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Regulatory and Pathophysiological Roles of Reactive Oxygen Species in Skeletal Muscle

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ABSTRACT

Skeletal muscle is a complex organ in the body that has pivotal roles in movement, respiration, metabolism, and other normal daily activities. Owing to its contractile activity, oxygen consumption and metabolic functions, oxidant species, such as Reactive Oxygen Species (ROS) or Reactive Nitrogen Species (RNS) are continuously generated in skeletal muscle. ROS/RNS have been reported to have dual functionality in skeletal muscle: They may induce oxidative damage, tissue dysfunction, and myopathy, but they can also regulate various biochemical processes, such as gene expression, calcium signaling, and contractility to confer beneficial effects on the organism. In skeletal muscle, the precise action of ROS/RNS has been found to be linked to their concentration. At lower concentrations, they generally act as regulatory molecules to enhance muscle force and muscle function; however, at higher concentrations, they may cause oxidative damage leading to a decreased muscle performance and occurrence of atrophy. The present review has shed light on the physiological and pathological roles of ROS/RNS in skeletal muscle health and discussed their possible mechanisms of action.

Keywords: Skeletal muscle; Oxidative stress; Reactive oxygen species; Reactive nitrogen species; Proteolysis; Mitochondrial dysfunction; Excitation-contraction coupling

INTRODUCTION

Skeletal muscle is a dynamic and plastic tissue in human body that contributes significantly to multiple bodily functions comprising mechanical and metabolic activities of the body. Mechanically, it maintains posture and supports health leading to functional independence; metabolically, it participates in basal energy metabolism, storage of amino acids and carbohydrates, thermogenesis, utilization of oxygen increased during physical activity and exercise etc [1]. Various factors including nutritional status, physical activity, age, exercise, and the activation of biomolecular pathways promoting function and metabolic activity of muscle are critical for muscle health [2]. Reactive oxygen species, commonly known as ROS, have long been considered entities harmful to skeletal muscle tissue. Research has determined the pathogenic role of ROS in inherited muscle health abnormalities and subsequently identified them a causative agent in multiple muscular diseases [3-5]. However, as the field of research has expanded, it has been proposed that the presence of ROS at physiological concentrations may play a beneficial role in physiology of skeletal muscle. ROS can regulate multiple processes in skeletal muscles such as transcription factor activity, ion transport, apoptosis, and metabolism, including various proteins critical for muscle cell function [6]. The major distinctions between physiological and pathological signaling exerted by ROS stem from their concentration, reactivity, and origin. At low concentrations, they increase muscle force and enhance adaptation to exercise, whereas at a high concentration, they lead to a decline in muscle performance [7]. During exercise, ROS promotes mitochondrial biogenesis *via* peroxisome Proliferator-activated receptor Gamma Coactivator-1α (PGC-1α)-activated signal transduction pathway, but at higher concentrations, mitochondria and mitochondrial DNA (mtDNA) may be adversely affected by ROS, which impairs the myogenic differentiation process [8-10]. Therefore, the regulatory and pathological effects of ROS on skeletal muscle func-

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tion are associated with the concentration of ROS targeting the muscle cells and the duration of exposure. Other factors that may impact the physio-pathological activities of muscle are the sources of ROS, their targets, reactivity of ROS, anti-oxidative capacity of cells, and the cells' defense mechanisms [11]. Presently, ROS are known to trigger many signaling pathways related to skeletal muscle homeostasis and adaptation. Hence, the present review has been drafted to discuss the various roles of ROS on the physiological and pathological condition of skeletal muscle, along with their possible mechanisms.

GENERATION OF ROS IN SKELETAL MUSCLE

ROS are chemically reactive molecules containing an unpaired electron produced from the incomplete reduction of molecular oxygen. Reactive Nitrogen Species (RNS) are substances produced by the reaction of NO with compounds containing ROS. Most ROS are produced as by-products of the mitochondrial Electron Transport Chain (ETC) [12]. The leakage of electrons or the uncoupled transfer of an electron during its movement from complex I to complex III in the ETC leads to superoxide radicals formation ($O_2^{\bullet-}$) [13]. Furthermore, during muscle contraction, oxygen consumption is increased which is utilized in the ETC. Oxygen is the final acceptor of electron in ETC. After accepting electron, it turns reactive and undergoes reduction with the proton (H^+) found in the matrix of mitochondria that ultimately forms water. Approximately 5% of O_2 is reported to be converted to superoxide. In addition to this, superoxide can be produced from various locations within muscle fibers including the mitochondrion, sarcoplasmic reticulum, transverse tubules, sarcolemma, and the cytosol [14].

Although mitochondria are thought as the primary source of ROS, studies reported that Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidases (NOXs), a multicomponent enzyme system located in the plasma membrane, sarcoplasmic reticulum, transverse tubules, and the sarcolemma also produce ROS [14]. NOXs catalyze the reduction of O_2 to $O_2^{\bullet-}$ by utilizing NADH or NADPH as electron donors. NOX2 and NOX4 are isoforms of NOX present in skeletal muscle and considered to be the major source of ROS in striated muscle [15]. Moreover, Xanthin Oxidase (XO), cytosolic in origin generates superoxide as a byproduct of oxidation of hypoxanthine to xanthine and uric acid in the cytosol of contracting skeletal muscle [16].

Phospholipase A2 (PLA2) also generates ROS. PLA2 acts on the cell membrane and releases arachidonic acid. The deoxygenation of arachidonic acid by lipoxygenase enzymes generates ROS [17]. Mechanistically, the activation of PLA2 can stimulate NOXs, which promotes ROS production in the mitochondria and cytosol of muscle and release ROS into the extracellular space [18,19]. Both the calcium-dependent and independent forms of PLA2 are present in skeletal muscle and participate to ROS generation in the muscle [6]. It is suggested that ROS activity under resting conditions is mediated *via* calcium-independent PLA2, whereas during inflammation, stress, and contractions, calcium-dependent PLA2 is activated to induce ROS production [19].

Superoxide molecules formed during the above processes act as a substrate for the generation of secondary ROS molecules. The dismutations of superoxide radical by Superoxide Dismutase (SOD) convert it to another non-radical ROS, namely hydrogen peroxide (H_2O_2). Hydroxyl radicals ($^{\bullet}OH$) are formed from H_2O_2 by Fenton reaction [20]. H_2O_2 is also converted to H2O by the enzymatic action of antioxidants catalase and Glutathione Peroxidase (GPx). Hence, in a nutshell, ROS/RNS include superoxide anions ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($^{\bullet}OH$), and the highly reactive peroxynitrite ($ONOO^-$), which is formed from the reaction of nitric oxide (NO) and $O_2^{\bullet-}$ (**Table 1**).

