

REVIEW

Mechanisms of glucocorticoid-induced myopathy

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Abstract

Glucocorticoid-induced muscle atrophy is characterized by fast-twitch or type II muscle fiber atrophy illustrated by decreased fiber cross-sectional area and reduced myofibrillar protein content. Muscle proteolysis, in particular through the ubiquitin–proteasome system (UPS), is considered to play a major role in the catabolic action of glucocorticoids. The stimulation by glucocorticoids of the UPS is mediated through the increased expression of several atrogenes ('genes involved in atrophy'), such as atrogen-1 and MuRF-1, two ubiquitin ligases involved in the targeting of protein to be degraded by the proteasome machinery. Glucocorticoids also exert an anti-anabolic action by blunting muscle protein synthesis. These changes in protein turnover may result from changes in the production of two growth factors which control muscle mass, namely IGF-I and myostatin respectively

anabolic and catabolic toward the skeletal muscle. The decreased production of IGF-I as well as the increased production of myostatin have been both demonstrated to contribute to the muscle atrophy caused by glucocorticoids. At the molecular level, IGF-I antagonizes the catabolic action of glucocorticoids by inhibiting, through the PI3-kinase/Akt pathway, the activity of the transcription factor FOXO, a major switch for the stimulation of several atrogenes. These recent progress in the understanding of the glucocorticoid-induced muscle atrophy should allow to define new therapies aiming to minimize this myopathy. Promising new therapeutic approaches for treating glucocorticoid-induced muscle atrophy are also presented in this review.

Journal of Endocrinology (2008) **197**, 1–10

Introduction

The catabolic effects of glucocorticoids have been well known for many years. Either as drugs used to treat several medical conditions or as endocrine hormones released in response to many stress situations, glucocorticoids may cause skeletal muscle atrophy. The resulting weakness of peripheral and respiratory muscles may have major clinical implications such as loss of quality of life, fatigue, impaired wound healing, compromised lung function, and poor immune response. The purpose of this review is to describe the cellular and molecular mechanisms of the catabolic actions of glucocorticoids toward skeletal muscle. Better understanding of the mechanisms of the steroid myopathy should lead to the development of new therapeutic avenues to preserve muscle mass and function in patients exposed to high doses of glucocorticoids.

insulinopenia, etc.) are associated with increase in circulating glucocorticoids levels (Lecker *et al.* 1999), suggesting that these hormones could trigger the muscle atrophy observed in these situations. In the case of sepsis, cachexia, starvation, and severe insulinopenia, adrenalectomy or treatment with a glucocorticoid receptor antagonist (RU-486) attenuate muscle atrophy, indicating that glucocorticoids are in part responsible for this muscle loss. In addition to glucocorticoid excess, several other factors such as poor nutrition, cytokines and bed resting may contribute to muscle atrophy observed in these wasting conditions (Hasselgren 1999, Lecker *et al.* 1999). In contrast, glucocorticoids do not appear to be required for disuse atrophy (Tischler 1994), but may clearly exacerbate the deleterious effects of disuse on skeletal muscle mass (Fitts *et al.* 2007).

Role of glucocorticoids in muscle atrophy of wasting conditions

Many pathological conditions characterized by muscle atrophy (sepsis, cachexia, starvation, metabolic acidosis, severe

Characterization of the glucocorticoid-induced muscle atrophy

Skeletal muscle atrophy is characterized by a decrease in the size of the muscle fibers. Glucocorticoids have been shown to cause atrophy of fast-twitch or type II muscle fibers

(particularly IIx and IIb) with less or no impact observed in type I fibers (Dekhuijzen *et al.* 1995, Fournier *et al.* 2003). Therefore, fast-twitch glycolytic muscles (i.e., tibialis anterior) are more susceptible than oxidative muscles (i.e., soleus) to glucocorticoid-induced muscle atrophy. The mechanism of such fiber specificity is not known.

Mechanisms of glucocorticoid-induced muscle atrophy

In skeletal muscle, glucocorticoids decrease the rate of protein synthesis and increase the rate of protein breakdown (Tomas *et al.* 1979, Goldberg *et al.* 1980, Lofberg *et al.* 2002) contributing to atrophy. The severity and the mechanism for the catabolic effect of glucocorticoids may differ with age. For example, glucocorticoids cause more severe atrophy in older rats compared with younger rats. Furthermore, glucocorticoid-induced muscle atrophy results mainly from increased protein breakdown in adult rats but mostly from depressed protein synthesis in the aged animals (Dardevet *et al.* 1998).

