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The Role of Reactive Oxygen Species in Muscle: Beneficial/Harmful

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ABSTRACT

Introduction: Skeletal muscle produces moderate quantities of oxidant species, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), due to its contractile action, high oxygen consumption, and metabolic rate (RNS). Under normal physiological circumstances, the generation and removal of ROS/RNS are in dynamic equilibrium.

Content: The body reaches a condition of oxidative stress, however, when the oxidation products surpass the antioxidant defense capability. Increased oxidative stress has significant ramifications for the molecular, structural, and functional integrity of muscle. The release of reactive oxygen species (ROS) under pathological circumstances leads to cellular dysfunction and the progression of muscle disorders.

Conclusion: The antioxidants can put ROS in optimal concentrations to perform physiological signals in muscle. At appropriate concentrations, ROS and RNS can regulate intracellular signal transduction. Thus, moderate quantities of radicals are advantageous to muscle, but high doses of ROS are harmful. The aim of this review is to know about the role of ROS in muscle.

Keywords: Reactive oxygen species; muscle; skeletal; oxidative stress

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Introduction

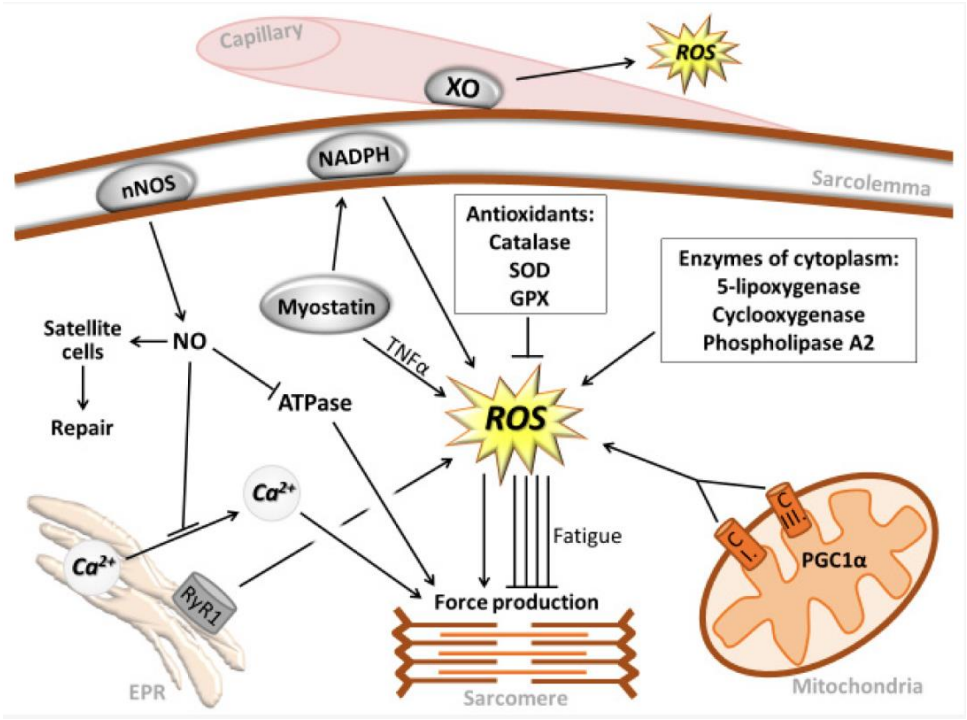
Cells suffer damage from oxidative stress (OS), which is characterized as a disruption in the pro/antioxidant balance since it causes an excessive amount of highly reactive oxygen species (ROS) and reactive nitrogen species to be produced (RNS). Cells generate and eliminate ROS/RNS to maintain redox equilibrium under typical physiological settings. OS participates in signal transmission and physiological adaptation, including the control of cell viability[1], but if the redox balance is upset, the ensuing sharp rise in ROS/RNS causes harmful alterations to cell components. As a consequence, inflammatory neutrophil infiltration, increased protease secretion, and the creation of many oxidation intermediates—all of which are thought to be significant players in aging and illness-occur [2].

The most prevalent tissue in the human body, accounting for 35–45% of its total mass, is striated skeletal muscle[3]. Skeletal muscle is a heterogeneous structure made up of muscle fibers, satellite cells of the basement membrane, and nerves[4], all of which are necessary for fundamental processes as breathing, movement, postural support, and thermogenesis.[4]

Skeletal muscles are remarkably capable of both adaptation and excellent regeneration. Loss of muscular function and a reduced capacity for muscle regeneration not only significantly lower quality of life, but may also have an impact on professional athletes' careers. Inflammation is present in non-inflammatory muscle ailments as well as inflammatory muscle illnesses, such as those that follow intense activity or different degrees of muscular injury. Such inflammation is mostly brought on by high ROS levels.

