

Oxidative Stress Impactson Exercising Skeletal Muscles: A Review

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Abstract

Skeletal muscle contraction as a consequence of physical activity is characterized by a significant rise in the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) known as the oxidants. In accordance with the intensity, duration, type of exercise, and fitness level of the athlete, the exercise-associated oxidative stress might result in negative or positive effects on muscle integrity and performance. At high and uncontrolled levels, ROS/RNS cause lipid peroxidation, oxidation of proteins and DNA molecules, dysfunction of excitation-contraction coupling, and muscle damage. In contrast, at lower physiological levels of ROS, these molecules are responsible for important signaling functions involved in promoting mitochondrial biogenesis, stimulating antioxidant defenses, and triggering adaptive responses to physical training in accordance with the concept of hormesis. The present review covers information about cellular sources of exercise-induced ROS/RNS, mechanisms of oxidative damage to contractile and metabolic components of muscle cells, a double-faced effect of oxidants in muscle fatigue and adaptation, effect of the athlete's training status and exercise type, and debates regarding the antioxidant supplementation among athletes.

Keywords: oxidative stress; reactive oxygen species; skeletal muscle; exercise; antioxidants; muscle fatigue; redox signalling

1. Introduction

The skeletal muscle is a tissue with high metabolic activity and great plasticity capable of increasing oxygen uptake by more than one hundred times during physical exercise compared to the resting state. The first connection between the dramatic increase in oxidative metabolism and free radical generation and tissue damage appeared in the late 1970s when it was found that exhaustive exercise increases lipid peroxidation in animals [1]. Later on, a considerable amount of scientific literature has shown that both at rest and during contraction skeletal muscles are constantly producing ROS and RNS due to aerobic metabolism and that exercise causes a significant increase in their formation [2,3]. Oxidative stress occurs in case when the rate of oxidant production becomes larger than the ability of endogenous antioxidant defence to cope with them leading to molecular damage of lipids, proteins, and nucleic acids [4,5]. Moreover, the connection between ROS

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and muscle function is not only negative; there is a growing amount of scientific literature showing that ROS produced by physical exercise work as second messengers inducing positive adaptations such as mitochondria biogenesis and induction of antioxidant enzymes [3,6]. This review examines the cellular origins of exercise-induced oxidants, their mechanistic effects on skeletal muscle, and the evolving understanding of oxidative stress as both a cause of fatigue/damage and a driver of training adaptation.

1. Sources of Reactive Oxygen and Nitrogen Species during Exercise

ROS and RNS are formed in various sources of both the cell and the extracellular environment during muscular contraction. Traditionally, mitochondria and their electron transport chain have been considered as the primary source of ROS formation due to the loss of some electrons from complex I and III to molecular oxygen during their transfer and subsequent reduction to the superoxide anion [4]. Nevertheless, non-mitochondrial sources are becoming more appreciated, and include such as NADPH oxidase enzymes (NOX) situated in the sarcolemma and transverse tubules, xanthine oxidase reducing hypoxanthine molecules accumulated through ATP metabolism, phospholipase A2 pathway [2,4]. Besides, intense exercise provokes the activation of neutrophils and macrophages in blood circulation and within skeletal muscles, respectively, and generates ROS in response to exercise-induced inflammation, whereas nitric oxide synthase synthesizes nitric oxide that can react with superoxide to produce peroxynitrite [2,5]. Table 1 provides information on the main sources of ROS and RNS in the exercising skeletal muscle.

Table 1. Principal sources of reactive oxygen and nitrogen species (ROS/RNS) generated in skeletal muscle during exercise.