Anti-anabolic action of glucocorticoids

The inhibitory effect on protein synthesis results from different mechanisms. First, glucocorticoids inhibit the transport of amino acids into the muscle (Kostyo & Redmond 1966), which could limit the protein synthesis. Secondly, glucocorticoids inhibit the stimulatory action of insulin, insulin-like growth factor-I (IGF-I), and amino acids (in particular leucine), on the phosphorylation of eIF4E-binding protein 1 (4E-BP1) and the ribosomal protein S6 kinase 1 (S6K1), two factors that play a key role in the protein synthesis machinery by controlling the initiation step of mRNA translation (Shah *et al.* 2000a,b, Liu *et al.* 2001, 2004). Finally, there is also evidence that glucocorticoids cause muscle atrophy by inhibiting myogenesis through the downregulation of myogenin, a transcription factor mandatory for differentiation of satellite cells into muscle fibers (te Pas *et al.* 2000).

Catabolic action of glucocorticoids

The stimulatory effect of glucocorticoids on muscle proteolysis results from the activation of the major cellular proteolytic systems (Hasselgren 1999), namely the ubiquitin-proteasome system (UPS), the lysosomal system (cathepsins), and the calcium-dependent system (calpains). The protein degradation caused by glucocorticoids affects mainly the myofibrillar proteins as illustrated by the increased excretion of 3-methyl histidine (Zamir *et al.* 1991, Tiao *et al.* 1996). To activate the protein degradation, glucocorticoids stimulate the expression of several components of the UPS either involved in the conjugation to ubiquitin of the protein to be degraded (ubiquitin; 14 kDa (E2), a conjugating enzyme; atrogin-1 and MuRF-1, two muscle-specific (E3) ubiquitin ligases;

Bodine *et al.* 2001) or directly responsible for the protein degradation by the proteasome (several subunits of the 20S proteasome; Mitch & Goldberg 1996). This gene transcription activation is associated with an increased rate of protein ubiquitination and increased proteolytic activities of the proteasome itself (Combaret *et al.* 2005). Using blockers of the different proteolytic pathways, evidence was found that glucocorticoids stimulate not only the UPS-dependent proteolysis but also the calcium-dependent and lysosomal protein breakdown (Hasselgren 1999). The role of lysosomal system in the atrophic effect of glucocorticoids is also suggested by the increase in cathepsin L muscle expression in glucocorticoid-treated animals (Deval *et al.* 2001, Komamura *et al.* 2003, Sacheck *et al.* 2004). Because the proteasome does not degrade intact myofibrils, it is thought that actin and myosin need to be dissociated (probably by calpains) from the myofibrils before they can be degraded by the UPS (Hasselgren & Fischer 2001). Finally, some *in vivo* data also suggest that caspase-3 can be implicated in the myofibrillar proteins breakdown induced by glucocorticoids. Indeed, in glucocorticoid-dependent muscle wasting models, such as diabetes mellitus and chronic renal failure, caspase-3 activity in muscle is increased and inhibition of caspase-3 by Ac-DEVD-CHO, a peptide inhibitor, suppresses the accelerated muscle proteolysis (Du *et al.* 2004). However, the role of glucocorticoids in the induction of caspase-3 activity in these models has not yet been explored.

Signaling pathways involved in glucocorticoid-induced muscle atrophy

FOXO

The muscle cell catabolism caused by glucocorticoids is thought to be mediated by the transcription factors FOXO. The role of these transcription factors in the glucocorticoid-induced muscle cell atrophy has been established by different observations. First, exposure of myotubes to glucocorticoids increases the FOXO gene expression, particularly -1 and -3 (Imae *et al.* 2003). Second, *in vitro* as well *in vivo*, FOXO overexpression causes muscle cell atrophy (Kamei *et al.* 2004, Sandri *et al.* 2004) together with activation of several genes characteristic of muscle cell atrophy or atrogenes such as atrogin-1, MuRF-1 and cathepsin L (Jagoe *et al.* 2002, Sandri *et al.* 2004). Finally, overexpression of a dominant negative form of FOXO-3a prevents muscle cell atrophy together with atrogin-1 induction caused by glucocorticoids *in vitro* (Sandri *et al.* 2004). Because FOXO, but not atrogin-1, overexpression is sufficient to cause muscle atrophy, it is thought that FOXO transcription factors activate a variety of genes, in addition to atrogin-1, that leads to atrophy. Taken together, these data indicate that increased expression of FOXO by glucocorticoids activates a gene transcriptional program responsible for triggering muscle atrophy. Among the genes most strongly induced in microarray analyses of muscle

