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Glucocorticoid-induced skeletal muscle atrophy☆

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ABSTRACT

Many pathological states characterized by muscle atrophy (e.g., sepsis, cachexia, starvation, metabolic acidosis and severe insulinopenia) are associated with an increase in circulating glucocorticoids (GC) levels, suggesting that GC could trigger the muscle atrophy observed in these conditions. GC-induced muscle atrophy is characterized by fast-twitch, glycolytic muscles atrophy illustrated by decreased fiber cross-sectional area and reduced myofibrillar protein content. GC-induced muscle atrophy results from increased protein breakdown and, decreased protein synthesis. Increased muscle proteolysis, in particular through the activation of the ubiquitin proteasome and the lysosomal systems, is considered to play a major role in the catabolic action of GC. The stimulation by GC of these two proteolytic systems is mediated through the increased expression of several Atrogenes ("genes involved in atrophy"), such as FOXO, Atrogin-1, and MuRF-1. The inhibitory effect of GC on muscle protein synthesis is thought to result mainly from the inhibition of the mTOR/S6 kinase 1 pathway. These changes in muscle protein turnover could be explained by changes in the muscle production of two growth factors, namely Insulin-like Growth Factor (IGF)-I, a muscle anabolic growth factor and Myostatin, a muscle catabolic growth factor. This review will discuss the recent progress made in the understanding of the mechanisms involved in GC-induced muscle atrophy and consider the implications of these advancements in the development of new therapeutic approaches for treating GC-induced myopathy.

This article is part of a Directed Issue entitled: Muscle wasting.

1. Introduction

Either as drugs used to treat several medical conditions or as endocrine hormones released in response to many stress situations (e.g., sepsis, cachexia, starvation, metabolic acidosis and severe insulinopenia), glucocorticoids (GC) may cause skeletal muscle atrophy. The resulting weakness of peripheral and respiratory muscles may have major clinical implications such as altered quality of life, fatigue, impaired wound healing, compromised lung function and poor immune response. This review is intended to highlight the recent progress made in understanding of the cellular and molecular mechanisms involved in the catabolic actions of GC on skeletal muscle. A better understanding of the mechanisms of the steroid-induced muscle atrophy should lead to the development of new therapeutic avenues to preserve muscle mass and function in patients exposed to high doses of GC.

2. Role of glucocorticoids in muscle atrophy of wasting conditions

Many pathological conditions characterized by muscle atrophy (sepsis, cachexia, starvation, metabolic acidosis, severe insulinopenia, etc.) are associated with increase in circulating GC levels (Braun

Abbreviations: FOXO, forkhead box O; GC, glucocorticoids; MuRF-1, muscle RING-finger protein-1; mTOR, mammalian target of rapamycin; IGF-I, Insulin-like Growth Factor-I; eIF4E, eukaryotic translation initiation factor 4E; S6K1, ribosomal protein kinase 1; 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; miR1, microRNA 1; eIF3F, eukaryotic translation initiation factor 3 subunit F; UPS, ubiquitin proteasome system; LC3, microtubule-associated protein light chain 3; GR, glucocorticoid receptor; IRS-1, insulin receptor substrate 1; PI3K, phosphatidylinositol 3′ kinase; PDK4, pyruvate dehydrogenase kinase 4; Gadd45, growth arrest and DNA damage; MYHC, myosin heavy chain; REDD1, regulated in development and DNA damage responses 1; KLF-15, Kruppel-like factor 15; BCAA, branched-chain amino acid; BCAT, branched-chain amino acid aminotransferase; eIF2B, eukaryotic initiation factor 2B; GSK3β, glycogen synthase kinase 3β; HAT, histone acetyltransferases; HDAC, histone deacetylases; siRNA, small interfering RNA; NFκB, nuclear factor-kappa B; C/EBP, CCAAT/enhancer binding protein; GRE, glucocorticoid-responsive element; Mstn, Myostatin; GHSR1, growth hormone secretagogue receptor 1; SARM, selective androgen receptor modulator; HMB, β-hydroxy-β-methylbutyrate; EDL, extensor digitorum longus; 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1.

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et al., 2011; Lecker et al., 1999), suggesting that these hormones could trigger the muscle atrophy observed in these situations. In the case of sepsis (Tiao et al., 1996), cachexia, starvation (Wing and Goldberg, 1993) and severe insulinopenia (Hu et al., 2009), adrenalectomy, treatment with a GC receptor antagonist (RU-486) or muscle-specific deletion of the GC receptor attenuate muscle atrophy, indicating that GC are at least partially responsible for this muscle loss. In addition to GC 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, GC (or their receptors) do not appear to be required for disuse (Tischler, 1994) or denervation-induced atrophy (Watson et al., 2012), but may clearly exacerbate the deleterious effects of disuse on skeletal muscle mass (Fitts et al., 2007). In some specific situations, often associated with inflammation, GC administration seems to exert paradoxically a positive effect on muscle function (Duchenne muscular dystrophy) (Crossland et al., 2010; Escolar et al., 2011; Maes et al., 2008), probably by blunting muscle pro-inflammatory cytokines production or by some unknown mechanisms.

