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Review Article

A Novel Insight into Signaling Pathways, Animal Models, and Interventions in Psychological Stress Induced Muscle Atrophy

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Abstract

A sedentary, inactive, and stressful lifestyle aggravates chronic psychological and stressful conditions in human health. Chronic stress may lead to prolonged release of glucocorticoids like stress hormones and proinflammatory mediators, which may affect the skeletal muscle mass and strength in humans as well as in rodents and eventually lead to muscle atrophy. IGF1/Akt/mTOR decreased when exposed to synthetic stress hormones like dexamethasone. While catabolic factors like FoxO1 and FoxO3a/MSTN/REDD1/KLF15/P85 increased in stress-induced muscle atrophy. IL-1/IL-6/TNFα was also activated under stressed conditions and has been reported to induce muscle wasting. Currently, only a few animal models of stress-induced muscle atrophy have been developed. The review focuses on the mechanism of glucocorticoid release via psychological stress leading to activation of various signaling pathways like IGF-1/Akt, Myostatin, FoxO, REDD1, P85, and inflammatory mediators like TNF-α and IL-1. The review also gives an overview of the animal models of stress induce muscle atrophy along with its manifestations in patients. Lastly, a brief discussion on medical interventions of muscle atrophy is described. This whole compilation of the information at one place will help in further understanding of the mechanisms leading to development of better therapeutics in future.

Keywords: *Psychological Stress; Glucocorticoids; Muscle Atrophy; Muscle Mass*

Abbreviations

ActRIIB: Activin Receptor Like Kinase; ACTH: Adrenocorticotropic Hormone; AT1: Atrogin; BCAA: Branched Chain Amino Acid; BCAT2: Branched Chain Aminotransferase 2; CRF-OE: Corticotropin Releasing Factor Overexpressing; Dex: Dexamethasone; DNA: Deoxyribonucleic Acid; EDL: Extensor Digitorium Longus; elF4E: Eukaryotic Translation Initiation Factor 4E; 4EBPs: elf4E Binding Protein; FoxO: Forkhead Box Protein O1; GN: Gastrocnemius; GC: Glucocorticoids; GRB: Glucocorticoid Binding Receptor; GRE: Glucocorticoid Receptor Element; GR: Glucocorticoid Receptor; GSK3β: Glycogen Synthase Kinase 3β; HPA: Hypothalamic Pituitary Adrenal; HSD11β: 11-Beta Hydroxysteroid Dehydrogenase; IGF1: Insulin-Like Growth Factor-1; IR: Insulin Receptor; IRS1: Insulin Receptor Substrate1; IL6: Interleukin 6; IL1: Interleukin1; IL6R: Interleukin 6 Receptor; IKK: IκB Kinase; JAK: Janus Kinase; KLF15: Kruppel-Like-Factor; KO: Knockout; mTOR: Mammalian Target of Rapamycin; MAFbx: Muscle Atrophy F: Box; MSTN: Myostatin; MuRF1: Muscle RING Finger 1; NF: κB: Nuclear Factor Kappa; NEMO: NFκB Essential Modulator; PKB: Protein Kinase B; PI3K: Phosphatidylinositol 3-Kinase; PIP2: Phosphatidylinosi-

tol 4,5-Bisphosphate; PIP3: Phosphatidylinositol-3,4,5-Trisphosphate; REDD1: DNA Damage Response1; Rheb: Ras Homolog Enriched in Brain; S6K: S6 Kinase; SOL: Soleus; SOCS3: Suppressor of Cytokine Signaling 3; STAT 3: Signal Transducer and Activator of Transcription 3; TA: Tibialis Anterior; TGFβ: Transforming Growth Factor Beta 1; TSC: Tuberous Sclerosis Complex; TNFα: Tumor Necrosis Factor Alpha; TNFR1: Tumor Necrosis Factor Receptor1; USP19: Ubiquitin: Specific Protease 19; WT: Wild Type

Introduction

Skeletal muscles are tissues present in the body profusely which plays a vital role in the daily routine of living organisms that range from *C. elegans* to humans by manifesting different significant functions like maintaining the posture and locomotor activity of the body according to their physiological body changes [1]. The skeletal muscles are soft tissues that can be acclimatized in the presence of various stimuli such as exercise, injury, disuse, and diseased states. The skeletal muscle of animals possesses high plasticity that needs to be nourished during the life cycle since it has a crucial role in performing activities and movements. Low muscle plasticity can lead to drastic changes in the body and quality of life. The stationary and inactive lifestyle left individuals suffering from various diseases such as diabetes, cardiovascular diseases, cancer, stress, sepsis, and many more, which are resulted in compromised skeletal muscle and loss [2]. Moreover, the alleviated muscle mass due to decreased physical activity can lead to serious condition of life and pose high risk of mortality and morbidity [3]. Behavioral components of lifestyle such as stress, bodily pursuit are also associated with muscle atrophy [4]. A clinical study showed that aging with stressed conditions may lead to the disuse of muscles and atrophy, which might have a chronic impact on life originating co-morbid conditions. They stated that stress hormones have a negative metabolic impact on the muscle mass of old age people and also reported reduced muscle strength [5]. Increased and prolonged induction of stress may elevate stress hormone levels like glucocorticoids (GC) in the body which results in increased catabolic conditions i.e. protein degradation, consequently, lead to reduced muscle mass and this is termed as stress-induced muscle atrophy [6]. Muscle atrophy, in short, is an imbalance between protein synthesis and protein degradation, which is an ultimate consequence of disused muscle. Factors majorly involved in protein synthesis are insulin-like growth factor-1 (IGF-1), protein kinase B (PKB), mammalian target of rapamycin (mTOR), and glycogen synthase kinase 3β (GSK3β) [7], while in protein degradation transcription factors are involved such as FoxO family, two muscle-specific ubiquitin ligases, Atrogin-1/MAFbx and MuRF1, which get activated when there are signs of atrophic conditions in skeletal muscles [8]. During the diseased and stressful physiological conditions, glucocorticoids have a major contribution, as they balance the metabolism and mobilization of fats, lipids, carbohydrates, and proteins, thereby perpetuating glucose hemostasis [9]. High glucocorticoid levels attenuate the overall protein content of muscle mass by increasing transcriptional genes involved in proteolysis systems such as REDD1 [10] and KLF15 through their inhibitory effect on mTOR. FoxO1/FoxO3a mainly gets dephosphorylated through GC and activates proteolytic genes such as MuRF1 and Atrogin-1 [11]. Besides, factors that are involved in protein synthesis signaling pathways like IGF1/PI3K/Akt/mTOR are decreased and lead to the deleterious effect of GC on muscles [9,12,13].

