suggested that estrogens play a role in male sexual behavior, and might influence the maintenance of cognitive function and the prevention of Alzheimer’s disease. Finally, although the importance of the enzymatic role of aromatase is clear, the extent and breadth of this topic is beyond the scope of this review.

Catabolic hormones

**GCs and skeletal muscle**

Severe traumatic physical injury, such as a burn injury, initiates a hypermetabolic response characterized by extreme hypercortisolemia and hypoandrogenemia. This predominantly catabolic hormonal environment acts to initiate skeletal muscle protein breakdown by dramatically increasing turnover and at the same time favoring a net efflux of amino acids from muscle intracellular pools. The hormonally driven imbalance between muscle protein synthesis and breakdown is further exacerbated by muscular inactivity [65], the apparent disruption in postabsorptive protein metabolism, and the diminished anabolic response of the muscle to feeding [66]. Not even high caloric intake can offset the loss of lean body mass associated with trauma-related hypermetabolism [67]. Most research has focused on methods to counteract the negative hormonal influence on skeletal muscle via androgen replacement, exercise and nutrition interventions. Although these interventions have been marginally successful, very little is understood regarding the events that initiate the neuroendocrine response to trauma.

**Myostatin and skeletal muscle**

Whereas IGF-I is associated with skeletal muscle hypertrophy, myostatin is associated with muscle loss and wasting. Myostatin (also designated growth differentiation factor 8) is a member of the transforming growth factor β superfamily, which was first recognized as important in muscle physiology when a deletion of the gene was detected in a double-muscled phenotype of cattle [68]. This initial finding resulted in several transgenic manipulations of myostatin in mice in an attempt to define its mechanism of action. Myostatin-deficient mice also display skeletal muscle hypertrophy [69], and develop a greater loss of muscle mass than do normal mice during hindlimb suspension [70]. This finding implies that myostatin-deficient mice cannot mount a myogenic response to muscle atrophy. As a corollary, muscle-specific synthesis of myostatin in male mice results in lower muscle mass [71]. However, this response of skeletal muscle is only found in male mice, for as yet undetermined reasons. Expression of the gene encoding myostatin is increased in the skeletal muscle of mice treated with dexamethasone to induce skeletal muscle atrophy [72]. Although the basic mechanism for myostatin suppression of skeletal muscle hypertrophy is inhibition of myoblast proliferation and differentiation [73,74], its regulation is complex because it associates with multiple proteins that can stimulate and inhibit its actions [75].

Studies of humans are generally consistent with data from the animal models described above. Muscle wasting in men with HIV infection is associated with higher serum and intramuscular concentrations of myostatin-immunoreactive protein [76]. Serum myostatin-immunoreactive protein concentrations are increased in 60–92-year-old men and women with muscle wasting from sarcopenia of aging [77]. Concentrations of mRNA encoding myostatin are decreased in skeletal muscle of young and older men and women after heavy-resistance exercise [78]. However, expression of mRNA encoding myostatin in skeletal muscle of older men is not different from that in younger men [79], and low-dose GH and testosterone administration in older men does not alter this expression [80]. Therefore, there is still a significant amount of knowledge to be gained about the actions of myostatin in skeletal muscle. Two recent studies, one showing that myostatin regulates muscle mass not only during embryogenesis but throughout development [81], and the other showing that myostatin deficiency in a mouse model of muscular dystrophy improved muscle function [82], give great promise to the possibility of using myostatin antagonists in syndromes of muscle wasting to promote muscle growth and improved muscle function.

**Summary**

The endocrinology of skeletal muscle is highly complex, and many issues of hormone action remain unresolved with regard to skeletal muscle and protein metabolism. As more is understood regarding the mechanism of action of these hormones on muscle anabolism and catabolism, hormone-mediated therapies could be developed to treat clinical conditions such as age-related sarcopenia and muscle wasting with chronic disease or trauma.

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**References**

62 Kenny, A.M. et al. (2003) Prevalence of sarcopenia and predictors of skeletal muscle mass in nonobese women who are long-term users of...
64 Simpson, E. et al. (2000) The role of local estrogen biosynthesis in males and females. Trends Endocrinol. Metab. 11, 184–188

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