OS will result from an imbalance between the generation and removal of ROS and RNS, hence it is critical to comprehend the origins of these species. Living things emit ROS as a typical byproduct of cellular metabolism. RNS are chemicals created when reactive oxygen species and other components interact with NO. ROS and RNS may be divided into two categories based on their chemical makeup: the second category is made up of radical and non-radical molecules[5]. Superoxide (O2) and hydroxyl radicals (HO) are examples of radical ROS species, while hydrogen peroxide is an example of a non-radical one (H2O2). Nitric oxide (NO) and peroxynitrite (ONOO) are examples of RNS.

ROS Generation in Muscle



Figures 1. Source of ROS in Skeleta Muscle[6]

1. Mitochondria

The majority of ROS in organisms is generated by mitochondria. In most cell types, mitochondria play a part in various cellular activities, including oxidative phosphorylation. The mitochondria found in skeletal muscle cells are numerous, physiologically active, and highly prone to create ROS. Because skeletal muscle consumes a lot of oxygen, ROS produced as byproducts of mitochondrial oxidative phosphorylation are especially harmful to the genome of skeletal muscle. 90% of the oxygen the body consumes under physiological circumstances is oxidatively phosphorylated in the mitochondria, with just 1% to 2% of that oxygen escaping via the mitochondrial respiratory chain due to reactive oxygen species. Excessive exercise may injure muscles by producing increased ROS and RNS, which can impede muscular contraction[7]. In mammalian cells, the mitochondrial transport chain (ETC) is the primary source of ATP, and the ETC has many sites on both sides of the mitochondrial inner membrane where it may create O2[8].The ETC complexes I and III are the primary O2 producing sites under physiological circumstances[9]. The tricarboxylic acid (TCA) cycle enzymes 2-oxoglutarate dehydrogenase (OGDH), malate dehydrogenase (MDH), and pyruvate dehydrogenase (PDH) will be activated by coupled respiration on glutamate/malate or pyruvate/malate, and this maintains a low membrane potential while complex V is producing ATP [10]. The electrons ultimately reach complex III and IV as they go down the ETC. Complex II is succinate, a substrate for succinate dehydrogenase (SDH), an enzyme involved in the TCA cycle[11]. Additionally, electrons return via complex I during mitochondrial hyperpolarization to convert NAD+ to NADH.

Muscle fibers are primarily responsible for the contractile activity. Due to changes in mitochondrial contents between fast-glycolytic, fast oxidative/glycolytic, and slow fiber types, there are disparities in oxidative capability. The quantity of mitochondria in a muscle impacts how well its fibers can oxidize. Fast contractions depend on glycolysis, which takes place in the cytosol and allows for quick ATP synthesis but is ineffective. Through mitochondrial oxidative phosphorylation, which is slower but more effective, slow contractions create ATP [12]. Fast II muscle fibers are different from slow type muscle fibers in that they stimulate greater amounts of ROS production[13]. Additionally, researchers discovered that Tap63 is involved in the regulation of myoblast metabolism. It was demonstrated that knockdown of Tap63 expression results in mitochondrial respiration, as evidenced by a decrease in spare respiratory capacity and an increase in the rate of myoblast proliferation[14].

2. NADPH Oxidases

Neutrophils and macrophages, which may generate high levels of ROS during the inflammatory response and serve as the body's first line of defense against pathogens, were the first cells to be found to have NADPH oxidases (NOX). NOX is a complex made up of six subunits, of which gp91phox is the functional one. The other five are p22phox, p47phox, p67phox, p40phox, and Rac. Pg91phox homologs have been discovered in a variety of cell types, including NOX1, NOX2, NOX3, NOX4, NOX5, DUOX1 and DUOX2. The principal ROS sources in skeletal muscle cells during skeletal muscle contraction are NOX isoforms 2 and 4, which are found in the plasma membrane, transverse striatum, and sarcoplasmic reticulum and function to control calcium release[15].

