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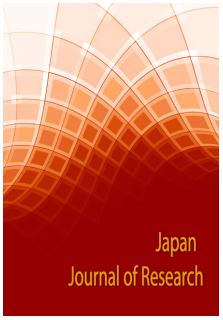

Glucocorticoid-Induced Muscle Atrophy: Insights And Therapies

Okorie Uchechukwu[1], Nweke Timothy Obinna[1], Ofodile Vitus Anayo[2], Okorie Loveth Onyekachi[1]

[1]Biochemistry, Alex Ekwueme Federal University Ndufu Alike, Ebonyi State, Nigeria.
[2]Chemistry Department, Eboni State University Abakaliki, Nigeria

Correspondence
Okorie Uchechukwu
Biochemistry, Alex Ekwueme Federal University Ndufu Alike, Ebonyi State, Nigeria.

Abstract

Excess of glucocorticoid (Gs) due to diseases of the adrenal gland, stress, aging, and immunosuppressant use can induce muscle atrophy (loss of muscle mass). Gs plays a crucial role in muscle atrophy by decreasing protein synthesis and increasing its breakdown. The fundamental implication of excess glucocorticoids is the up-regulation of the atrophy-related genes atrogin1, MuRF1, and MUSA1. E3 ubiquitin ligases are typically muscular-specific catalyzing ubiquitination of target protein. Additionally, glucocorticoids increase the expression of parts of the Notch signaling pathway in muscle, activate a significant amount of UPS components that help conjugate a protein to be degraded, decrease the cellular level of MyoD, a transcription factor required for muscle mass development, and increase the production of Myostatin, a growth factor that is known to inhibit muscle mass development. IGF-1 induction, myostatin inhibition, and cAMP phosphodiesterase inhibitors are examples of potential treatments to stop muscle atrophy brought on by glucocorticoids. Similarly, administration of androgens and branched-chain amino acids, particularly leucine could restore muscle atrophy. This review discussed glucocorticoid-induced muscle atrophy and therapeutic approaches.

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Keywords
Glucocorticoids; malnutrition; Atrophy; Myostatin; Phosphodiesterase

Introduction

Since many years ago, it has been known that glucocorticoids (GCs) exert a variety of catabolic actions. It can be used as a medicine to treat a variety of medical conditions, and it can also be released in reaction to certain health triggers, such as stress, and the event of endocrine hormone production. glucocorticoid protects against insulin resistance during obesity by activation of anti-inflammatory adipose tissue macrophages (ATMs) [1]. According to Ayroldi et al [2], stress exposure leads to dysregulation of the hypothalamic-pituitary-adrenal axis and elevated levels of endogenous GCs. However, skeletal muscular atrophy (loss of muscle mass) has been linked to glucocorticoids. The increased fracture risk associated with glucocorticoid excess is mostly caused by the interactions between bone and muscle [3]. It is necessary to understand the mechanisms of skeletal muscle atrophy and the contribution of glucocorticoids to safeguard consumers from potential side effects. The development of a novel therapeutic agent with efficient biological activity that can preserve muscle mass and function in patients who are exposed to high doses of glucocorticoids as a result of its application in the management of illnesses will be facilitated by X-raying the mechanisms of the steroid myopathy to fully understand it [4]. It is well known that glucocorticoids control how proteins are metabolized in skeletal muscle, having a catabolic effect in contrast to insulin. In several catabolic disorders, including sepsis, malnutrition, and cancer cachexia, endogenous glucocorticoids are raised, which contributes to the loss of muscle mass and subsequently its function [5]. Glucocorticoid-induced muscle atrophy is typically characterized by fast-twitch or type II muscle fiber atrophy, which is typically manifested by decreased fiber cross-sectional area and decreased myofibrillar protein. The ubiquitin-proteasome system, in particular, plays a substantial role in the catabolic activity of glucocorticoids by breaking down muscle protein [6]. The increased production of certain antrogenes, such as atrogin-1 and MuF-1, which are ubiquitin ligases required for the targeting of the protein to be destroyed by the proteasome machinery, is how glucocorticoids activate UPS [6,7]. The primary proteolytic mechanism of muscle atrophy, the enhanced expression and activity of the ubiquitin-proteasome pathway is typically caused by the activity of glucocorticoids. The growth hormones IGF-1 and myostatin, which regulate muscle mass, can modify how anabolic and catabolic processes are directed toward skeletal muscle. So, atrophy of the muscle caused by glucocorticoids presents a critical challenge in conditions such as chronic stress, aging, and prolonged steroid use, where excessive

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glucocorticoids disrupt muscle protein balance, leading to significant muscle loss. Understanding the underlying mechanisms provides valuable insights for developing targeted therapies, including IGF-1 induction, myostatin inhibition, and androgen and leucine supplementation, offering promising avenues for preventing and reversing muscle atrophy in affected individuals. This review highlighted the roles played by glucocorticoids in the induction of skeletal muscle atrophy, and recent findings on therapeutic approaches.