In this review, we have aimed to decipher how glucocorticoid receptors get activated and tend to cause proteolysis of muscles and catabolic processes on its longer exposure. Also, we have fascinated the effects of chronic stress on the human skeletal muscles, albeit the increased number of patients all over the world, the pathology is not frequently studied and hence requires more rigorous research on it.

Communication between glucocorticoids and molecular targets of stress-induced muscle atrophy

Under chronic stressed conditions, the hypothalamic-pituitary-adrenal (HPA) axis responds to stimuli and activates the production of corticotropin-releasing factor which causes the activation of the anterior pituitary and reviving the release of adrenocorticotropic hormone (ACTH). Stimulation of ACTH provokes the adrenal cortex and thereby increases the secretion of glucocorticoids which act through the negative feedback mechanism [14]. When treated with repeated stress, glucocorticoid levels are exacerbated which leads to catabolism and anti-anabolism of protein, therefore, causes loss of skeletal muscle strength and mass [15]. To understand the mechanism of stress-induced muscle atrophy at the molecular level, targets were identified which are regulated through glucocorticoids and affect the protein synthesis of muscle and other inter-linked factors (Figure 1).

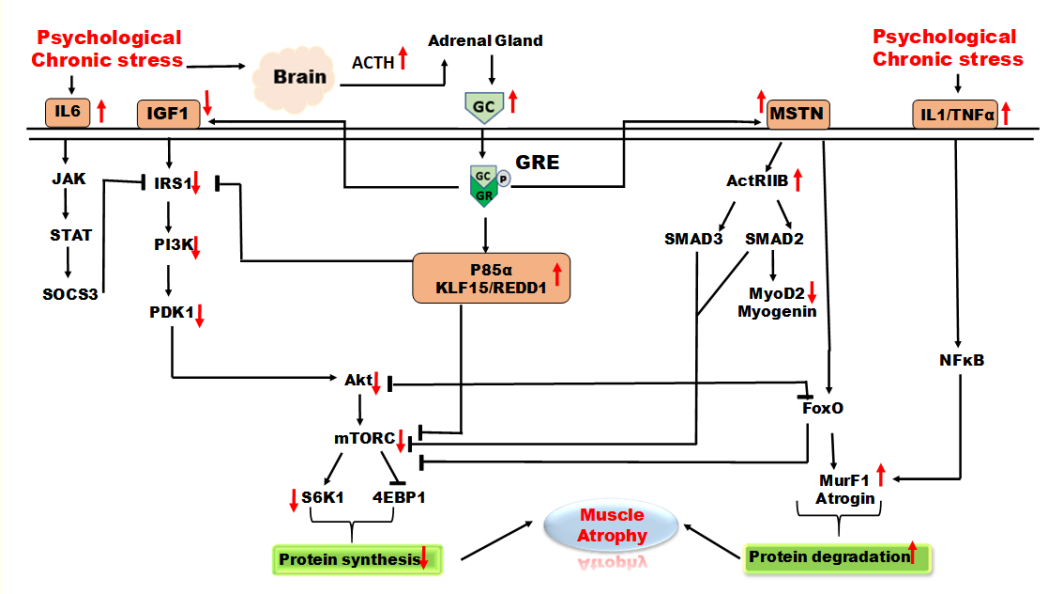

Figure 1: *Signaling pathways involved in stress-induced muscle atrophy: Psychological chronic stress activates ACTH and increase the release of glucocorticoid (GC) cortisol from adrenal gland which bind to its receptor Glucocorticoid receptor (GR) and become activated as glucocorticoid receptor element (GRE) that triggers activation IGF1 (Insulin Growth Factor1) and MSTN (Myostatin) that results in synthesis of protein through Akt/mTOR and degradation of protein via ActRIIB respectively. Other gene transcription factors also become activated P85α, KLF15, REDD1. The proinflammatory markers TNFα/IL1 and IL6 increased and regulates muscle atrophy signaling pathways negatively through NFκB and JAK/STAT.*