3. Xantin Oxidase

As a cytosolic molybdoflavoenzyme that catalyzes the hydroxylation of hypoxanthine to xanthine and of xanthine to uric acid, xanthine oxidase (XO) is known as a crucial enzyme in purine catabolism[16]. Both the related endothelial cells and the cytosol of muscle contain XO. As a result of the large increase in XO activity brought on by contraction, there is an increase in lipid peroxidation, protein oxidation, muscle injury, and edema[17]. Hypoxanthine and xanthine levels increase during vigorous activity, which uses a lot of ATP, and they act as substrates for XO to produce ROS[18]. It's interesting to note that PGC-1, a peroxisome proliferator-activated receptor, appears to play a role in the regulation of exercise-induced mitochondrial biogenesis[19].

4. Myostatin

Myostatin isa muscle differentiation inhibitor, has recently been shown to signal muscle cell ROS generation via canonical Smad3, nuclear factor (NF)-B, and TNF- alpha[20]. Myostatin increases ROS generation in the absence of Smad3 by activating the p38 and ERK mitogen-activated protein kinase (MAPK) pathways, which are mediated by TNF-, IL-6, NOX, and XO [21].

5. Phospholipase A2

During muscular contraction, members of the phospholipase A2 (PLA2) family of enzymes also help to increase intra- and extracellular ROS. They the separate arachidonic acid from phospholipids in the mitochondrial, sarcoplasmic, and plasma membranes. Arachidonic acid is a crucial lipid signaling molecule and a source of ROS via its use as a substrate by lipoxygenases [22].

Antioxidant

All mammalian cells are equipped with regulatory mechanisms to maintain oxidation/reduction (redox) balance since it is essential for cellular health. The cellular antioxidant system is a crucial aspect of redox regulation. Antioxidants are often described as any chemical that considerably slows down or stops a substrate from oxidizing. Readers who want additional information about antioxidant systems are referred to more in-depth evaluations since a thorough study of cellular antioxidants is beyond the purview of this article. However, a short description of cellular antioxidant systems is given here to set the stage for further talks in this study. Antioxidants in cells, both enzymatic and non-enzymatic, function as a sophisticated regulatory network to regulate ROS levels. In order to reduce ROS and maintain redox equilibrium, antioxidants are, segregated throughout the cell in both organelles and the cytoplasm. Additionally, there are antioxidants in the blood and interstitial fluid, and these extracellular antioxidants are crucial in removing ROS from extracellular fluids.

Cells are shielded from harm caused by ROS via three main antioxidant techniques. First, cells and extracellular space both contain a large number of low-molecular-weight compounds that may scavenge ROS. Second, certain enzymatic antioxidants work by converting reactive oxygen species (ROS) into less reactive molecules, which suppresses oxidation and stops these ROS from changing into more harmful species. The binding of pro-oxidant transition metals, such as iron and copper, by metal binding proteins, which act as chelating molecules to stop these transition metals from contributing to the generation of ROS, is the last antioxidant method.