Table 1: ROS in skeletal muscle

Species	Producing site/enzyme
Superoxide ($O_2^{\bullet-}$)	Mitochondria, NADPH oxidase, Xanthin oxidase, PLA2
Hydrogen peroxide (H_2O_2)	Dismutation of superoxide by superoxide dismutase
Hydroxyl radicals ($^{\cdot}OH$)	Produced from H_2O_2 by Fenton reaction
Peroxynitrite ($ONOO^-$)	Reaction of nitric oxide (NO) and $O_2^{\bullet-}$

ANTIOXIDANT DEFENSE IN SKELETAL MUSCLE

Antioxidants are the compounds that scavenge or neutralize the ROS and prevent the cellular damages induced by ROS. They are essential molecules to maintain the equilibrium between production of ROS and its neutralization i.e., redox homeostasis in the body [6]. There are two types of antioxidants exist: Enzymatic and non-enzymatic antioxidants.

Enzymatic Antioxidants

Primary enzymatic antioxidants include Superoxide Dismutase (SOD), catalase, and Glutathione-Peroxidase (GPx). Other secondary or ancillary enzymatic antioxidants that function to protect cells from oxidation are Peroxiredoxins (PRXs), Thioredoxin (TRX), and Glutaredoxins (GRX) etc. Superoxide Dismutase (SODs) dismutates superoxide radicals ($O_2^{\bullet-}$) and convert it to H_2O_2 and Oxygen (O_2). They exist in three isoforms namely SOD1, SOD2 and SOD3 [21,22]. All these three isoforms of SOD contain the transition metal to their active sites to exert the dismutation reaction. SOD1 has Copper-Zinc as cofactor and found in the cytosol and mitochondrial intermembrane space. SOD2 contain manganese as a cofactor and situated in the mitochondrial matrix. SOD3 acquires copper-Zinc as cofactor and located in extracellular space [22]. In skeletal muscle, the maximum amount of SOD is found in cytosol (65%-85%) whereas (15%-35%) is present in the mitochondria of muscle [23]. Moreover, the activity of SODs in oxidative muscle fiber was found higher than glycolytic fibers [24,25]. The deficiency of SOD1 in skeletal muscle found to markedly increase oxidative stress whereas the contraction of myogenic fiber activates SOD1 and SOD2 [26]. Catalase, which incorporates iron as a cofactor, is ubiquitously distributed in the cells. It catalyzes the breakdown of H_2O_2 into H_2O and O_2 [27]. Like SOD, the activity of catalases is maximum in oxidative muscle fibre than the glycolytic muscle fibres [28]. It also shows lower affinity for H_2O_2 compared to GPx. Glutathione-Peroxidase (GPx) is a Se-dependent enzyme that catalyzes the reduction of H_2O_2 or organic hydroperoxide (ROOH) to water and alcohol (ROH) respectively

[29]. It is found in both the cytosol and mitochondria of the cell. It shows maximum activity in type-I muscles fiber (slow-twitch muscle fiber) compared to fast-twitch muscle fibres [30]. Among secondary antioxidants, the TRX antioxidant system is situated in the cytosol and mitochondria and protects the proteins from being oxidized. It also prevents apoptosis and exerts protection against oxidative stress [31]. Thioredoxin reductase, exhibit antioxidant effect by reducing hydroperoxides [31]. GRX is also found in cytosol and mitochondria and participate in the protection and repair of protein and non-protein thiols under oxidative stress condition [32]. Lastly, PRX, a cysteine dependent peroxidase, located in skeletal muscle cells either in mitochondrion or in cytosol, peroxisome, and nuclei. It can reduce peroxides, hydroperoxides and peroxynitrite using electrons given by physiological thiols [33] (**Table 2**).

Table 2: Antioxidants in skeletal muscle (Enzymatic)

Name	Types	Localization	Functions
Superoxide Dismutase (SOD)	SOD1 (Cu-Zn SOD)	Cytosol, Mitochondria, Intermembrane space	Superoxide neutralization
	SOD2 (MnSOD)	Mitochondrial matrix	Superoxide neutralization
	SOD3 (Cu-Zn SOD)	Extracellular fluid	Superoxide neutralization
Catalase		Cytosol, Mitochondria, Peroxisome	Breakdown of H_2O_2 into H_2O and O_2
Glutathione Peroxidase (GPx)	GPx1, GPx2, GPx3, GPx4, GPx5, GPx6, GPx7, GPx8	Cytosol, mitochondria, extracellular fluids, GIT, and kidney tissues	Reduction of H_2O_2 or organic hydroperoxide (ROOH) to water and alcohol (ROH).
Secondary or ancillary enzymatic antioxidants			
Peroxiredoxins (PRXs),	PRDX1, PRDX2, PRDX3, PRDX4, PRDX5, PRDX6	Mitochondria, cytosol, Peroxisome, and nucleus	Reduces peroxides, hydroperoxides and peroxynitrates
Thioredoxin (TRX)		Cytosol, Mitochondria	Prevent protein oxidation, apoptosis, and oxidative stress
Glutaredoxins (GRX)		Cytosol, Mitochondria	Protection and repair of protein and non-protein thiols under oxidative stress

Non-Enzymatic Antioxidants

Non-enzymatic antioxidants include Glutathione (GSH), vitamin-C, vitamin-E, α-lipoic acid, uric acid, bilirubin, coenzyme Q10 (CoQ10), carotenoids, and polyphenols etc [34]. GSH is one of the most important non-enzymatic antioxidants in the muscle fibre. The availability of GSH in the cells corresponds to the extent of exposure of oxidants to that cell. Moreover, it was found that the concentration of GSH in slow-twitch muscle fiber (type-I) is 4-5-fold higher than fast twitch muscle fibre (type-II) [35]. Among various roles of GSH, it acts as a substrate for GPx to eradicate H_2O_2 and other organic hydroperoxide [36]. It is also associated with the reduction of antioxidants like vitamin-C and vitamin-E to maintain them in reduced state. The adaptation of skeletal muscle fiber to high intensity exercise in linked to improved GSH level [37]. Likewise, vitamin C and vitamin E also exert antioxidant effect. They play vital roles in protecting cellular membrane and plasma lipoprotein against lipid peroxidation, as they can scavenge ROS/RNS specially peroxyl radicals ($ROO^{\bullet}$) [38]. α lipoic acid is another non-enzymatic antioxidant. It is naturally found and distributed in various foods. It acts as a cofactor for α-dehydrogenase complex and associated with other cellular reactions. Various studies have suggested that α-lipoic acid can exert antioxidant effect by recycling vitamin-C [39]. Uric acid is a by-product of purine metabolism and a low molecular weight antioxidant [40]. It acts as an effective scavenger of peroxyl radical, hydroxyl radical, and singlet oxygen [41]. Bilirubin is the end-product of hemoprotein degradation. It shows antioxidant activity against peroxyl radicals and prevents cellular damage induced by H_2O_2 [42]. CoQ10 is a component of mitochondrial electron transport chain which functions as a non-enzymatic antioxidant by scavenging ($ROO^{\bullet}$ radicals) and preventing lipid peroxidation [43]. Polyphenols (PPs) are naturally occurring organic compounds that are distributed in different plants, fruits, vegetables, nuts, seeds, flowers, tea, and beverages. They exert strong antioxidant activity by scavenging the free radicals and preventing the upregulation of oxidative stress-induced pathways [44] (**Table 3**).