IGF-1: Correlation with stress and glucocorticoids (GC): Glucocorticoids perform different biological processes in skeletal muscle repression of protein synthesis and stimulation of glucose uptake by antagonizing insulin growth factor-1 (IGF-1) pathway through insulin inhibition and thus, elevates the process of proteolysis. GC exposed mice possess decreased levels of tyrosine-phosphorylated insulin receptor (IR) and total insulin receptor substrate-1 (IRS-1) in skeletal muscle [16]. Also, two other signaling molecules were identified and reduced upstream with IR and IRS-1 that is Akt and phosphatidylinositol 3-kinase (PI3K) while mTOR downstream of Akt and upstream of p70 S6K decreased markedly [16]. GC tends to decrease the insulin/IGF response by enhancement of phosphorylation at IRS-1 through serine 307 which distorts the relation between IR and IRS-1 that results into muscle atrophy and muscle wasting [17]. The descriptive mechanism of the IGF/Akt signaling pathway to induce muscle atrophy is illustrated in detail. IGF-1 causes phosphorylation of IRS consequently when attached to its receptor, results in the stimulation of intrinsic tyrosine kinase and its autophosphorylation thereby constructing docking sites for IRS which in return cause the stimulation of phosphoinositol-3-kinase (PI3K). The stimulated PI3K has a role to produce PIP3 from PIP2 by causing phosphorylation of membrane phospholipids. The activation of PIP3 is provided as the docking site for Akt which acts as a protein synthesis regulator by causing phosphorylation of the FoxO family. This will suppress the transcription factors of the FoxO family, while its activation is responsible for the cause of muscle atrophy since these factors are necessary to regulate ubiquitin ligases atrogin-1 that too exclaimed as muscle atrophy F-box and MuRF1. Therefore, suppression of FoxO family transcription factors that initiate protein synthesis through mTOR and GSK3b activation is essential for protein synthesis [16,18].

Akt pathway further vitalizes mTOR signaling by obstruction of two GTPase activating protein named as tuberous sclerosis complex (TSC) 1 and 2 and consequently retards Ras homolog enriched in brain (Rheb- a small G protein). There are two types of mTOR: mTORC1 and mTORC2 so, for stimulation and phosphorylation of Akt, mTORC2 is needed while mTORC1 is needed to phosphorylate (S6 kinase) S6K. Activated S6K causes the phosphorylation of S6 ribosomal protein, translational factors, and elongation factors for protein synthesis. Besides, mTORC1 has important functioning in actuating eukaryotic translation initiation factor 4E (elF4E) through phosphorylation of elf4E binding protein (4EBPs). Also, Akt increases the synthesis of proteins by releasing of eukaryotic translational initiation factor 2B through phosphorylation and suppression of GSK3β [19]. As a result, the reverse of all the above events may decrease IRS-1, which cause the blocking of signaling i.e. PI3k/Akt and stimulation of FoxO proteins, and in response to its stimulation, it causes the activation of atrogin-1 and atrophic events in myotubes and myofibers. Thus, it can be concluded that GC exposure is responsible for attenuation of IRS-1 followed by the PI3K/Akt signaling pathway described above while it elevates the level AT-1, Ubiquitin transcription factor, and IRS-2 which are considered as the markers of muscle atrophy. FoxO 3a plays the role of a mediator through its reciprocal relation between IRS-1 and IRS-2 which expresses ubiquitin expression during muscle atrophy [20]. Hence, it is pertinent to check the sensitivity of IGF during the exposure of unpredictive chronic stress to confirm the presence of atrophic events in muscles and could have one of the major targets to intervene in the pathways.

Myostatin expression: Correlation with stress and glucocorticoids (GC)

Myostatin also familiar as growth factor differentiation factor-8 is TGF-β family member having a key role in the regulation of skeletal muscle mass therefore considered as an important target when GC content is increased in response to the exposure of unpredictive stress. Likewise, IGF signaling, two applicable pathways are following to regulate skeletal muscle mass, one is through the Akt/mTOR which balances protein synthesis other is Akt/forkhead box O (FoxO) pathway which regulates protein degradation. MSTN regulates Akt/mTOR through its negative regulation. Increased expression of myostatin significantly increases the MSTN protein as a result of which, the mass of skeletal muscle is alleviated. The following pathway describes the effect of MSTN protein when an increase in skeletal muscle downstream causes the reduced phosphorylation of Smad2/3 and phosphorylation of Akt on Thr 308 which is activated by TSC2 phosphorylation on Thr 1462. Further, S6 on serine and 4EBP1 on Thr 37/146 get unphosphorylated and their level goes down as a result of overexpression of MSTN. Other than these biomarkers, some markers affect proteolytic pathways including AT-1, MuRF-1, and cathepsin-L when the expression of mRNA enzymes increased [21].