Glucocorticoid Muscle Atrophy Induction Mechanisms

Glucocorticoids in skeletal muscle are the source of the increased rate of protein breakdown and the decreased rate of protein synthesis in skeletal muscle, which results in muscular atrophy [8,9]. Different factors, such as age, may affect the related problems and the mechanism for the catabolic action of glucocorticoids (Figure 1).

The anti-anabolic action of glucocorticoids:

The inhibitory effects of glucocorticoids on protein synthesis are caused by many methods. Protein synthesis may be hampered by the initial suppression of amino acid transport into the muscle [10,11]. Second, glucocorticoids block insulin, insulin-like growth factor 1 (IGF-1), and leucine's stimulatory effects on the phosphorylation of elF4E-binding protein 1 (4E-BP1) and the ribosomal protein S6 kinase 1 (S6K1), suggesting the two factors may play a significant role in the synthesis of protein machinery by altering the initiation step of mRNA translation. Additional evidence suggests that glucocorticoids cause muscle atrophy by inhibiting myogenesis through the down-regulation of myogenin, a crucial transcription factor for the differentiation of satellite cells into muscle fibers [6].

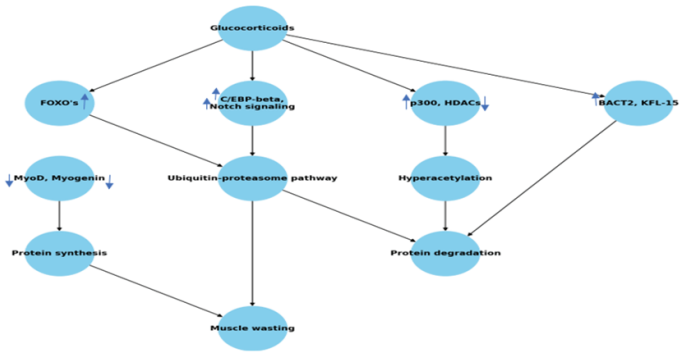

***Figure 1**: Multiple actions of glucocorticoid on muscle atrophy*

Glucocorticoids act as the central element, initiating multiple pathways. The up-regulation of FOXO's and C/EBP-beta, Notch signaling pathways are activated by glucocorticoids and further stimulate the Ubiquitin-proteasome pathway, which is crucial for protein degradation. p300 and HDACs are influenced by glucocorticoids leading to hyperacetylation which in turn, promotes protein degradation. BACT2, KFL-15 are directly activated by glucocorticoids, contributing to protein degradation. Down-regulation of MyoD and Myogenin which are involved in muscle differentiation, and are inhibited by glucocorticoids, leads to a reduction in protein synthesis. Ubiquitin-proteasome pathway is central to the breakdown of proteins, contributing to both muscle wasting and Protein degradation. Muscle wasting is the final outcome of reduced protein synthesis and increased protein degradation. Glucocorticoids (GCs) exert their muscle-wasting {final outcome of GCs} effects by tilting the balance towards increased protein degradation and reduced protein synthesis

Catabolic action of glucocorticoids: Protein breakdown caused by glucocorticoids primarily affects the myofibrillar proteins, usually typified by the increased excretion of 3-methylhistidine 12,13. Muscle proteolysis stimulation is induced by the activation of the major cellular proteolytic systems (UPS; the lysosomal system (Calpains)) [14]. Degradation of proteins, however, requires that glucocorticoids activates the expression of the various components of the UPS {(ubiquitin, 14kDa (E2), a conjugating enzyme; atrogin-1 and MuF-1, two muscle-specific (E3) ubiquitin ligases. Atrophy caused by a variety of wasting diseases is caused by several genes (atrogin-1, MuRF-1, cathepsin L, PDK4 and 4E-BP) controlled by the FOXO transcription factors; other components are the 20S proteasome catalytic core particle (20S CP) and the 19S proteasome regulatory particles (19S RP)[15]} linked to conjugation of ubiquitin to the protein to be catabolized [16-18].

Interaction of Local Growth Factors And Glucocorticoid

MIGF-1 as a local growth factor: IGF-1 is a growth factor promoting myogenesis and protein synthesis, and suppressing proteolysis and apoptosis to promote the increase of muscle mass [19,20]. Alternatively, glucocorticoids promote muscular atrophy by changing the production of the growth factors that locally regulate the development of muscle mass. It is well known that glucocorticoids prevent muscles from producing IGF-1 [21].