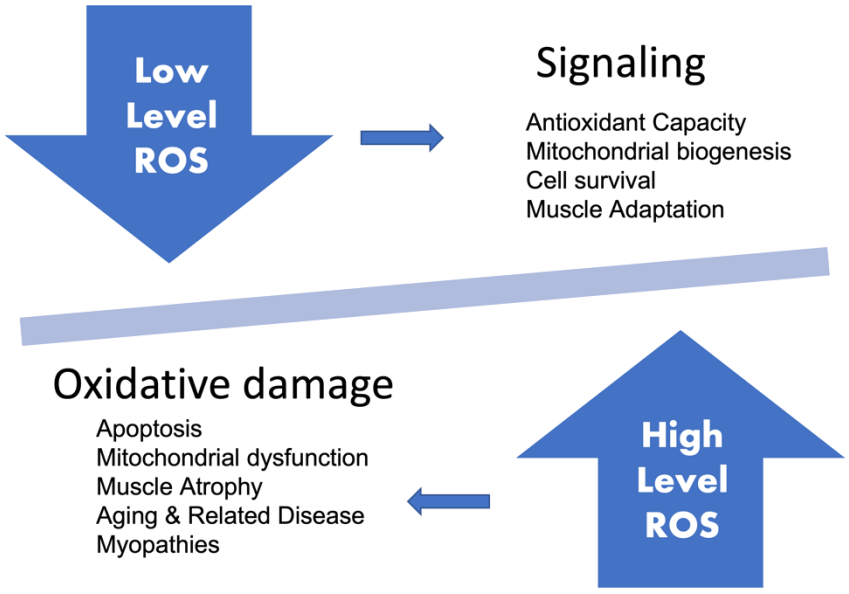
The Role of ROS in muscle

There is accumulating evidence that low levels of reactive oxygen species stimulate the production of antioxidant enzymes and other defensive systemsPhysical activity is connected with the formation of reactive oxygen species, which may play a crucial role in the positive benefits of physical activity. Endurance exercise induces oxidative, metabolic, and thermal stress on skeletal muscle, which triggers some cellular signaling pathways that result in advantageous muscle changes. Mitochondria and ROS generation are essential components of this system. Increased mitochondrial content (mitochondrial biogenesis) improves the regulation of energy metabolism, resulting in increased oxidation of fatty acids and decreased glycogen for ATP synthesis. In addition, endurance exercise may increase mitochondrial integrity through two mutually exclusive routes: changes in mitochondrial dynamics and selective autophagic destruction of mitochondria

(mitophagy). Increased mitophagy after exercise is advantageous because it improves overall mitochondrial quality by selectively eliminating damaged or malfunctioning mitochondria. It has been shown that long-term regular exercise in humans preserves functioning autophagy, ensuring that senior athletes have more muscle mass and strength than old inactive patients[23].

Under physiological settings, skeletal muscles probably engages an endogenous antioxidant defense mechanism to keep the ROS product at a "functional" level. Regular/moderate exercise has been demonstrated to increase the activity of endogenous antioxidant enzymes such as SOD, glutathione peroxidase, and catalase, hence inducing an antioxidant defense.

Muscle homeostasis factors nuclear factor-kappaB (NF-kB), activator protein-1 (AP-1), mitogene activated proteine kinases (MAPKs), heat shock transcriptional factor-1 (HSF-1) and insulin receptor kinase are sensitive to redox changes as well as typical biological components.[24,25] Notably, moderate exercise stimulates MAP kinases, which in turn activates NF-kB, which enhances the production of antioxidant enzymes such as superoxide dismutase (SOD) and ferritin heavy chain (FHC), counteracting ROS formation and promoting adaptation to exercise (eNOS and iNOS). [26]



Figures 2. The Role of ROS in Skeleta Muscle

Recent research has revealed skeletal muscle as an endocrine organ capable of producing, expressing, and releasing cytokines and other peptides, known as myokines, that exert paracrine, autocrine, or endocrine effects.[27] Incongruously, prolonged and hard exercise may cause oxidative damage to cellular elements, indicating that free radicals contribute to muscular tiredness under specific situations, such as eccentric labor (i.e. lengthening of contracted muscles like in running downhill or squatting with weights). It has been hypothesized that rigorous exercise might exacerbate disturbance of the cellular milieu via increased

oxidative damage and inflammatory process, which may have a detrimental synergic effect on the senescent muscle in particular.

Consequently, the exercise of severe length and intensity under likewise extreme circumstances, such as hypoxia, creates considerably larger quantities of free radicals that exceed cellular antioxidant defenses, resulting in protein carbonylation, DNA damage, and RNA oxidation. Notably, the elimination of excess ROS by enzymatic and nonenzymatic antioxidants reduces muscle exhaustion during submaximal contractions. [28]

Following excessive ROS generation, proinflammatory cytokines, and NF-kB the activation, the search for molecular explanations found that severe exercise inhibits pathways for preserving mitochondrial integrity. In addition, vigorous exercise in elderly participants decreased fusion (Mfn2) and fission (Drp1) proteins, which may lead to alterations in mitochondrial morphology. PGC-1, which is known to regulate mitochondrial biogenesis and be the major regulator of an oxidative phenotype inside contracting muscle, is another route in which the presence and balance of reactive oxygen and nitrogen species must be appropriately regulated.[29] Additionally, high ROS generation might disrupt calcium homeostasis. Ca2+ dysregulation may stimulate aberrant NF-kB transcriptional activity, resulting in activation of proteolytic systems and muscle atrophy. [30]Growing data suggest that excessive ROS generation may function as second messengers in cellular signal transduction pathways, activating proteolytic systems such as calpain and caspase. Different concentrations of ROS exhibit opposing effects, which may be explained by the idea of hormesis, in which a little dosage of a chemical is stimulatory and a large amount is inhibitory. Thus, modest concentrations of radicals are beneficial to muscle, but excessive dosages of ROS are detrimental.

Conclusion

ROS are not necessarily harmful to cells. Accumulating evidence has shown that antioxidants can put ROS in optimal concentrations to perform physiological signal in muscle. At appropriate concentrations, ROS and RNS can regulate intracellular signal transduction.

Conflict of Interest

There is no conflict of interest

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