In fish animal models, exposed to handling stress, has shown its effects on different paralogues like MSTN-1a/1b/2a and myogenic markers like Myf5, MyoD1, MyoD2, myogenin, MLC. It is also evidenced in studies that IGF-1 has a direct effect on MSTN expression through its antagonizing effect [22]. Hence, the Signaling pathway of IGF-1 blocks the differentiation of myosatellite cells, MSTN-1a, and MSTN 2-a gene expression which is facilitated through myostatin [23]. As the effects of GC induction, skeletal muscle, and MSTN-1 found to have a role in negative regulation of expression of mTOR, MyoD-2, and myogenin via the pathway of Smad/FoxO3b complex and downstream the increased level of atrophic genes [24]. The overexpression of MSTN has significantly alleviated the level of MyoD and myogenin as an outcome of decreased expression of MHC-IIb, troponin, and desmin [25]. The mechanism of myostatin to induce muscle atrophy depends on both Smad 2 and Smad 3 downstream to the activin A (another member of TGF-β family) via activin receptor like kinase ActRIIB receptor which is responsible for muscle differentiation blockade and up-regulation of ubiquitin E3 ligases MuRF1 and MAFbx. Thus, these down-regulated and up-regulated factors contribute to myostatin mediated typical atrophy [26]. The activation of transcription factors Smad 2 and Smad 3 through AktIIB/Alk4/5 on binding with myostatin causes activation of other atrophic genes. Smad 2 activation inhibits mTOR through inactivation of mTORC2 which has the ability to inhibit phosphorylation of Akt that results in decreased protein synthesis followed by activation of atrophic genes [24,26]. While Smad3 activation produces an inhibitory effect on mTOR leading to reduced protein synthesis. Moreover, the binding of FoxO3 has increased to FoxO responsive element-Smad responsive element i.e. promoter site of MuRF1. Therefore, Smad 3 is observed to cause suppression of myoblast differentiation via inactivation of MyoD gene transcription and myostatin blockade, thus inhibiting protein synthesis [24].

FoxO family: Correlation with stress and glucocorticoids (GC)

Fork headbox class O families are extremely preserved proteins, having an important role as transcriptional factors in maintaining cellular homeostasis. Four types of FoxO proteins have been characterized in humans, namely FoxO1, FoxO3, FoxO4, and FoxO6. FoxO1 and FoxO3 found to have a key role in the human skeletal muscle in which FoxO expression regulates muscle energy homeostasis through the regulation of protein breakdown including modifications in pathways such as ubiquitin-proteasome and autophagy, mitophagy, lysosomal proteolytic pathway, apoptosis and muscle regeneration. In the family of FoxO's, FoxO1 and FoxO3 have exceptional attributes due to its actuation in every type of atrophy. The gene expression of FoxO1 increased by activating the elements of the ubiquitin-proteasome system and autophagy lysosomal system in the skeletal muscle mass during fasting and diabetic conditions [27]. As a result of gene expression of the FoxO1 transcription factor, there is a significant decrease in the skeletal muscle mass which causes atrophy that is linked with increased expression of MAFbx/Atrogin-1 and MuRF1 [28]. Also, the stimulation of FoxO3 causes atrophy, which is linked to the increased level of MAFbx/Atrogin-1 in skeletal muscles. The subsequent atrophy due to FoxO3 can be prohibited on its knockdown SiRNA [29]. On exposure to chronic stress, GC receptors become intensified therefore, FoxO becomes activated because of alleviated expressions of PI3/Akt signaling in the following pathway [30]. FoxO1 and FoxO3 mRNAs are also observed to get expressed and activated in a fish experimental study treated with dexamethasone and is involved in GC induced skeletal muscle atrophy [24]. Therefore, the FoxO pathway is directly linked to GC simulation through HPA which is one of the major factors for the activation of proteolytic systems and inhibition of IGF1 production along with increased production of TNF-α/NF-κB pathway [31]. Another experimental study on Chromatin immunoprecipitation sequencing, four types of GR binding regions were identified for FoxO3 gene of C2C12 myotube [32]. Both FoxO1 and FoxO3 genes have a crucial role in the metabolism of skeletal muscle protein and glucose [27]. The metabolism through oxidation is suppressed by these transcription factors via initiation of Pyruvate Dehydrogenase kinase-4 (PDK-4). Surprisingly, GC also stimulates the transcription of the PDK4 gene promoter which binds to both FoxO1 and FoxO3 in humans and this binding is important to cause elevation of GC-induced transcription [33]. More importantly FoxO3 has similar activity as GCs to activate degradation of protein like MuRF-1, AT-1 and EiF4epl genes which are also involved in decreased protein synthesis. The activated FoxO3 is utilized to preclude muscle atrophy which is stimulated through either by disuse or GCs. Thus, FoxO acquires a necessary role in Glucocorticoid mediated atrophy as a major consequence of chronic unpredictable chronic stress exposure [24,28,30,34,35].

Genes modulation: Correlation with stress and glucocorticoids (GC)

The continuous enhancement of glucocorticoid in the body activates other transcriptional gene factors on activation of GC which attracts binding of GR to GRE, these GRE accumulate neighboring transcriptional genes and cofactors like KLF15 (Kruppel-like-factor), REDD-1(DNA damage response1) and p85α. p85α through GBR (Glucocorticoid binding receptor) is an intermediary to activate Glucocorticoid-induced muscle atrophy by diminishing the IGF1-signaling pathway [32]. Other genes like KLF-15and REDD1 are activated under the chronic stress and depressive state by over secretion of GC [36]. Induced muscle atrophy, further translocation of GR into the nucleus increased the expression of Atrogin-1 and MuRF1. KLf-15 stimulates the activation of Atrogin-1, MuRF1 and branched-chain aminotransferase 2 (BCAT2) expression, hence together these cofactors interrupting the mTOR signaling pathway, causing decreased protein synthesis and muscle atrophy [37].