atrophy due to a variety of wasting diseases are several genes (atrogin-1, MuRF-1, cathepsin L, PDK4, p21, Gadd45, and 4E-BP1) controlled by the FOXO transcription factors (Jagoe *et al.* 2002, Komamura *et al.* 2003, Lecker *et al.* 2004, Almon *et al.* 2007). The establishment of an active transcriptional program necessary for the induction of muscle atrophy has thus challenged the view that atrophy is a passive adaptation of the muscle to a lack of anabolic stimuli. All these observations support the role of FOXO in muscle atrophy induced by glucocorticoids but there is not yet direct *in vivo* evidence for the requirement of FOXO in this muscle atrophy model (Fig. 2).

mTOR

The inhibition of protein synthesis by glucocorticoids mainly results from the inhibition of *mTOR*, the kinase responsible for the phosphorylation of 4E-BP1 and S6K1. Repression of mTOR signaling results in a reduction in the initiation phase of mRNA translation with downregulation of protein synthesis. Recent studies indicate that the repression of

mTOR signaling in response to glucocorticoids is the result of enhanced transcription of REDD1, a repressor of mTOR signaling (Wang *et al.* 2006). Through an as yet unidentified mechanism, REDD1 represses mTOR function, leading to decreased phosphorylation of both 4E-BP1 and S6K1. Recent evidence suggest that mTOR signaling could also be inhibited directly by FOXO (Southgate *et al.* 2007). Whereas the effects of glucocorticoids on protein synthesis have been explained at the molecular level, comparatively little is known about how these hormones alter anabolic gene expression. Recent studies identified ATF-4 as an anabolic transcription factor that is repressed by glucocorticoids (Adams 2007). ATF-4 has been shown to be required for the activation of a genetic program for the cellular uptake of essential amino acids and the synthesis of non-essential amino acids and aminoacyl-t-RNAs. This observation suggests that glucocorticoids inhibit protein synthesis at least partially by downregulating ATF-4, which could limit intracellular amino acid availability. It is interesting to note that insulin, an anabolic hormone, has been shown to induce ATF-4 transcription, even in the presence of glucocorticoids (Fig. 1).