In an in-vitro investigation [22,23], showed that IGF-1 can prevent muscular atrophy brought on by glucocorticoids. The systemic injection or local overexpression of IGF-1 in skeletal muscle has been linked to the suppression of glucocorticoid-induced muscle atrophy, according to the reports of Tomas; Shakman et al [24-27]. This indicated that IGF-1 has a principal effect, overriding glucocorticoids, to impair catabolism. Hence, it could be employed in the management of glucocorticoid-induce muscle atrophy

Myostatin as a growth factor: The glucocorticoid stimulates the muscle's synthesis of myostatin [28,29]. It is a growth factor that inhibits the increase of muscle mass by reducing satellite cell differentiation and proliferation [30,31], as well as protein synthesis [32]. By preventing Akt phosphorylation, myostatin is said to enhance the amounts of active FoXo, allowing for greater atrogene expression [33]. Moreover [34,35], findings demonstrated that purposeful disruption of myostatin gene expression in mice could result in a stunning increase in skeletal muscle mass due to fiber hyperplasia and/or hypertrophy. Also, transgenic mice modified to express myostatin selectively in skeletal muscle demonstrated muscle atrophy [36,37].

MyoD, a transcription factor. A transcription factor known as MyoD is essential for the regeneration and self-renewal of skeletal muscle satellite cells, as well as for the regulatory control it exerts over muscle differentiation and development. A family of inhibitors of DNA-binding (Id) proteins, of which Id1 is the most significant component in terms of MyoD binding, adversely affects the transcriptional activities of MyoD [38,39]. MyoD expression is lowered in muscle wasting, at least in part due to the transcription factor's ubiquitin-proteasome-dependent degradation [40,41]. Studies indicate that TNF can decrease the level of MyoD protein in skeletal muscle cells as a result of activating NF-kB, and these effects of TNF may contribute to muscular atrophy [41]. One of the mechanisms of glucocorticoid-induced muscle

wasting has been theorized to be the simulated breakdown of MyoD by glucocorticoids [39,41]. Dexamethasone boosted the proteasome-dependent degradation of MyoD in cultured C2C12 muscle cells, a mouse skeletal muscle cell line [39]. The dexamethasone-induced degradation of MyoD in the nucleus has been attributed to an N-terminus dependent mechanism [39,42]. MyoD may be variably regulated in distinct cellular compartments as evidenced by the possibility that cytoplasmic MyoD degradation is independent of dexamethasone regulation [39]. These findings suggest that muscle atrophy is caused by glucocorticoid-dependent nuclear degradation of MyoD via the N-terminus pathway, which is thought to be a key mechanism of muscle protein catabolism [39,43]. Muscle deterioration and cachexia may be caused by NF-kB-induced loss of MyoD messenger RNA [44].