Inflammatory markers: Correlation with stress and glucocorticoids (GC)

Under continuous exposure to chronic stress and depression, inflammatory conditions become pertinacious and cause the marked production of TNFα/IL1 and IL-6, the proinflammatory cytokines [38] which may be responsible to elevate muscle wasting and disuse [39]. The proinflammatory markers TNFα/IL1 and IL-6 have a synergistic effect on homeostasis of the body when there is a high level of GC may be as a response of stressful conditions [38,40]. Although its mechanism of action to induce muscle atrophy is still unclear in several experimental studies relative to stress conditions. The over bursting of the HPA axis cause the activation of hypercortisolemia

and inflammatory state which mutually cause an interruption in the metabolism of muscle mass proteins and overall exerts a negative effect on muscle mass [41]. Also, other factors become aggressive such as nuclear factor κB, a crucial transcription factor that balances the expression of E3 ligases. TNFα and IL1 bind to their receptor TNFR1 and IL-1R respectively and gets phosphorylated which causes proteasomal degradation of the blocker of κB through IκB kinases/NFκB essential modulator (NEMO/IKK) complex [42]. Due to the formation of the NEMO complex, NFκB is translocated into the nucleus thus inducing gene transcription of TRIM6 also known as MuRF1 [42,43]. Other proinflammatory markers also regulate muscle proteolysis along with the activation of NFκB and TNFα/IL1 i.e. IL6 mediated muscle atrophy which is regulated through the signal transducer and activator of transcription 3 and Janus Kinases (JAKs) which further phosphorylates STAT3 and translocated that results in transcription of genes namely suppressor of cytokine signaling 3 (SOCS3). SOCS inhibits protein synthesis by showing its inhibitory action on IRS-1 [44]. Hence IL6 and JAK signaling are a potential target to cause a remarkable decrease in inflammation induced by muscle wasting as a response to chronic stress [45]. IL6/IL6 receptor (IL6R) interrelation gives rise to the initiation of STAT, contributes to muscle differentiation and regeneration. Therefore, IL6 exerts an effect on the signaling pathway of hormones secretion and insulin resistance which corresponds to muscle atrophy [44,46]. In an experimental study on CRF-OE mice, the IL6 level and visceral adipose tissues were rose in plasma when muscle mass and its function were observed to be decreased, [34] hence from such previous studies the role of inflammatory markers in stress-induced muscle atrophy can be concluded.

Animal models of stress-induced muscle atrophy

To the best of our knowledge, there are only a few stress-induced muscle atrophy models which are illustrated here in detail to widen the prospects of research in the following area.

Transgenic model- CRF OE mice

Recently, Kang et al have used male corticotropin-releasing factor (CRF) over-expressing mice as a model of chronic stress-induced muscle atrophy [34] which was previously initiated by other research groups. In this study, he had evolved transgenic mice which proved to be a novel animal model for the study of various diseases associated with hormonal imbalances and disorders. The developed transgenic mice has provided wider scope for more research and provided the physiological outcomes of overproduction of a central neuropeptide that would have many repercussions like behavioral modulations, autonomic, and neuroendocrine functions. CRF gene expressed in transgenic mice under the control of metallothionein promoter which resulted in abnormal endocrine functions e.g. increased plasma levels of ACTH, glucocorticoids and physical abnormalities *viz.* fat agglomeration, muscle wasting, alopecia and delicate skin [47], therefore, Kang et al. had chosen these transgenic mice as a model of stress-inducing muscle atrophy. As per the previous studies, the pathological conditions due to high corticosteroids, were pronounced from 6 weeks to 14 weeks of age [48] thus CRF-OE mice of 7 and 19 weeks of age and littermates (as a control group) were used to examine muscle atrophy. According to their studies, it has been depicted that mice under chronic stress and corticotropin-releasing factor (CRF) jointly promoted muscle atrophy in CRF-OE mice. The average cross-sectional area of myofiber mass of skeletal muscle, and total protein content in muscle were remarkably increased in 19 weeks old male CRF-OE mice when compared to their WT littermates, moreover, they were found to have weakened physical ability and muscle function which is demonstrated by wire-hang test, muscle grip strength and open-field test. The muscle mobility disabilities were may be aroused as result of anxiety like behavior of rats that developed during handling. There is also decreased expression of factors necessitate in the IGF/AKT/mTOR/S6K signaling pathway of protein synthesis and elevated FoxO/MurF-1/Atrogin1/KLF15/REDD1/MSTN protein degradation genes were observed in skeletal muscles of CRF-OE male mice [34].

Acute physical stress induced mice model

Another animal model was generated in which daily physical acute psychological stress was given and raised atrophic gene expression, and myostatin (MSTN)-dependent muscle atrophy was observed. Three-month old male WT C57/black6J mice and MSTN null mice

were acclimatized to the semi-natural environment for four weeks before the start of the experimental study. The mice were subjected to two types of stressors, one is daily cage switching stress and the other is 1-hour daily restraint stress. Therefore, two different models of psychological stress were used to evaluate the effects on skeletal muscle size (mass TA and SOL muscles) and atrophy-related gene-expression (MSTN, Atrogin-1, MuRF-1) in mice for day 1, 3 or 7 days [49].

Acute physical stress induced fish model

An important marine fish red cusk-eel (*Genypterus chilensis*) with high quality of the flesh is another example of an animal model of stress-induced muscle atrophy in which RNA-seq analysis was utilized to determine the consequences of stress in skeletal muscle transcriptome. In the present model of G. *chinensis*, handling stress caused physiological changes which result in increased circulating levels of cortisol (glucocorticoid) and other skeletal gene expressions. These changes were associated with the catabolic signaling pathway and muscle system processes [35]. There are also other examples of such models of fishes like the rainbow trout (*Oncorhynchus mykiss*) [50] which are exposed to handling stress to increase the level of cortisol associated with skeletal muscle atrophy [35].