Table 3: Antioxidants in skeletal muscle (non-enzymatic)

Name	Functions
Glutathione (GSH)	Acts as a substrate of GPx to remove H_2O_2 and other organic hydroperoxide
Vitamin C and Vitamin E	Scavenging of ROS/RNS specially peroxyl radicals ($ROO^{\bullet}$)
α-lipoic acid	Acts as a cofactor for α-dehydrogenase complex
Uric acid	Scavenging of peroxyl radical, hydroxyl radical, and singlet oxygen
Bilirubin	Prevent cellular damage induced by H_2O_2
Coenzyme Q10	Scavenging ($ROO^{\bullet}$ radicals) and preventing lipid peroxidation
Polyphenols	Scavenging ($ROO^{\bullet}$ radicals) and preventing lipid peroxidation

ROLE OF ROS AS REGULATORY MOLECULES

ROS act as signaling molecules to regulate various physiological activities. They are imperative to maintain oxidation-reduction homeostasis and correct functioning in the body [45]. They regulate signaling pathways for proper cell cycle and apoptosis and play vital roles in gene activation, cellular growth, and the modulation of chemical activities in the cells [46]. Skeletal muscle maintains redox equilibrium between ROS/RNS generation and antioxidant defense that is in constant equilibrium even after contraction [45]. At basal ROS level, they regulate protein phosphorylation, ion channels, transcription factors, immune defense, and muscle function [47]. ROS activate the PI3K-NFE2-like2 (Nrf2)-antioxidant response element to protect cells from oxidative damage and maintain the redox homeostasis [48]. Similarly, during exercise, numerous signaling pathways such as PGC-1α, 5'-AMP-Activated Protein Kinase (AMPK), mitogen-activated protein kinase, insulin-like growth factor-1 (IGF-1), and calcium are regulated by the physiological concentration of ROS [49]. Furthermore, ROS induce the

phosphorylation of transcription factors and hence increase protein synthesis due to their kinase activation (e.g. ERK, JNK, and p38) and phosphatase deactivation [50]. ROS induced by H_2O_2 in C_2C_{12} cells significantly enhanced IGF-I-induced phosphorylation of the IGF-I receptor (IGF-IR) which was attenuated by treatment of antioxidants, suggesting ROS are necessary for IGF-1 myocyte hypertrophy [51]. The pathways mentioned above are foundational for muscle adaptation owing to their modulation of mitochondrial biogenesis and function, anti-oxidative capacity, proliferation and differentiation of myoblast, and growth of muscle.

EXCITATION-CONTRACTION COUPLING

Excitation-Contraction (EC) coupling is a series of events that propagates the action potential through sarcolemma causing activation of Dihydropyridine Receptors (DHPRs) and Ryanodine Receptors (RyRs) to release calcium from sarcoplasmic reticulum into cytoplasm/sarcoplasm leading to force generation and contraction into sarcomere [52]. Dihydropyridine Receptors (DHPRs) are present in the t-tubules of sarcotubular system. The activation of DHPR activates Ryanodine Receptors (RyRs) closely located to t-tubules [52]. Mammalian cells express three types of RyRs: RyR1, RyR2, and RyR3. RyR1 is the dominant isoform in skeletal muscle [53]. The activation of RyR1 stimulates the release of calcium stored in sarcoplasmic reticulum into the cytoplasm/sarcoplasm. The released calcium then binds to the regulatory protein troponin and causes confirmational change to another protein tropomyosin to initiate the contraction, which is basically the interaction between actin and myosin [52]. This process requires ATP along with Ca^{2+} [54]. During relaxation, released calcium transported back to the sarcoplasmic reticulum through SR Ca^{2+} ATPase (SERCA) pumps. SERCA is an ATP-dependent Ca^{2+} pump located in the free sarcoplasmic reticulum [52]. Disturbance of calcium channels like RyRs and SERCA in the sarcoplasmic reticulum membrane can interrupt the Ca^{2+} regulation leading to uncoupling of excitation and contraction events [55]. The calcium (Ca^{2+}) ion modulates various cellular functions such as contraction, secretion, metabolism, gene expression, cell survival etc. Therefore, proper Ca^{2+} handling in the muscle fiber is pivotal as calcium dysregulation may impair muscle force generation and with oxidative stress [56].

ROS IN EXCITATION-CONTRACTION COUPLING

The excitation-contraction coupling in skeletal muscle is modulated by ROS [57]. Depolarization of skeletal muscle upregulates NOX enzymes found in the t-tubules and sarcoplasmic reticulum of sarcotubular system. The activation of NOX generates ROS which modulates Ca^{2+} release by the RyR1 and regulate excitation-contraction coupling [58,59]. However, excessive increase of ROS can exert adverse effects to EC coupling. Oxidative stress-induced leaking of RyR1 Ca^{2+} and SERCA oxidation may induce muscle atrophy and muscle weakness as reported by Qaisar et al. [60,61]. Similarly, increased ROS ($O_2^{\bullet-}$, $OH^{\bullet}$ and H_2O_2) due to high copper concentration impaired myocardial excitation-contraction coupling, decreased force generation capacity, Ca^{2+} release and reuptake and diminished myosin-ATPase activity [62].

High level of Ca^{2+} in cytosol can also promote mitochondrial ROS production and proteolysis by calpain activation [63]. Oxidative stress reduces the activity of SERCA pump as reported by Sharov et al. (2006) where aging-induced oxidative stress increased oxidation of cysteine residue of SERCA proteins [64]. In skeletal muscle, cysteine residues like Cys674 and Cys675 regulate the SERCA activity by reversible oxidation through peroxynitrite-induced glutathionylation; however, increased oxidative stress may cause irreversible oxidation of cysteines including sulfonylation leading to reduced SERCA activity [65,66]. Oxidative stress-induced mice lacking antioxidant enzyme CuZnSod (sod1-/-) showed reduced membrane excitability and RyR stability, decreased fiber Ca^{2+} sensitivity and suppressed SERCA activity *via* modification of the Cys674 residue, dysregulated SR and cytosolic Ca^{2+} homeostasis, and impaired mitochondrial Ca^{2+} buffering and respiration [67]. Thus, the above arguments suggest that physiological ROS regulate EC coupling however oxidative stress condition causes impairment of EC coupling.