3. Characterization of the glucocorticoid-induced muscle atrophy

Skeletal muscle atrophy is characterized by a decrease in the size of the muscle fibers. GC 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 GC-induced muscle atrophy. In muscles with mixed fiber type, such as gastocnemius muscle, type II fibers preferentially atrophy over type I. The mechanism of such fiber specificity might be related to the higher GC receptor expression in tibialis anterior than soleus muscles (Shimizu et al., 2011).

4. Mechanisms of glucocorticoid-induced muscle atrophy

In skeletal muscle, GC decrease the rate of protein synthesis and increase the rate of protein breakdown (Goldberg et al., 1980; Lofberg et al., 2002; Tomas et al., 1979), both contributing to atrophy. The severity and the mechanism for the catabolic effect of GC may differ with age. For example, although GC cause muscle atrophy of the same magnitude, the recovery is much slower in older rats compared with younger rats (Dardevet et al., 1998). Furthermore, GC-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). In humans, short-term GC excess blunts the insulin-induced protein anabolism, suggesting that muscle loss occurs most likely through inhibition of the anabolic response to insulin (Short et al., 2009). Indeed, GC do not seem to alter skeletal muscle protein metabolism in the postabsorptive state.

4.1. Anti-anabolic action of glucocorticoids

The inhibitory effect on protein synthesis results from different mechanisms. Firstly, GC inhibit the transport of amino acids into the muscle (Kostyo and Redmond, 1966), which could limit the protein synthesis. Secondly, GC inhibit the stimulatory action of insulin, 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 which play a key role in the protein synthesis machinery by controlling the initiation step of mRNA translation (Liu et al., 2004, 2001; Shah et al., 2000a,b).

4.2. Catabolic action of glucocorticoids

The stimulatory effect of GC on muscle proteolysis results from the activation of the major cellular proteolytic systems (Hasselgren, 1999), namely the ubiquitin proteasome system (UPS), the lysosomal system (autophagy) and the calcium-dependent system (calpains). The protein degradation caused by GC affects mainly the myofibrillar proteins as illustrated by the increased excretion of 3-methyl histidine (Tiao et al., 1996; Zamir et al., 1991) and also muscle extracellular matrix proteins. To activate the protein degradation, GC 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 and 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 GC stimulate not only the UPS-dependent proteolysis, but also the calcium-dependent and lysosomal protein breakdown (Hasselgren, 1999). The role of lysosomal system, also called autophagy, in the atrophic effect of GC is suggested by the increase of Cathepsin L muscle expression (Deval et al., 2001; Komamura et al., 2003; Sacheck et al., 2004) and by the increased conversion of microtubule-associated protein 1 light chain 3 (LC3)-I to LC3-II, an indicator of autophagy (Yamamoto et al., 2010), in the muscle of GC-treated animals. Because the proteasome does not degrade intact myofibrils, it is thought that actin and myosin need to be dissociated from the myofibrils before they can be degraded by the UPS. Indeed, activation of caspase-3 is required for the conversion of actomyosin and myofibril proteins into substrates degradable by the UPS (Du et al., 2004; Hasselgren and Fischer, 2001; Lee et al., 2004; Wang et al., 2010). However, the possibility for the UPS to degrade directly the sarcomere structure has been also suggested (Cohen et al., 2009).

5. Signaling pathways involved in glucocorticoid-induced muscle atrophy

5.1. Glucocortcoid receptor (GR)

The GR is mandatory for muscle atrophy in response to GC excess both *in vitro* (Zhao et al., 2009) and *in vivo* (Watson et al., 2012). Thus, the muscle-specific GR-knock out mice are resistant to the atrophy-inducing action of GC (Watson et al., 2012). Although these observations establish the requirement of muscle GR for activation of molecular signals that promote muscle catabolism, they do not allow to determine the mechanisms by which GC cause muscle atrophy. Indeed, GC have been reported to act either by interference with the insulin/IGF-I signaling pathway (non-genomic action) or by transcriptional stimulation of Atrogenes (or genes involved in muscle atrophy), via several transcriptional factors, in particular FOXO (genomic action).

5.2. PI3K/Akt

Several evidences indicate that GC can exert their catabolic actions by inhibiting the PI3K/Akt pathway, which mediates the anabolic actions of insulin/IGF-I. First, in L6 myoblasts, GC decrease IRS-1 protein, the first upstream component of the PI3K/Akt cascade (Nakao et al., 2009; Zheng et al., 2010). This could result from the stimulation of C1-Ten, a protein tyrosine phosphatase which accelerates IRS-1 degradation (Koh et al., 2013). GC can also

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