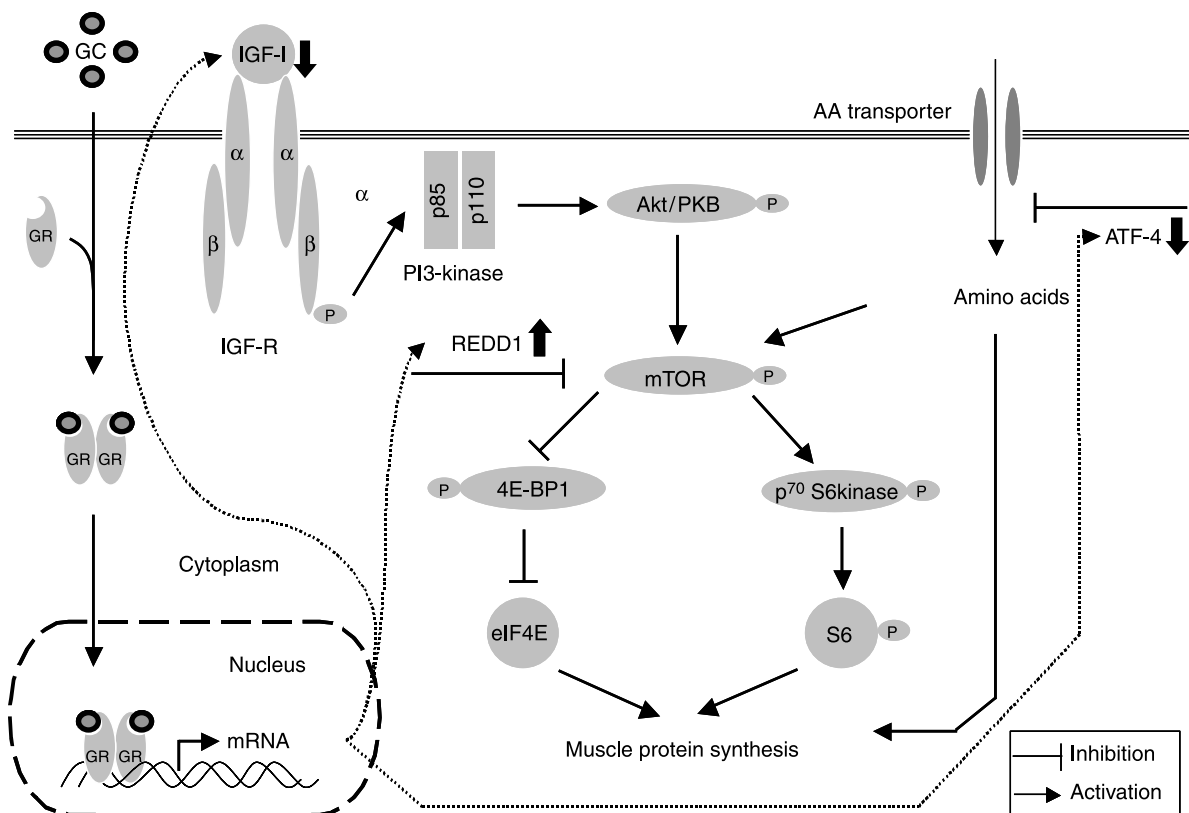


Figure 1 Alterations in protein synthesis signaling pathway induced by glucocorticoids. Inhibitory effects on protein synthesis results from different mechanisms. First, glucocorticoids (GC) impair protein synthesis by inhibiting the transport of amino acids into the muscle. Secondly, glucocorticoids inhibit the stimulatory action of insulin, IGF-I, and amino acids on eIF4E-binding protein 1 (4E-BP1) and the ribosomal protein S6 kinase 1 (S6K1) through mTOR activity repression.

GSK3 β

A downstream target of IGF-I/Akt signaling, glycogen synthase kinase 3 β (GSK3 β), which is phosphorylated and inhibited by Akt, could also be involved in the atrophic effect of glucocorticoids. GSK3 β is known to suppress protein synthesis by inhibiting eukaryotic transcription factor 2B-dependent translation (Jefferson *et al.* 1999). Furthermore, not only is inhibition of GSK3 β sufficient to cause myogenic differentiation (Van Der Velden *et al.* 2006) and muscle cell hypertrophy (Vyas *et al.* 2002) but also contributes to the hypertrophic effect of IGF-I on skeletal muscle cells (Vyas *et al.* 2002). More interestingly, inhibition of GSK3 β by overexpression of a dominant negative GSK3 β or pharmacologic inhibitors prevents the proteolysis and cell atrophy caused by glucocorticoids *in vitro* (Rommel *et al.* 2001, Evenson *et al.* 2005, Fang *et al.* 2005). The mechanism by which GSK3 β inactivation inhibits muscle protein degradation caused by glucocorticoids is not known. However, the observation that inhibition of protein degradation by GSK3 β inhibitors is associated with the blockade of the upregulation of atrogin-1 and MuRF-1 gene expression suggests that this reduction in muscle proteolysis is mediated at least in part by inhibiting the UPS (Evenson *et al.* 2005). Although the role of GSK3 β in muscle atrophy

induced by glucocorticoids has not yet been demonstrated *in vivo*, the anti-catabolic effect of GSK3 β inhibitors suggests that GSK3 β may become an important target to inhibit muscle wasting in the future (Fig. 2).

p300–C/EBP β

Finally, recent *in vitro* data suggest that glucocorticoid-induced muscle proteolysis is at least in part regulated by p300–histone acetyl transferase activity. Indeed, p300 protein levels and activity are increased, in a time- and dose-dependent manner, in dexamethasone-treated myotubes (Yang *et al.* 2005). Additionally, dexamethasone increases protein–protein interaction between p300 and C/EBP β , which increases the transcription activity of C/EBP β by acetylation (Yang *et al.* 2005). This interaction is particularly important since C/EBP β may regulate multiple genes in the UPS pathway (Penner *et al.* 2002). Finally, treatment of myotubes with p300 small interfering RNA prevents the dexamethasone-induced increase in protein degradation, whereas overexpression of wild-type p300 potentiates the effect of dexamethasone on protein degradation (Yang *et al.* 2007). Taken together, these results point out the main role of p300 in muscle proteolysis induced by glucocorticoids.