ROS DURING MYOGENESIS

Myogenesis is an organized process that involves the activation of satellite cells into myoblasts followed by proliferation and differentiation to form myotubes [68]. It occurs both during neonatal growth and muscle injury. In adult skeletal muscle, tissue homeostasis is maintained *via* self-renewal of skeletal muscle satellite cells that compensate for the turnover of terminally differentiated cells [69]. Myogenic regulatory factors MyoD, Myf5, Myf6, myogenin, myocyte enhancer factors, and the serum response factor are the vital players for myogenesis regulation [70]. In the injured muscle signals such as Wnt signaling, JAK/STAT1/STAT3 Signaling, PI3K/AKT signaling etc. are stimulated which stimulate muscle satellite cells to migrate toward the injury site and initiate cell cycle to undergo proliferation [71]. In the early stages of regeneration, IL-6 signaling promotes muscle satellite cell proliferation by activating the JAK/STAT1/STAT3 signaling pathway [72] and the PI3K/Akt signaling pathway which not only promotes muscle protein synthesis but also activate the proliferation of muscle satellite cells [73]. Both the IL-6 and PI3K/Akt signaling were found to be mediated by ROS in skeletal muscle [74,75]. ROS are likely to function as a double-edged sword in myogenesis.

POSITIVE EFFECTS OF ROS IN MYOGENESIS

At the physiological level, ROS modulate cellular proliferation, migration, differentiation, and muscle contractions [76]. However, under oxidative stress condition, it led to muscle damage and injury impairing muscle function [77]. Study conducted by Hansen et al. (2007) reported that lower intracellular redox potential promotes differentiation of skeletal muscle cell whereas higher redox potential exerts inhibitory effect [76]. Treatment of ROS scavenger, phenyl-N-tert-butylnitrone, decreased oxidative stress and increased C_2C_{12} differentiation while addition of 25 µM H_2O_2 to cells in the presence of 20% O_2 significantly impaired differentiation process [76]. Similarly, the physiological expression of Nrf2 attenuated the production of excessive ROS and enhanced myoblast proliferation and viability. However, overexpression of Nrf2 prevented C_2C_{12} cell differentiation

along with the downregulation of Myogenic Regulatory Factors (MRFs) [78]. Furthermore, differentiation of C_2C_{12} cells was found to be associated with the increased ROS as indicated by increased expression of ROS related molecules such as hypoxia inducible factor1-alpha (HIF1-α), hypoxia inducible factor1-beta (HIF1-β), Von Hippel-Lindau (VHL), lysyl oxidase (Lox), EGL-9 family hypoxia-inducible factor 1 (EGLN1), proline 4-hydroxylase alpha 1 (P4HA1) and decreased level of heme oxygenase-1 (HOMX1) [79]. The moderate production of ROS during exercise or regeneration induces myogenic differentiation of satellite cells and myoblasts, while excessive accumulation of ROS results in their senescence, apoptosis, and regenerative failure in muscle repair [80,81]. These arguments suggest that moderate level of ROS is involved in regulation of myoblast differentiation while its inhibition by overactivation of antioxidants may interfere myogenesis.

NEGATIVE IMPACTS OF ROS IN MYOGENESIS

High ROS may target mitochondria and mitochondrial DNA causing blockage of myogenesis [9]. Excess ROS inhibited myogenesis with decreased expression of satellite cell markers, reduced expression of myoblast differentiation markers and reduced phosphorylation of MAPK signaling pathways [77,82]. The p38-MAPK signaling pathway is crucial in regulating skeletal muscle gene expression at different stages of the myogenic process [83]. ROS induced NF-kB activation lowers expression of MyoD, thereby inhibiting myogenesis [84]. Moreover, NF-κB was also found to suppress myofibrillar gene expression by mediating the regulation of myogenic transcriptional repressor Yin Yang 1 (YY1) [85,86]. Oxidative stress and $p66^{ShcA}$, a mammalian adaptor protein localized in the mitochondria and functions as a redox enzyme that generates mitochondrial ROS, in skeletal muscle negatively modulate myogenic differentiation; in contrast, p66ShcA deletion enhances skeletal muscle regeneration after ischemia [87]. The deficiency of Nrf2 gene increased oxidative stress and decreased regeneration with decreased expression of Pax7/MyoD along with apoptosis [88,89]. Mild ROS produced by low dose gelatin in mice skeletal muscle stimulated ROS production from NOX2 with increasing antioxidant defense. It increased myokine IL-6 expression that enhance myogenesis and muscle regeneration. In contrast, high dose of gelatin produced excessive ROS (O_2–, •OH) from NOX2 and mitochondrial chain complex, and suppressed antioxidant defense. This in turn released TNF-α preventing myogenesis and muscle regeneration [90]. Therefore, for proper understanding of the role of ROS in myogenesis, future studies are warranted to define an optimal intracellular redox environment that could facilitate the activation of muscle stem cells and promote differentiation of myoblasts into myotubes, thereby triggering the regeneration process in response to injury or damage.

ROS DURING EXERCISE

ROS stimulate antioxidant response and adaptations to exercise by activating redox signaling pathways such as peroxisome Proliferator-activated receptor Gamma Coactivator-1α (PGC-1α), Mitogen-Activated Protein Kinase (MAPK) and NFκB [91,92]. Exercise-induced ROS participates in improving muscle regeneration and recovery from muscle damage with insulin sensitivity [93,94]. Oxidative stress induced by exercise depends on the type, intensity, and duration of the exercise. Many studies have found that regular exercise and endurance training attenuates exercise-mediated oxidative stress along with improving the antioxidant status [95,96]. Regular exercise enhances angiogenesis, mitochondrial biogenesis, and muscle hypertrophy with improved physical fitness [97,98].

A clinical investigation found that ROS produced by physical exercise increase insulin sensitivity showing an adaptive response with the upregulation of ROS-mediated transcriptional coactivators PGC1-α, PGC1-β, and the transcription factor PPAR-gamma along with their target antioxidant SOD1, SOD2, GPx1 [99]. Surprisingly, the supplementation of antioxidants (vitamin C and E) revoked the beneficial effect of physical exercise as well as ROS mediated transcriptional activation [99]. Moreover, moderate-intensity exercise activates NOX2 that increased cytosolic ROS in human and mice. This in turn promoted the muscle glucose uptake *via* GLUT4 translocation [100]. Strikingly, lack of NOX2 subunits (either p47phox or Rac1) impaired ROS production and the glucose uptake *via* GLUT4 [100]. Exercise increases the concentration of FGF23 (Fibroblast growth factors) in skeletal muscle which improves endurance performance by controlling the ROS produced by exercise and enhancing mitochondrial functions [101].