Glucocorticoids' stimulation of nuclear factors. The excess of glucocorticoids has a potent ability to up-regulate the expression and activity of the transcription factors C/EBPbeta and delta, Forkhead box O 1, 3, and 4, as well as the nuclear cofactor p300 (Fig.1), which are associated with muscle wasting, according to Ciechanover A, Ben-Saadon R [42] and Menconi, M, et al. [45]. Per-Olof Hasselgren, et al. [39] had highlighted a strong link between glucocorticoid-induced C/EBP activation and muscle atrophy. Myotube shrinkage, an increase in protein degradation, the expression of atrogin-1/MAFbx, and MuRF1 were all reversed when CCAAT-enhancer-binding proteins (C/EBP) were silenced using siRNA [39]. The important mediator of glucocorticoid-induced muscle atrophy is the class O transcription factors (FOXOs), FOXO 1, 3, and 4 found in the forkhead domain [46]. Variety of circumstances that boost endogenous glucocorticoids [39] exposure to exogenous glucocorticoids in skeletal muscle consistently generates Forkhead box O (FOXOs). The decrease of FOXOs activity either genetically or by injection of growth factors, remarkable reduction of muscle atrophy, and associated gene expressions are usually observed [46]. In a variety of cell types, including skeletal muscle, another transcription factor known as kruppel-like factor 15 (KFL-15) is strongly induced and directs the target GR. It also plays a role in the regulation of MuRF1 and MAFbx as well as significant enzymes involved in the metabolism of branched-chain amino acids [47]. KLF15 transcriptionally upregulates Branch-chain aminotransferase 2 (BCAT2), a mitochondrial enzyme that starts the primary step in the catabolism of BCAA, to hasten BCAA degradation and alanine production in skeletal muscle [4]. BCAT2 also suppresses protein synthesis and degrades mTOR activity. Direct targets of GR, the glucocorticoid-induced genes REDD1 and KLF15 are known to restrict mTOR activity by sequestering 14-3-3 proteins and elevating TSC1/2 activity [4]. A unique mechanism by which glucocorticoids can affect muscle mass in addition to their effects on mature muscle fibers is provided by the overexpression of the widely induced GR target gene glucocorticoid-induced leucine zipper (GILZ), which is strongly up-regulated in primary and C2C12 myoblast [2]. GILZ functions as a sequence-specific transcriptional repressor that blocks the transcription of the PPAR-2 gene by interacting with tandem repeats of CCAAT/enhancer-binding protein (C/EBP) binding sites in the promoter. Adipocyte differentiation is inhibited by GILZ [48]. GILZ may also interact with a number of cytoplasmic signal transduction proteins in order to affect muscle cells [49]. In the skeletal muscles of dKO mice, excessive Notch activity can lead to persistent inflammation, impair muscle regeneration, and increase muscle progenitor cell aging and death [50,51]. Glucocorticoids, which boost the expression of Notch signaling pathway components in the muscle, may also be able to activate the UPS components that are required for the conjugation of the proteins targeted for destruction to ubiquitin. Because MPC senescence and depletion were delayed or reduced by the control of Notch in the skeletal muscle of dKO mice, the ability for myogenesis may have been restored while inflammation and fibrosis were reduced [50]. Furthermore, Amy Y, et al [3] found that, with the exception of bone, inhibiting Notch signaling led glucocorticoids to produce a decrease in the diameter of myotubes and an increase in the expression of atrophy-related genes in muscle. This study suggests that inhibiting the up-regulation of Notch by glucocorticoids may be an effective method for avoiding atrophy.

Glucocorticoid-Induced Muscle Atrophy Risk to Health

High glucocorticoid doses given to the animals have been associated with decreased muscle mass and muscle dysfunction, as seen by weakened vitality and strength [52]. Additionally, Decramer et al. [53] discovered a strong link between steroid use and the strength of the respiratory and peripheral muscles in people with cystic fibrosis and chronic pulmonary disease. High levels of glucocorticoids, poor diet, cytokines, and bed rest can all contribute to muscle atrophy or wasting illnesses [14,17,67]. However, glucocorticoids might not be required for disuse atrophy [54]. However, inactivity or disuse can greatly worsen the lethal effects on skeletal muscle mass [27,55,56]. Peripheral muscle weakness has been observed in Cushing's syndrome patients with high endogenous glucocorticoid levels [27]. The glucocorticoid-induced muscle atrophy may exacerbate critical medical conditions because cellular dysfunctions can initiate a cascade of events that leads to a range of disease states.

Therapeutic Approaches of Muscle Atrophy

IGF-1 stimulation and myostatin inhibition, as was previously indicated, have proven to be effective therapeutic approaches to reverse glucocorticoid-induced muscle atrophy [25]. Protein synthesis appears to be triggered by the administration of androgens (such as testosterone) or nandrolone (a weakly aromatizable analog) [57,58] as well as branched-chain amino acids, particularly leucine [59]. Alanyl-glutamine and glutamine are protective against glucocorticoid-induced muscle atrophy Hickson et al. [60]. However, Hickson et al. [60] found no connection between the reduction of muscle atrophy brought on by glutamine infusion and a change in circulating IGF-I levels. The finding that glutamine administration decreases glucocorticoid-induced Myostatin production suggests that glutamine may instead avoid the atrophic effects of glucocorticoids on muscle strength by decreasing Myostatin [61]. Additionally, it has been demonstrated that adding creatine monohydrate to diets can effectively block glucocorticoid-induced muscle atrophy and gastrocnemius type IIb fiber atrophy [62,63]. This has also been linked to a reduction in the impairment of daily impulsive running in animals treated with glucocorticoids [64] N-myristoylated ubiquitin ligase Cbl-b inhibitor had been shown to block gucocoricoid-induced atrophy in mouse skeletal muscle [65]. According to Ohno et al. [66], Cblin was found to be less effective than N-myristoylated Cblin at preventing wet weight loss, IRS-1 degradation, and the expression of MAFbx/atrogin-1 and MuRF-1 in the gastrocnemius muscle of DEX-treated mice. High-calorie nutritional supplements and necessary amino acids that promote the synthesis of