Dexamethasone induced *ex-vivo* fish model

Skeletal muscle-related atrophic genes, an *ex-vivo* model of fishes is at a high rate in the research field. Endpoints for muscle sampling was done by an overdose of anesthesia tricaine methane sulfate MS222 then fish was cleaned to dissect the dorsal muscles into fragments under aseptic conditions, and at last dexamethasone (Dex-synthetic glucocorticoid) was added in different concentrations in culture to evaluate the participation of myostatin-1 signaling in glucocorticoid-induced muscle atrophy by the negative regulation of genes which take part in muscle growth like mTOR, Myo D-2 and myogenin and stimulation of atrophic genes such as FoxO3 and MuRF-1 [24]. In this model of muscle atrophy, researchers have demonstrated that under the stressed conditions there is a secretion of glucocorticoid via the activation of the adrenal pituitary gland and ACTH, so they used a new approach to understand the links between unpredictive chronic stress and glucocorticoid induce- muscle atrophy as well as discovered that stress conditions may cause muscle atrophy (Figure 2).

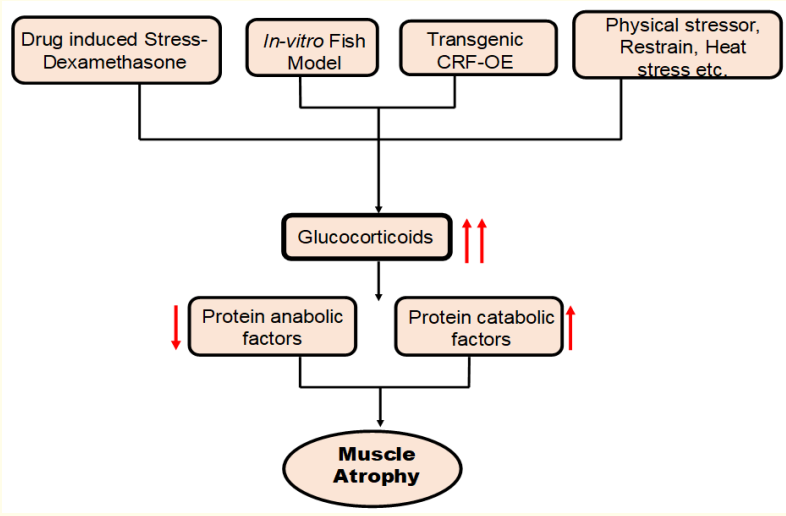

Figure 2: *Muscle atrophy interrelation with glucocorticoids as a response to stress.*

Dexamethasone induced *in vitro/in vivo* rat model

Apart from the dexamethasone models of fish [24], *in vitro* C2C12 myotubes [51] and *in vivo Kun-Ming* mice [52] are also established models used for induction of stressful conditions and release of high level of glucocorticoid to determine its effect on muscles to cause atrophy. In the *in vitro* study of differentiated C2C12 myotubes, myosin heavy chain (MHC) protein reduced as result of dexamethasone treatment that leads to increased level of MuRF1, responsible for atrophic conditions in muscle fibres [51]. Kun-ming mice are other *in vivo* rat model prepared for the study of dexamethasone induced damages on the muscles through the increased Myostatin, a negative regulator of skeletal muscles. On high dose exposure of dexamethasone over tibialis anterior, the size and length of fibres were found to be reduced compared to control group due to increased glucocorticoid receptor element expression [52]. Since dexamethasone has been found to exert an effect on the brain such as cognitive impairment, hippocampal and cortical neuronal atrophy, it has shown deleterious effects on muscle mass as well, therefore, one can conclude that dexamethasone is a chemical/drug that can be used to simulate the model of chronic stress induced-muscle atrophy [51-53].

Stress-induced muscle atrophy and clinical settings

Over the recent years, it has been noticed that the major population of humans are suffering from stress, depression, and anxiety state of diseases which impregnated negative effect on the homeostasis of the body. The tensed episodes in the life of people alter state of mind developing depression and stress-associated diseases. The pathology can be driven by ancestral changes (gene-related) or when subjected to previous stressed experiences, and the unbalanced hormonal changes [54]. The subsequent pathology of chronic stress activates the HPA axis through which GC over-secretion occur and negatively modulates the signaling pathways of transcriptional genes for translation of synaptic proteins in humans. Moreover, in human studies also GC has revealed the various deleterious effects on the human body including reduced brain plasticity, neuronal atrophy of hippocampus, and distressed muscles through the atrophy and decreased collagen fabrication [55,56]. Presence of GC receptors all over the major organs of the body also interferes with the diversified effects on liver enzymes necessitated in energy metabolism, immune cells activation, and cytokine activation [56]. It is interesting to note that under the chronic stress conditions, escalated growth in IL6 cytokine levels has also shown detrimental effects on muscles leading to muscle atrophy and muscle wasting in old human generations [57], suggesting that chronic stress may accumulate the negative impression on human skeletal muscles as muscle atrophy may be in the form of sarcopenia.