Signaling pathways such as Adenosine Monophosphate-activated Protein Kinase (AMPK), Mitogen Activated Protein Kinase (MAPK), nuclear respiratory factor2 (Nrf2), and PGC-1α are regulated by exercise-mediated ROS production and participates in skeletal muscle responses [102,103]. Nrf2, a redox sensitive transcription factor, activates in response to exercise [104]. During its activation, it dissociates from its cytoplasmic inhibitor Keap1 and move to the nucleus to interact with Antioxidant Response Element (ARE) for transactivating downstream antioxidant genes such as oxidase Cytochrome Oxidase (COX), Superoxide Dismutase (SOD), Glutathione Peroxidase (GPX) activities and Glutathione (GSH) thereby alleviating the oxidative damage and promoting exercise-induced adaptations [105]. Merry et al. (2016) further reported that exercise-induced ROS and Nitric Oxide (NO) can activate Nrf2 which regulates skeletal muscle mitochondrial biogenesis markers such as Nuclear Respiratory Factor 1 (NRF-1), mitochondrial Transcription Factor A (mtTFA), and antioxidant defense gene, SOD1, SOD2 and catalase expression [106]. Deficiency of Nrf2 reduced mitochondrial biogenesis as well as decreased antioxidant defense [106]. Similarly, lactate produced by exercise can be coupled with ROS generation which can increase PGC1-α expression. To this connection, Nalbandian et al. (2019) has shown that treatment of C_2C_{12} cells with lactate increased PGC1-α expression which was diminished by treatment of antioxidant NAC [107]. Exercise-induced ROS can stimulate generation of myokines in human skeletal muscle as treatment of antioxidants (Vitamins A, C and E) abrogated the myokines release such as IL-6 which regulates glucose homeostasis and inhibit pro-inflammatory effects of cytokines like TNF-a [108-110].

Exercise may also cause oxidative stress in skeletal muscle [111]. Various studies suggest that exercise particularly high-intensity exercise increased accumulation of ROS due to increased metabolic rate [112-114]. Intense or exhaustive exercise can produce excessive ROS and weakens the antioxi-

dant defense system in skeletal muscle leading to muscle damage by modifying lipid, protein, DNA etc. [115,116]. Oxidative stress induced by exercise also cause post-exercise proteinuria [117]. Similarly, intense bicycling raised oxidative DNA damage along with DNA strand break down [118]. Therefore, intense or overtraining would elevate respiration rate and imbalance the redox homeostasis causing abnormality to physiological functions. Balanced and well-designed exercise training should be adopted as a preferred way to acquire the best benefits exerted by exercise (**Figure 1**).

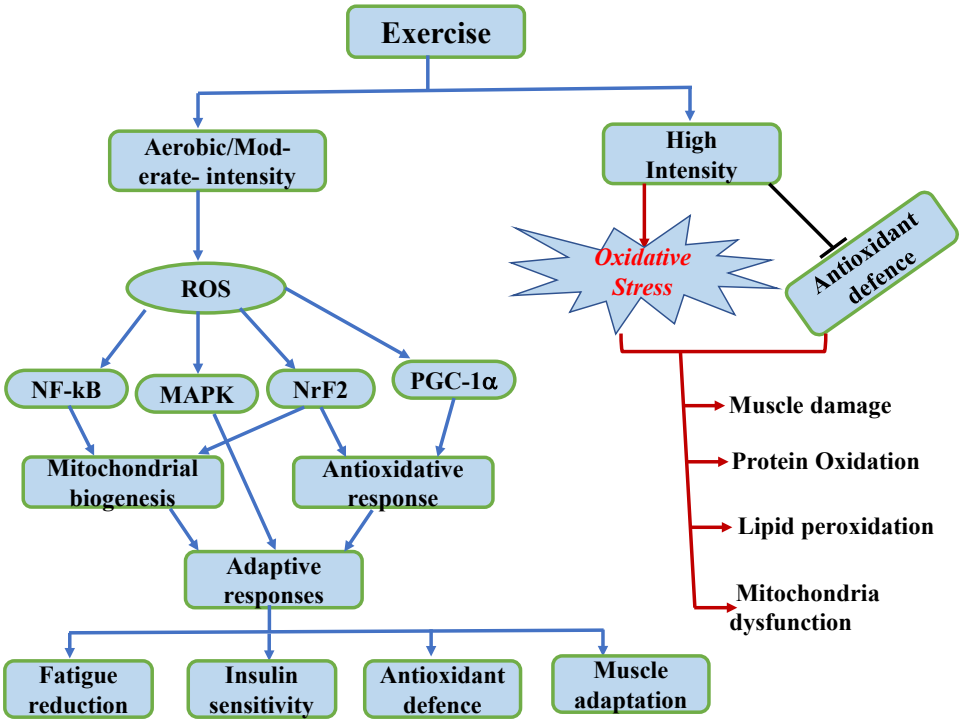

Figure 1: Diagram illustrating exercise-mediated ROS production and oxidative stress under moderate and high intensity exercise and their roles in muscle adaptation. Pointing arrows indicates induction/stimulation. ⊣ Indicates inhibition

DISCUSSION

ROS in Pathophysiological Conditions

High level of ROS and RNS has been closely linked with many pathophysiological conditions including skeletal muscle aging, inflammation, and atrophy [119]. Chronic exposure of ROS/RNS lead to macromolecular degradation, redox deregulation, impaired calcium signaling, chronic inflammation, mitochondrial dysfunction and activation of the apoptotic pathway through NF-κB causing muscle atrophy, sarcopenia, and aging [120]. Moreover, it can damage skeletal muscle and cause metabolic syndrome [121,122]. Selenium (Se), an essential trace element plays vital role against oxidative stress induced pathologies. Se is involved in Selenoprotein, the main form of selenium in animal, synthesis in the form of Selenocysteine [123]. Se^- deficiency increased generation of ROS and lipid peroxidation, and decreased activities of Glutathione Peroxidase (GPx), Total Antioxidant Capacity (T-AOC), Superoxide Dismutase (SOD), and Catalase (CAT) in skeletal muscle [124]. Moreover, Se- deficiency showed decreased level of muscle differentiation genes like Myog, Myod, Myh2, Myh3, and Myf5 [124]. It impairs antioxidant activities of Glutathione Peroxidase (GPx) and thioredoxin reductase, and also reduced the level of other antioxidant selenoproteins [125]. Glutathione Peroxidase (GPx) like GPx1, GPx2, GPx3, GPx4 are Selenium containing enzymes and involved in the protection against oxidative stress [126]. GPx reduces lipid hydroperoxide to their corresponding alcohol, and hydrogen peroxide (H_2O_2) to water. Selenoprotein, particularly Selenoprotein N (SelN) contributes to oxidative and calcium homeostasis, with a potential role in the regulation of the ryanodine receptor activity [127,128]. SelN1 is ubiquitously expressed in the body and found early in muscle precursors [129]. The mutation or deficiency of SelN was associated with muscular disorder. SelN deficient myotubes showed increased intracellular oxidant activity (ROS and Nitric oxide), excessive oxidation of proteins including the contractile proteins actin and myosin. Moreover, SelN-knockout myotubes exhibited impaired Ca^{2+} homeostasis, potentially by dysfunction of the redox-sensor Ca^{2+} channel RyR1 [130].