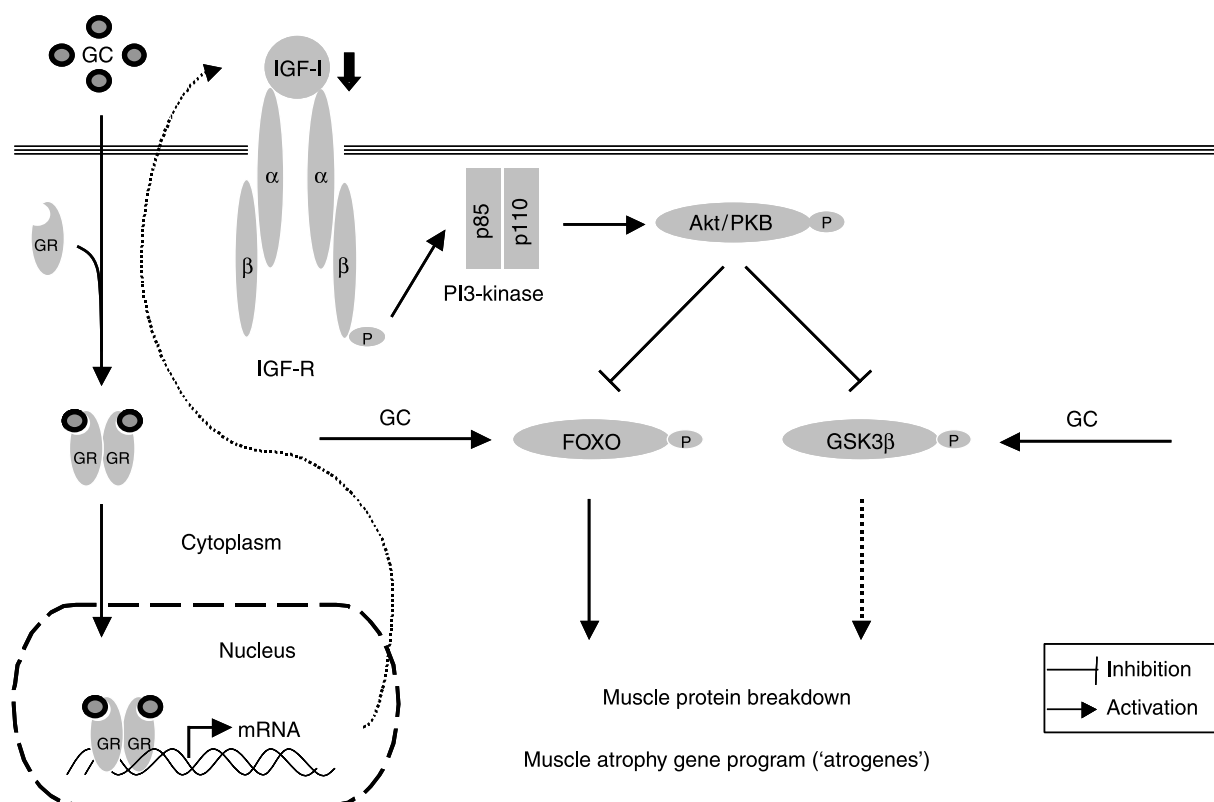


Figure 2 Alterations in protein breakdown signaling induced by glucocorticoids. Stimulatory effects on protein breakdown results from different mechanisms. First, glucocorticoids (GC) stimulate several proteolytic systems by activating transcription factor FOXO. Secondly, stimulation of GSK3 β may also be involved in the stimulatory effects of glucocorticoids on protein breakdown.