muscle fibers are examples of nutritional therapies. The use of small molecules, histone deacetylase (HDAC) activators, dissociated glucocorticoid receptor antagonists, and 11beta-hydroxysteroid dehydrogenase type 1 inhibitors are additional novel potential treatments or preventions for glucocorticoid-induced muscle atrophy [14,67]. Recent studies suggest that cAMP phosphodiesterase inhibitors (raising muscle levels of cAMP), growth hormone-releasing peptide-2 (GHRP-2), and 2-agonists may also be able to prevent glucocorticoid-induced muscle atrophy [68,69]. It is hypothesized that small molecule HDAC activators [70,71] may become a real tool in preventing and treating muscle wasting [14] based on the recent discovery that hyperacetylation may be involved in glucocorticoid-induced muscle wasting [67,72,73]. Other potential therapies, including dissociated glucocorticoid receptor (GR) agonists and 11-hydroxysteroid dehydrogenase type 1 (11-HSD1) inhibitors, described as two novel classes of drugs, may soon be tested in the context of glucocorticoid-induced muscle wasting. By reducing transactivation activity, which is responsible for the metabolic side-effects of glucocorticoids [74,75], a designed dissociated GR agonist can induce glucocorticoid-regulated transrepression pathways, which may lead to muscle atrophy. Dissociated GR ligands may prove useful in preventing muscle mass loss in patients taking glucocorticoids as well as in situations defined by glucocorticoid-regulated muscle loss. The enzymes 11-HSD1 and 11-HSD2, which change inactive corticosteroids into active corticosteroids and active corticosteroids into inactive corticosteroids, respectively, control the action of glucocorticoids in peripheral tissues [39,76]. Several new classes of 11-HSD1 inhibitors are currently being developed to lower tissue levels of active glucocorticoids [77,78]; even though their main applications are in the treatment of diabetes and the regulation of insulin resistance by glucocorticoids, they equally hold promise for the treatment of glucocorticoid-induced muscle atrophy [77,79]. Treated cultured C2C12 myotubes with retinoic acid, resulted in down-regulation of 11-HSD1 expression and activity leading to myotube resistance to the effects of glucocorticoids [80].

A RING-type ubiquitin ligase is Cbl-b. Muscle atrophy brought on by unloading stress is facilitated by Cbl-b-mediated ubiquitination and proteasomal degradation of IRS-1 [45,81]. According to Shiao-Ya et al. [82], the ubiquitin modification caused by CBL may act as a signal to guide aEGFR toward lysosomal destruction. In both in vitro and in vivo settings, the phospho-pentapeptide DGpYMP (Cblin) imitates Tyr612-phosphorylated IRS-1 and prevents Cbl-b-mediated ubiquitination and degradation of IRS-1 [66]. Cblin and the TKB domain of Cbl-b directly interact with one another. According to Ohno et al. [66], the shorter tripeptide GpYM binds to the TKB domain. Through hydrogen-bond networks and hydrophobic interactions, the pY in Cblin inserts into a positively charged pocket in the TKB domain [83]. The Cblin structure in this complex closely mimics the TKB-bound form of Zap-70-derived phosphopeptide, a different substrate-derived phosphopeptide [66]. Because these peptides lack the conserved intrapeptidyl hydrogen bond between pY and a conserved residue important in TKB-domain binding, they exclusively connect with the TKB domain in place of the conserved interaction [66,82]. It is suggested that it is possible to construct medicines to prevent unloading-mediated muscle atrophy based on the binding mechanism of Cblin to the TKB domain.

Conclusion And Recommendations

Glucocorticoids play a crucial role in muscle atrophy by decreasing protein synthesis and increasing its breakdown. IGF-1 stimulation or myostatin notch and signaling blockade may constitute potent therapeutic models to prevent muscle atrophy. Androgens administration and provision of branched-chain amino acids especially leucine mitigates muscle atrophy. Future research focusing on optimizing IGF-1 delivery mechanisms, such as tissue-specific gene therapy or sustained-release formulations, to enhance its anabolic effects on muscle while minimizing systemic side effects is recommended. Also, further studies exploring the long-term safety and efficacy of myostatin inhibitors, and potential combination therapies of myostatin blockers and other anabolic agents. Again, future studies should target developing selective androgen receptor modulators (SARMs) with fewer side effects compared to traditional anabolic steroids, targeting muscle tissue specifically without affecting other organs. Investigating the personalized supplementation of branched-chain amino acids (BCAAs), principally leucine, based on individual metabolic needs or genetic factors could optimize its effectiveness in muscle preservation during atrophy.

Ethics approval and consent to participate

Certified

Consent for publication

Authors gave consent for publication

Authors' contributions

- UC-Conceiving the review title, provision of materials, proof read the manuscript
- TO-Edited the manuscript
- OVA- Edited manuscript
- LO-Wrote the draft of the manuscript

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