ROS in Age Related Sarcopenia

Sarcopenia, a term coined by Rosenberg in 1989, has been derived from the Greek phrase means “loss of flesh.” It is a progressive and generalized disorder of skeletal muscle identified by reduced muscle strength, muscle mass or quality with impaired physical performance [131], generally regarded as a geriatric syndrome. It leads to significant difficulties in performing routine daily activities conferring a high risk of fall and fractures causing loss of independence and mortality. There are multifarious causative factors for aging-induced sarcopenia such as diminished regenerative potency, imbalance of protein degradation and synthesis equilibrium, oxidative stress, mitochondrial dysfunction, and inflammation etc. [132]. ROS accumulation is increased in muscles during aging which instigate oxidation of macromolecules (lipid, DNA, and protein), mitochondrial dysfunction, inhibition of muscle cells differentiation, suggesting that oxidative stress plays role in sarcopenia-induced muscle

loss [133-135].

Skeletal muscle commonly maintains its mass by the homeostasis of protein synthesis and breakdown; however, during aging this equilibrium is disrupted due to various signaling induced by oxidative stress and inflammation. In aging, ROS production is increased as well as mitochondrial dysfunction occurs due to mitochondrial DNA mutation and damage [136]. Moreover, aged muscle cells unable to replace dysfunctional mitochondria that further stimulate ROS accumulation [137]. A study by Sullivan-Gunn et al. (2013) reported that aging triggers NOX2 mediated H_2O_2 production and reduces antioxidant enzymes such as catalase and Glutathione Peroxidase (GPx) [138]. H_2O_2 activates calpain system of myofibrillar protein degradation [139]. Calpain system may also be activated due to increased intracellular Ca^{2+} concentration during aging [140]. Agarwal et al. (2020) showed that redox remodeling induces a leaky ryanodine receptor that disturbs Ca^{2+} reuptake *via* Sarcoplasmic Reticulum Ca^{2+}-ATPase (SERCA) pumps [141-143], and increase Ca^{2+} concentration that lead to increased ROS which may activate calpain that increases susceptibility of protein degradation [144].

The CuZn-superoxide dismutase (SOD1) knockout aged mice (Sod1(-/-)) showed increased oxidative stress, decreased muscle mass and gait disturbance leading to sarcopenia [26]. Furthermore, the study of same sod1(-/-) deficient mice model reported that oxidative stress induced by SOD1 deficiency enhanced oxidative damage with upregulation of cysteine proteases, calpain and caspase-3 [145]. The activation of calpain and caspase-3 subsequently initiate proteolytic process in skeletal muscle [146]. In aged female Balb/c mice, the expression of NOX component was increased significantly followed by increment of superoxide ($O_2^{\cdot-}$), H_2O_2 and reduction of key endogenous antioxidant enzymes SOD1, catalase and GPx. This study further suggests the contribution of H_2O_2 in the development of sarcopenia [138]. Aging wistar rat muscle increased mitochondrial H_2O_2 generation in the tibialis anterior muscle with sarcopenia compared to their younger counterparts [147]. A similar result was reported in vastis lateralis muscle of aged human subjects [148]. Neuralization of H_2O_2 by muscle specific Peroxiredoxin3 (PRX3) overexpression decreased mitochondrial H_2O_2 production and improved mitochondrial function along with alleviating loss of muscle mass and quality in murine model of redox-dependent sarcopenia [149]. Sarcopenia is also induced due to imbalance of protein turnover in elderly age. Muscle protein synthesis is regulated by well-known anabolic pathway PI3K/AKT/mTOR. Anabolic resistance develops in aging that prevents protein synthesis in sarcopenic condition. Increased ROS may prevent phosphorylation of components of synthesis pathways such as Akt, mTOR and mTOR downstream targets p70S6K and 4E-BP1 [150] (**Figure 2**).

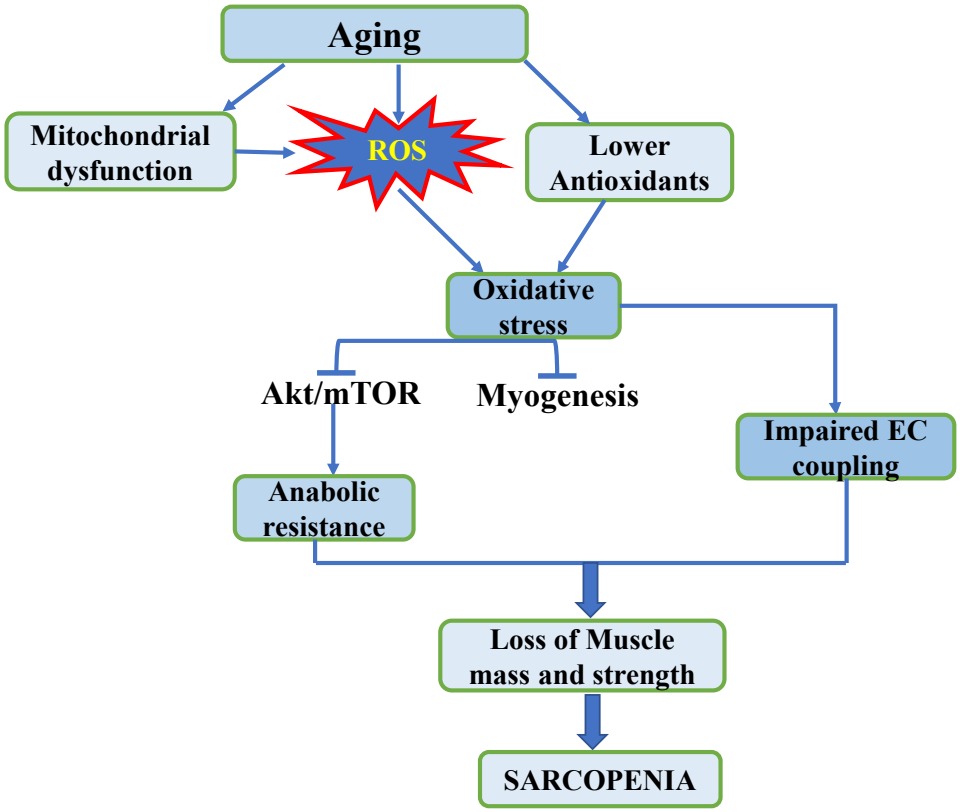

Figure 2: Diagram illustrating aging-induced ROS production and their roles in sarcopenia. Pointing arrows indicates induction/stimulation. ⊣ Indicates inhibition.