Seeing that several transcription factors involved in muscle wasting are regulated in part by acetylation (Mink *et al.* 1997, Schwartz *et al.* 2003, Chen & Greene 2005, Perrot & Rechler 2005), it appears crucial for the future to determine which proteins are acetylated in muscle atrophy and whether their acetylation controls glucocorticoid-induced muscle proteolysis.

Role of local growth factors in glucocorticoid-induced muscle atrophy

IGF-I

Glucocorticoids can also cause muscle atrophy by altering the production of growth factors that control locally the muscle mass development. Glucocorticoids inhibit the production by the muscle of IGF-I (Gayan-Ramirez *et al.* 1999), a growth factor that stimulates the development of muscle mass by increasing protein synthesis and myogenesis while decreasing proteolysis and apoptosis (Florini *et al.* 1996, Frost & Lang 2003). For these reasons, decreased muscle IGF-I has been thought to play a key role in glucocorticoid-induced muscle atrophy. This hypothesis has recently been confirmed both *in vitro* and *in vivo*. First, by activating the PI3K/Akt/mTOR pathway and blocking nuclear translocation of the transcription factor FOXO, IGF-I downregulates the different proteolytic systems (lysosomal, proteasomal, and calpain dependent) and the expression of atrogenes such as atrogen-1, MuRF-1, cathepsin L induced by glucocorticoids (Dehoux *et al.* 2004, Latres *et al.* 2005, Li *et al.* 2005). Secondly, IGF-I suppresses the muscle cell atrophy caused by glucocorticoids *in vitro* (Li *et al.* 2004, Sacheck *et al.* 2004). Thirdly, systemic administration (Tomas *et al.* 1992, Tomas 1998, Kanda *et al.* 1999, Fournier *et al.* 2003) or local overexpression of IGF-I into skeletal muscle prevents glucocorticoid-induced muscle atrophy (Schakman *et al.* 2005). Taken together, these results indicate that IGF-I has a dominant effect, overriding glucocorticoids to turn off catabolism. In addition, they support the key role of decreased muscle IGF-I in the atrophy caused by glucocorticoids. Therefore, restoration of IGF-I may provide a strategy to reverse the catabolic effects of glucocorticoid excess (Fig. 3).

Myostatin

Glucocorticoids also stimulate the production by the muscle of myostatin (Mstn; Ma *et al.* 2001, 2003, Artaza *et al.* 2002), a growth factor that inhibits the muscle mass development by downregulating the proliferation, and differentiation of satellite cells (Thomas *et al.* 2000, McCroskery *et al.* 2003) and downregulating protein synthesis (Taylor *et al.* 2001, Welle *et al.* 2006). Recent evidence collected *in vitro* indicate that Mstn also causes muscle cell atrophy by reversing the IGF-I/PI3K/Akt hypertrophy pathway. Through inhibition of Akt phosphorylation, Mstn increases the levels of active

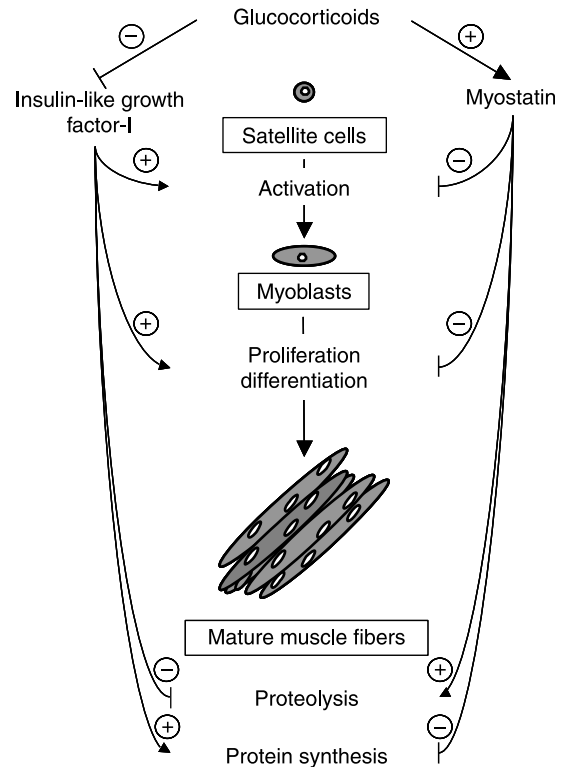


Figure 3 Local growth factors production plays a crucial role in glucocorticoid-induced muscle atrophy. Glucocorticoids can cause muscle atrophy by altering the muscle production of IGF-I and myostatin, two growth factors exhibiting opposite effects on muscle mass development. Decrease in IGF-I together with increase in myostatin both induced by glucocorticoids inhibit satellite cells activation as well as myoblast proliferation and differentiation. In mature muscle fibers, these growth factor changes cause down-regulation of protein synthesis and stimulation of protein degradation.