To evident the above statements few clinical studies which were experimented on humans for the human health care are exemplified in this review. One is the cross-sectional study carried out on males and females at charitable old age home in Chennai. The human subjects were given with perceived stress and observed their score through perceived stress scale questionnaire. The study has compared the effect of perceived stress on the health of muscles of old age people and concluded the negative outcomes of stress on muscles like before time diminishing of muscle strength. Hence provided the proof that stress may have a stand-alone threat to muscle health and its functions [5]. One more example is a large study done by Noh *et al.* on the old age Korean population of 2,652 to examine the clinical effect of chronic stress, depressive mood, and mental health on the strength of muscles and relation with sarcopenia. They evaluated the complete handgrip strength and relative handgrip strength to the body mass index. The conclusion of the study was people with depressed mood are found to have lower hand grip strength and therefore muscle strength act as clinical indicator under stressed conditions. Although the study has implicated various drawbacks such as they desired prospective studies to elaborate the unknown mechanism of mental health in correlation with decreased muscle strength and sarcopenic factors [58]. So far, the studies, there are almost negligible data on adults who have developed muscle atrophy because of chronic stress. Thus, a meta-analysis report presented by K.V. Chang *et al.* provided relation of depression with sarcopenia since both pathologies stake familiar risk factors, like physical immobility, inactivity, elevated inflammatory cytokines and altered modulation of hormones in the HPA-axis. Hence, they figure out that sarcopenia exerts a link with depression independently and further needs confirmation using cohort studies [59]. Although these studies need a deep study

on the mechanism which is involved here. Nevertheless, to understand the underlying mechanism of muscle atrophy in old age people in relation to chronic stress through glucocorticoids (stress hormone), primary human skeletal myoblasts and myotubes were cultured with dexamethasone to validate its effects on the human skeletal muscle to cause muscle atrophy compared to *invitro* animal studies. The atrophic genes MuRF1 and MAFbx markedly increased and elevated expressions of myogenic markers confirming the future prospective to initiate human cell experiments [60]. The effect of stress does not retain only up to the old age people but has also impact on the young age population. An experimental study on healthy young age volunteers, has depicted that prolonged exposure of stress hormone *i.e.* GC and stressed conditions lead to the decreased lean muscle mass and leg extension strength also reduced the synthesis of muscle protein. These outcomes of the study evidenced the origination of muscle atrophy in healthy and young volunteers [61].

The overall conclusion on human clinical studies has provided a novel approach to find the unanswered questions related to the mechanism of stress mediating muscle atrophy through the glucocorticoids. This review has engrossed an interesting approach to divert the sight of researchers by targeting the secondary negative effects of chronic stress on muscles through glucocorticoid regulation and inflammatory markers activation. Till the date only few researchers have noticed and put efforts to the development in research of this consequent pathology of chronic stress, that is significant on old age as sarcopenia and normal muscle atrophy in young people thus, it can be the provocative pathway to assess the aftereffects of chronic stress on human skeletal muscles.

Intervention in muscle atrophy

The persistent exposure to stress may harm body locomotory functions through various physiological and psychological changes that occur in muscles and muscle mass fibers as illustrated above. Perhaps, the overall mechanism involved to cause muscle degeneration through GC under stressful conditions is not clearly understood [16]. The chronic stress morbidity is responsible for various pathological circumstances which are directly linked to GC receptors activation and other factors such as IGF-1 pathway, myostatin, FoxO, Inflammatory markers, etc. which has been already discussed. The catabolic transcription genes involved were FoxO, IRS1, REDD1, GSK3β identified in previous studies as major potential targets to ameliorate skeletal muscle atrophy. In the following table, the interventions are classified based on their target, category mechanism, and impact on muscle mass.

S. N	Intervention / medication	Category	Target	Effect on muscle	Mechanism	Type of study	Ref.
1	IGF-I overexpression	Growth factor	IGF-1 signaling	Increased muscle mass in TA muscles	IGF1 cDNA gene transfer by electroporation	Pre-clinical	[62]
2	Myostatin deletion	Growth factors	Myostatin signaling, decreased atrogenes (atrogin1, MurF1 and cathepsin-L) level and FoxO 3a	Increased muscle mass in TA, GN, and SOL	Myostatin gene knockout	Pre-clinical	[63]
3.	GRβ overexpression	Gene regulators	GC resistance, enhance insulin signaling, decrease FoxO 3a, MuRF1	Increase MyoD1 and myogenin mRNA expression	Inhibit GRα isoform effects of protein catabolism	Pre-clinical	[64, 65]
4.	USP19 knockout (KO)	Deubiquitinating enzyme	Decrease GR target genes (Pi3kr1 (P85a), KLF15, and Ddit4) and increase Insulin signaling	Increased muscle mass in GN and TA	silencing USP19, USP19 short hairpin RNA-expressing	Pre-clinical	[66]
5.	11β-HSD Knockout	Enzyme inhibition	FoxO1, Trim63 and Fbxo32 mRNA expression decreased and modification in ribosomal protein S6 phosphorylation	Increase muscle mass and muscle fibers	Conversion of cortisone to cortisol	Pre-clinical	[67]
6.	Branched chain amino acids (BCAAs) or leucine	Amino acid supplement	Plasma creatinine increase, activate mTOR1	Decreased soreness of thigh, calf, Hamstring muscle mass and total muscle mass	GR signaling inhibition, Stimulate muscle protein synthesis	Pre-clinical and clinical	[68, 69]