Ros in Disuse-Induced Muscle Atrophy

Disused/inactivity conditions like limb immobilization, chronic bed rest, spaceflight, spinal nerve injury, unloading etc. increases ROS productions and decreases antioxidants enzymes [151-153]. ROS are generated by several oxidants producing pathways such as xanthine oxidase, nitric oxide synthase, NADPH oxidase, and mitochondria. Although both xanthine oxidase and NADPH oxidase participates to disuse-induced oxidants production in skeletal muscle, mitochondria considered to be the dominant site of ROS production [154-156]. Inactivity results to decreased skeletal muscle mass and functions due to

increased protein breakdown and decreased protein synthesis [157,158]. We previously reported that denervation-induced disused muscle significantly produced mitochondrial H_2O_2 followed by muscle atrophy in mice [159]. The Ubiquitin-Proteasome System (UPS) is one of the major proteolytic systems in the body. Ubiquitin ligases such as Atrogin-1, MuRF-1, Cbl-b participates in protein degradation in UPS and causes muscle atrophy [160]. Previously, we found that microgravity and clinorotation increased ROS production and ROS mediated Cbl-b upregulation *via* ERK1/2 early-growth response protein (Egr)1/2-Cbl-b signaling pathway to induce muscle atrophy in L6 myotubes. Notably treatment with antioxidants like N-acetylcysteine and TEMPOL significantly decreased ROS mediated activation of ERK1/2 [161]. Cbl-b prompts degradation of IGF-1 signaling intermediate Insulin Receptor Substrate-1 (IRS-1) which ultimately activates FoxO3 dependent Atrgoin-1 and MuRF-1 expression and initiates muscle protein degradation [162]. Treatment of myotubes derived from COPD patient by H_2O_2 induced ROS production and myotube atrophy by increasing component of UPS such as Atrogin-1 and MuRF-1 [163]. In a nutshell, Inactivity-induced oxidative stress upregulates the expression of vital components of the ubiquitin-proteasome system of proteolysis.

Secondly, inactivity increases autophagy in skeletal muscle suggesting its role in disused induced muscle proteolysis [164]. ROS induces autophagy and increases autophagy related genes by activating various ROS-mediated signaling like mitogen-activated kinase (p38-MAPK), AMPK etc. ROS-induced activation of p38-MAPK increased myotube atrophy and level of multiple autophagy-related genes (e.g., Atg7, LC3 and Beclin-1) [165]. Mitochondrial targeted antioxidant SS-31 treatment decreased autophagy related genes LC3, cathepsin etc. in soleus and plantaris muscle of inactivity induced rat muscle [156]. Similarly, ventilator-induced oxidative stress inhibition significantly reduced autophagy markers in muscle fibers. Reduction of oxidative stress in diaphragm by antioxidant during mechanical ventilation decreased levels of LC3, Atg7, Atg12, Beclin-1, cathepsin B, cathepsin D, and cathepsin L in diaphragm muscle [164]. The above facts suggest that oxidative stress is involved in activating autophagy that contributes to inactivity induced proteolysis.

Calpains, a Ca^{2+} dependent proteolytic system is also involved in disuse-induced muscle loss [166], as muscle-specific overexpression of calpastatin (endogenous inhibitor of calpains) prevented muscle mass loss in hindlimb unloading mediated disuse model [167]. Oxidative stress increases the expression of Calpain-1 and Calpain-2 [139,168]. Treatment of mitochondrial targeted antioxidant SS-31 decreased calpain induced muscle proteolysis by suppressing oxidative stress in immobilization and mechanical ventilation-induced muscle atrophy in rodents [169]. Based on all above reports it can be summarized that inactivity and disuse mediates muscle atrophy *via* activating different proteolytic system due to increased oxidative stress, and supplementation of antioxidant decreases the severity of muscle loss during prolong inactivity, although some contradiction exist [170] (**Figure 3**).

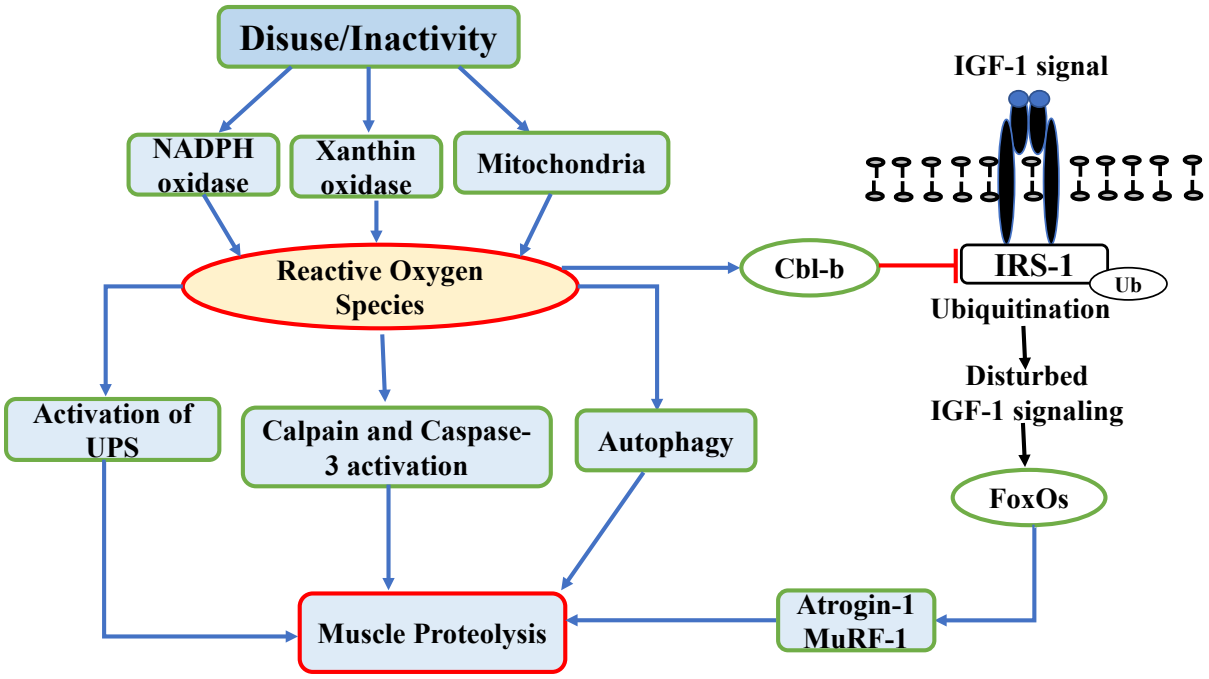

Figure 3: Diagram illustrating disuse/inactivity-induced ROS production and their roles in muscle proteolysis. Pointing arrows indicates induction/stimulation. ⊣ Indicates inhibition.

ROS in Glucocorticoid-Induced Muscle Atrophy

Glucocorticoids (GCs) are steroidal drugs commonly prescribed in inflammatory and autoimmune diseases. Prolong or high intake of GCs is associated with multiple side effects such as osteoporosis, adrenal gland dysfunction, hyperglycemia, and muscle atrophy [171]. The level of GCs increased during different pathological states e.g., sepsis, cachexia, starvation, metabolic acidosis, and severe insulinopenia, that are characterized by muscle atrophy, indicating the possibility that GC could trigger muscle atrophy. GCs induce muscle atrophy by decreasing protein synthesis and increasing protein degradation [171]. The major proteolytic pathway for GC-induced muscle atrophy is the activation of the ubiquitin proteasomal system (UPS) and the lysosomal system through the increased expression of sev-

eral atrophy-inducing genes such as FOXOs, Atrogin-1, MuRF-1 etc. Moreover, the reduction of protein synthesis is mediated *via* inhibition of PI3K/AKT/mTOR pathway of protein synthesis [171].