FOXO, allowing increased expression of atrogenes (McFarlane *et al.* 2006). Furthermore, targeted disruption of Mstn gene expression in mice leads to dramatic increase in skeletal muscle mass due to fiber hyperplasia and/or hypertrophy (McPherron *et al.* 1997, Grobet *et al.* 2003). Finally, transgenic mice that express Mstn selectively in skeletal muscle have muscle atrophy (Reisz-Porszasz *et al.* 2003, Durieux *et al.* 2007).

For these reasons, increased muscle Mstn has been thought to play a key role in glucocorticoid-induced muscle atrophy. This hypothesis has recently been confirmed *in vivo* (Gilson *et al.* 2007) using a model of Mstn knockout (KO) mice. In contrast to wild-type mice, Mstn KO mice did not develop a reduction of muscle mass nor fiber cross-sectional area after glucocorticoid treatment. This observation indicates that Mstn is mandatory for the atrophic effects of glucocorticoids on muscle. The mechanism by which Mstn deletion prevents muscle atrophy caused by glucocorticoids is not known. However, the observation that prevention of muscle atrophy

by Mstn deletion is associated with the blockade of the upregulation of atrogenes expression and proteosomal activity caused by glucocorticoids suggests that this protection of muscle mass results at least in part from the inhibition of the muscle proteolysis (Gilson *et al.* 2007). Taken together, these results suggest that increased Mstn contributes to the atrophic effects of glucocorticoids on skeletal muscle. Therefore, besides stimulating IGF-I, inhibition of Mstn may provide another strategy to reverse the catabolic effects of glucocorticoid excess (Fig. 3).

Consequences of glucocorticoid-induced muscle atrophy

Administration of high doses of glucocorticoids to animals causes not only decreased muscle mass but also muscle dysfunction characterized by reduced force and weakness (Shin *et al.* 2000). Also, in humans, a significant relationship between steroid usage and both peripheral and respiratory muscle strength has been reported in chronic pulmonary disease (Decramer *et al.* 1994) and cystic fibrosis (Barry & Gallagher 2003). Peripheral muscle weakness has also been observed in patients with Cushing's syndrome, who exhibit high levels of endogenous glucocorticoids (Khaleeli *et al.* 1983, Mills *et al.* 1999). Therefore, glucocorticoid-induced atrophy may have significant clinical implications.

Prevention of glucocorticoid-induced muscle atrophy

Growth factors

As already presented, stimulation of IGF-I and inhibition of Mstn appear promising therapeutic tools to attenuate glucocorticoid-induced muscle atrophy (Kanda *et al.* 1999). Indeed, muscle IGF-I overexpression (Schakman *et al.* 2005) or myostatin deletion (Gilson *et al.* 2007) prevents glucocorticoid-induced muscle atrophy. Therefore, IGF-I stimulation or Mstn blockade might be beneficial for a variety of myopathies, such as the ones caused by high doses of glucocorticoids. Further experiments are needed to test this possibility.

Branched chain amino acids (BCAAs)

Provision of the BCAAs mimics the effect of a complete mixture of amino acids in stimulating protein synthesis in skeletal muscle (Kimball & Jefferson 2006). Of the BCAAs, leucine appears to be the most important in stimulating protein synthesis (Lynch 2001). Therefore, it seems logical to propose to override the catabolic effects of glucocorticoids toward skeletal muscle by administration of BCAAs or leucine alone. However, the fact that glucocorticoids make the muscle protein synthesis resistant to exogenous BCAAs

(Liu *et al.* 2001, 2004, Kobayashi *et al.* 2006) and leucine (Rieu *et al.* 2004) does not support this hypothesis.