7.	Glutamine (BCAA)	Amino acid supplement	Expression of Myostatin	Increased muscle weight of gastrocnemius, soleus and EDL, femoral (in human study)	GR signaling inhibition Decreased, expression of MSTN, Increase Akt/p-Akt	Pre-clinical and clinical	[70, 71]
8.	Creatine	Amino acid supplement	IGF-1 signaling	Increased muscle mass in EDL and plantaris	Increased insulin sensitivity, Glucose and GLUT4 translocation	Clinical	[72]
9.	Clenbuterol	Drug (β-adrenergic receptor agonist)	IGF-1 and myostatin expression, Muscle mTOR expression	Increased the muscle mass in soleus, reduced fat and increased muscle weight	Inhibit GR binding to GRE	Preclinical and clinical	[73, 74]
10.	Bimagrumab	Monoclonal antibody	Myostatin signaling	Inter-muscular adipose tissue, Thigh muscle volume increased	Inhibition of activin type-II receptor	Clinical	[75]
11.	Psoralen	Naturally derived	TNF-α	Increased myoblast viability	Anti-TNFα action. Decreased protein expression of MURF1, MAFbx, TRIM62 and GDF15	Pre-clinical	[76]
12.	Salidroside	Natural compound (biologically active ingredient of *Rhodiola rosea*)	IL6	Increased mass of TA muscle	Downregulation of IL6/STAT3	Pre-clinical	[77]
13.	S-allyl cysteine	Natural compound (active component of garlic-*Allium sativum*)	TNFα, IL-6, IL-1	Myotube regains length	Anti-inflammatory action	Pre-clinical	[78]
14.	Vitamin-D	Vitamins supplement	GC induced FoxO1	Protected myoblast cells	Inhibits FoxO1 signaling pathway	Clinical	[79, 80]
15	*Cassia occidentalis* (CSE-Bu)	Natural compound (ethanolic extract of *C. occidentalis*'s stem)	GLIZ mRNA expression, skeletal muscle atrogenes	GC induced expression decreased in GN muscles	Inhibit Glucocorticoid-induced leucine zipper (GILZ)	Pre-clinical	[81]
16	Glabridin	Natural compound (licorice flavonoid oil)	Glucocorticoid receptor	Reduced diameter atrophic C21C2 Myotubes	Inhibit nuclear translocation of glucocorticoid receptor and phosphorylation of FoxO3a	Pre-clinical	[82]
17	Heat-killed *Lactobacillus curvatus* CP 2998	Probiotic Agent	GR-dependent transcription	Restore diameter size of atrophic C2C12 myotubes	Inactivation of GR, reduced mRNA expression of MuRF1, MAFbx, E3Ubiquitin ligase	Pre-clinical	[83]
18	Schisandrin A (SNA)	Natural component (fruits of *Schisandra chinensis*	Akt/FoxO and Akt/70S6K pathway, expression of MSTN	increased grip strength, muscle weight, and muscle fiber size	Reduction of MAFbx, atrogin1, MuRF1expression, Increase expression of myosin heavy chain	Pre-clinical	[84]

Table 1: *Interventions to ameliorate chronic stress-induced muscle atrophy. The given table is briefly highlighting the source of intervention, targets, their effects on muscle, type of study performed, and mechanism involved for the prevention of muscle atrophy.*

In the given table 1 portrayed the recent and newly found interventions which target different transcriptional genes and cofactors mediating stress-induced muscle atrophy. Targeting on direct GC receptors, various medications are under research clinically and preclinically such as GRβ overexpression as a transcription factor [64,65,85], 11β-HSD inhibiting enzyme [67], BCCAs (like- leucine, glutamine, creatine) [68-72] provided as a supplement to increase muscle protein synthesis, glabridin as a natural component which direct targets GR receptors [82], natural butanol extract from *Cassia occidentalis* and probiotics like *Lactobacillus curvatus* (CP2998) [83]. All these categories of remedies also affect other signaling pathways such as IGF1 signaling, Akt/mTOR, and altering F box expression [65,72,82,83]. It was previously described that the factors directly influencing GC are identified as the potential targets to mitigate the atrophic conditions like myostatin inhibition through the delivery of these ongoing research ameliorations like myostatin deletion [63], use of Bimagrumab [75] and Glutamine [70,71]. Clenbuterol is a drug that has a stimulatory effect on IGF1 signaling as well as inhibitory effect on myostatin [73,74]. Vitamin D is under clinical research while Schisandrin A is under preclinical study targeting FoxO and Akt/FoxO [79,80,84]. Another potential factor to target is the inflammatory effects produced on exposure to stress and can be reduced using Psoralen [76], and S-allyl cysteine [78].

Conclusion

Stress-induced muscle atrophy has been proved to have the potential to emerge in-research targets, innovations, and biological tools which might have a role in mediating the induction of muscle atrophy. Although there are few numbers of stress-induced muscle atrophy models but are proved to cause atrophy in rodents, also on chronic exposure may have the same effect on humans, categorically in the elderly population with sarcopenia that is still under research. From these, under research studies, we may conclude that IGF1/Akt/mTOR//FoxO and myostatin are the major targets to cause muscle atrophy while there are factors that cannot be considered as minor but have potential to degenerate muscle fibers and cause loss of muscle mass such as REDD1, KLF15, USP19 and inflammatory markers like IL6, IL1 and TNF-α. Thus, on understanding the protein degradation targets and biomarkers, the effect of stress on human skeletal muscles, the development of remedies for muscle atrophy induced by stress through increased GC levels might become possible since we already know that there is scarcity for the treatment of this ailment. This is the first review that represents muscle atrophy provoked by psychological stress pathologies and all the relevant information to target therapeutics. Perhaps, this co-relation still needs to be fully understood by undertaking in-depth clinical studies on humans.

Conflict of Interest

None.

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