GCs have been reported to increase the production of ROS in skeletal muscle in various cell and animal models [172-174]. In humans, chronic GC administration increased 8-OHdG level (an indicator of DNA damage) along with mitochondrial DNA damage mediated by ROS in skeletal muscle [175]. Hydroxyl radicals ($OH^{\bullet}$) were also increased by GC treatment in steroid myopathy induced by dexamethasone (Dex) [176]. Previously, we reported that Dex increases ROS production *via* glucocorticoid receptor-mediated pathway that induced muscle atrophy by increasing Atrogin-1 and MuRF-1 with the upregulation of Cbl-b [177]. Cbl-b is an oxidative stress-sensitive ubiquitin ligase that is upregulated by ROS and causes muscle atrophy by increasing Atrogin-1 and MuRF-1 [161,162]. Dex also decreased antioxidant enzymes such as SOD1 and catalase. A study conducted by Espinoza et al. reported that GC treatment upregulates NADPH oxidase (NOX) mRNA expression which generates ROS by catalyzing the transfer of electrons to O_2, producing superoxide or H_2O_2, using NADPH as an electron donor [178]. NOX1 is upregulated by Dex in smooth muscles [179]. Moreover, Dex-induced hydroxyl free radical ($OH^{\bullet}$) production decreased cell viability and increased apoptosis to C_2C_{12} cells which was reversed by treatment with the antioxidant quercetin [180]. Dex increased cellular ROS levels and induced oxidative damage to proteins and lipids in skeletal muscle [181]. Moreover, it causes mitochondrial dysfunction by impairing mitochondrial respiration and decreasing the activities of mitochondrial complexes I, II, and IV, and ATP synthase [181,182]. Supplementation of antioxidant compound *Psoralea corylifolia L.* seed extract decreased Dex-induced muscle atrophy by decreasing oxidative stress and inflammation [183]. Based on above reports, it can be suggested that ROS may be a causative agent in glucocorticoid induced muscle atrophy. The schematic diagram of glucocorticoid-induced muscle atrophy has been shown below (**Figure 4**).

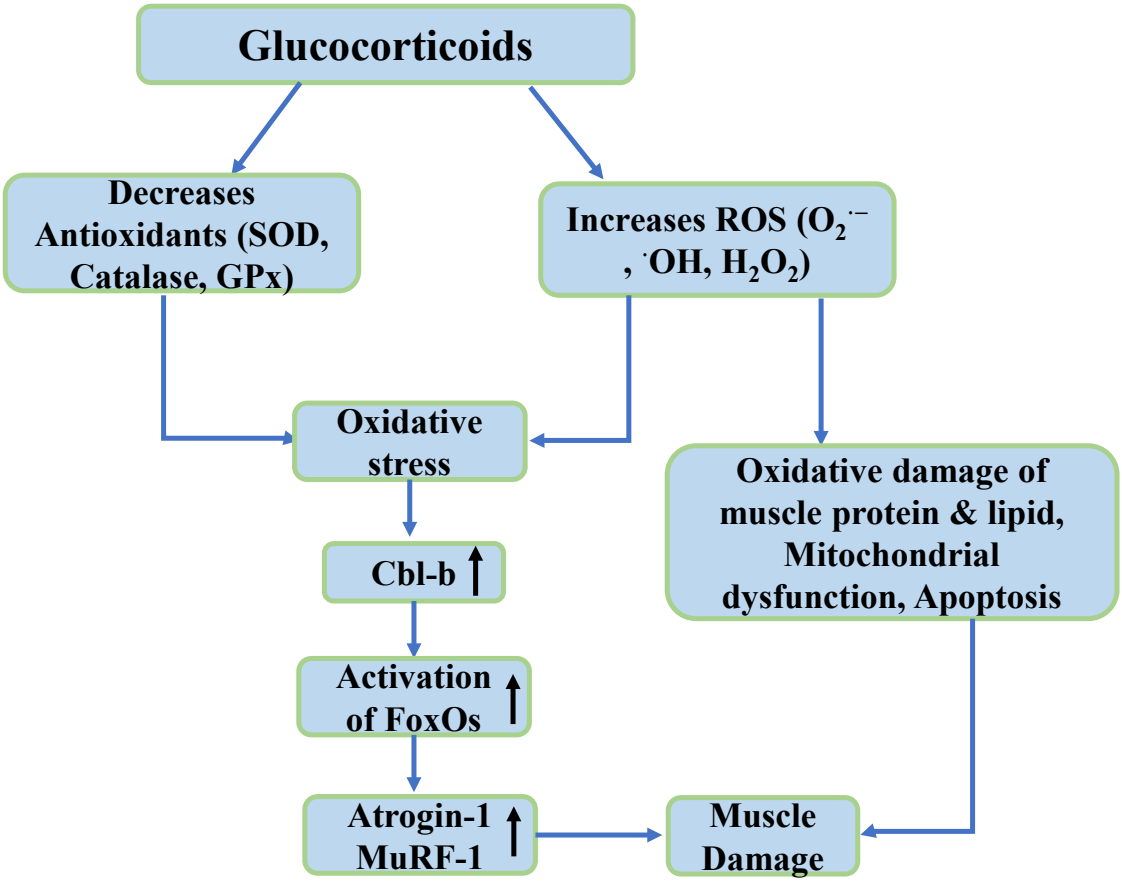

Figure 4: Diagram illustrating ROS generation during glucocorticoid induced muscle atrophy. Pointing arrows indicates induction/stimulation. ↑ Indicates increase of shown component

CONCLUSION

Critical Overview and Future Perspective

This review has summarized the role of ROS as regulatory and pathological agent in skeletal muscle. The production of ROS in the skeletal muscle occurs *via* multiple mechanisms. This review has tried to explain both the positive and negative effects of ROS on skeletal muscle health along with their mechanism. According to the results discussed above, ROS act as a dual agent in performing physiological and pathological functions of muscle health. The precise action of ROS is intricately associated with concentration and origin of ROS. At physiological concentrations, ROS stimulate the pathways that induce myogenesis, muscle differentiation, exercise adaptation, EC coupling etc. However, at high concentrations, ROS initiate macromolecular damage, mitochondrial dysfunction, activation of proteolytic pathways, impaired calcium signaling, and altered redox regulation that led to muscle dysfunction such as sarcopenia

and muscle atrophy. So, our knowledge gap to understand the physiological and pathological functions of ROS lies on defining the boundaries of the redox window. Further research focusing measurements of the precise nature of ROS and their effect on muscular cells is required along with the deeper study of redox-sensitive pathways to clearly differentiate the pathological and physiological roles of ROS in skeletal muscle.

AUTHOR CONTRIBUTION

A.U.: Conceptualization, data curation, writing-original draft, and visualization; T.N.: Conceptualization, writing-review and editing, visualization and Funding acquisition.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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