Glutamine

Glutamine is a conditional essential amino acid in catabolic states. Glutamine and alanyl-glutamine have been reported to prevent glucocorticoid-induced muscle atrophy (Hickson *et al.* 1995, 1996). However, attenuation of this muscle atrophy by glutamine infusion is not associated with changes in circulating IGF-I levels (Hickson *et al.* 1997). In contrast, administration of glutamine prevents glucocorticoid-induced Mstn expression, which suggests that glutamine may inhibit the atrophic effect of glucocorticoids on muscle strength through inhibiting Mstn (Salehian *et al.* 2006).

Taurine

Since ablation of taurine transporter gene results in susceptibility of exercise-induced weakness *in vivo*, it has been suggested that this transporter is essential for skeletal muscle function (Uozumi *et al.* 2006a). The role of taurine in the prevention of glucocorticoid-induced atrophy is suggested by two observations. First, taurine attenuates muscle cell atrophy caused by glucocorticoids *in vitro* (Uozumi *et al.* 2006b). Second, induction of taurine transporter prevents glucocorticoid-induced muscle cell atrophy (Uozumi *et al.* 2006a). Although attractive, the possibility for taurine to attenuate glucocorticoid effects on skeletal muscle warrants further investigations.

Creatine

Dietary supplementation with creatine monohydrate has been shown to attenuate the muscle weight loss and the atrophy of gastrocnemius type IIb fibers caused by glucocorticoids (Roy *et al.* 2002, Menezes *et al.* 2007). Furthermore, this protective effect was associated with an attenuation of the impairment of daily spontaneous running of animals receiving glucocorticoids (Campos *et al.* 2006). Although further work is required to determine the specific mechanisms underlying the effects of creatine on muscle, evidence collected *in vitro* suggests that creatine may act on muscle cells by increasing IGF-I expression (Deldicque *et al.* 2005).

Clenbuterol

Clenbuterol, a β_2 -adrenergic receptor agonist used to increase muscle mass in cattle, has been tested to prevent glucocorticoid-induced muscle atrophy. Experiments have shown that clenbuterol is able to blunt at least partially the skeletal muscle atrophy caused by dexamethasone (Agbenyega & Wareham 1992, Huang *et al.* 2000, Pellegrino *et al.* 2004). However, on diaphragm, attenuation of muscle atrophy was not associated with a protective effect on muscle dysfunction (Jiang *et al.* 1996). Evidence collected *in vivo* suggest that

clenbuterol may exert its anti-catabolic effect on muscle by increasing IGF-I expression (Awede *et al.* 2002) while downregulating Mstn expression (Pearen *et al.* 2006).

Androgens

Administration of androgens, such as testosterone or nandrolone, a minimally aromatizable analog, prevents decreased muscle mass and strength caused by glucocorticoids in animals (Van Balkom *et al.* 1998) and humans (Crawford *et al.* 2003). Although the molecular mechanisms by which testosterone attenuates the effects of glucocorticoids are not fully elucidated, testosterone, like many other anabolic stimuli, appears to stimulate muscle IGF-I expression (Ferrando *et al.* 2002, Wu *et al.* 2007).

Conclusion

Glucocorticoids appear to play a crucial role in muscle atrophy observed in various pathological conditions. Decrease in protein synthesis and increase in protein degradation both contribute to this muscle atrophy. Different intracellular mediators, such as FOXO, GSK3 β , C/EBP β , p300, REDD1, and ATF4, are involved respectively in the muscle catabolic and anti-anabolic effects of glucocorticoids. IGF-I stimulation or myostatin blockade constitutes some of the most promising future therapeutical approaches to prevent muscle atrophy caused by glucocorticoids. Although many unanswered questions remain, understanding the cellular basis of the glucocorticoid-induced skeletal muscle atrophy will contribute to the rational development of therapeutic interventions and therefore minimize the debilitating effects of the muscle atrophic response to glucocorticoids.

Acknowledgements

The work of the authors was supported by grants from the Fund for Scientific Medical Research (Belgium), the National Fund for Scientific Research (Belgium), the Association Française contre les Myopathies (France), and the Fonds Spéciaux de Recherche (Université Catholique de Louvain, Belgium). The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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Received in final form 28 January 2008

Accepted 31 January 2008

Made available online as an Accepted Preprint
31 January 2008