Source	Representative ROS/RNS	Primary Cellular Site
Mitochondrial electron transport chain	Superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2)	Inner mitochondrial membrane
NADPH oxidase (NOX2/NOX4)	$O_2^{\bullet-}$, H_2O_2	Sarcolemma, T-tubules
Xanthine oxidase	$O_2^{\bullet-}$, H_2O_2	Cytosol, capillary endothelium
Phospholipase A2 activation	Lipid hydroperoxides	Sarcoplasmic and mitochondrial membranes
Nitric oxide synthase (NOS)	Nitric oxide ($NO^{\bullet}$), peroxynitrite ($ONOO^-$)	Endothelium, sarcoplasm
Activated neutrophils/macrophages	$O_2^{\bullet-}$, hypochlorous acid (HOCl)	Infiltrating inflammatory cells (post-exercise)

2. Mechanisms of Oxidative Damage in Skeletal Muscle

The excessive production of ROS/RNS will lead to the oxidation of macromolecules, resulting in structural and functional defects in muscle fibers. The lipoperoxidation of

sarcolemma and mitochondrial membranes will lead to deterioration of membrane function and ion permeability, while the oxidation of muscle proteins involved in contraction, such as actin, myosin, and ryanodine receptor/Calcium release channels of the sarcoplasmic reticulum, will decrease the sensitivity of myofilaments to calcium and impair the mechanism of excitation-contraction coupling [3,5]. Oxidation of the sarco/endoplasmic reticulum calcium-ATPase (SERCA) will further prevent Ca^{2+} uptake and prolong relaxation time. Another target for oxidation is DNA, where 8-hydroxydeoxyguanosine (8-OHdG) is widely regarded as a marker of oxidative DNA damage of muscles during exercise [6]. These oxidations lead to a decline in the ability to develop force, onset muscle soreness, and even muscle damage in case of intense or unusual exercise [4,5].

3. Oxidative Stress, Muscle Fatigue, and Contractile Dysfunction

There are various factors that can contribute to muscle fatigue and recent evidence shows that redox imbalances play a major role in this process. Normal force generation requires low levels of ROS, but supraphysiological levels of ROS, which occur during prolonged, intense or unfamiliar exercises, result in contractile dysfunction and increase fatigue development [2,3]. This two-way relationship, which can be represented as an inverted U shape graph or

hormesis, is due to the signaling and harmful functions of ROS molecules. Evidence from antioxidant supplementation experiments corroborates this idea – pharmacological elimination of ROS with N-acetylcysteine has been reported to prevent muscle fatigue, while total blockade of ROS signaling impairs muscle contraction and indicates the need for regulation of the redox state of muscles [2,3].

4. The Hormetic Role of ROS: Exercise-Induced Adaptations

An important theory in redox exercise physiology states that temporary and moderate ROS generation serves as signalling molecules to induce adaptive responses, which agrees well with the concept of hormesis. ROS produced during exercise activates MAPKs and transcription factors, NF- κ B and Nrf2, which moves into the nucleus and binds to ARE to induce SOD, GPx and catalase genes [3,6]. ROS activate PGC-1 α , which is a master regulator of mitochondrial biogenesis to increase oxidative capacity through repeated exercise sessions [6,7]. Experimentally, blocking the production of ROS via xanthine oxidase using allopurinol has been demonstrated to attenuate these positive adaptations caused by exercise in animals. It provides clear evidence that ROS play an important role in generating signals for exercise adaptation rather than merely being harmful by-products of exercise [7]. The following table summarizes important antioxidants in the endogenous antioxidant defense system and their regulation through training.

Table 2. Endogenous antioxidant defenses in skeletal muscle and their adaptation to regular exercise training.

Antioxidant /Enzyme	Primary Function	Typical Response to Regular Training
Superoxide dismutase (Cu/Zn-SOD, Mn-SOD)	Converts $O_2^{\bullet -}$ to H_2O_2	Increased expression and activity
Glutathione peroxidase (GPx)	Reduces H_2O_2 and lipid hydroperoxides	Increased activity
Catalase	Decomposes H_2O_2 to water and oxygen	Modest, muscle-fibre-type-dependent increase
Reduced glutathione (GSH)	Non-enzymatic scavenger; cofactor for GPx	Improved GSH:GSSG ratio
Nrf2–ARE signalling pathway	Master transcriptional regulator of antioxidant genes	Enhanced nuclear translocation and gene transactivation

5. Influence of Exercise Mode, Intensity, and Training Status

The severity of oxidative stress following exercise is dependent upon the mode of exercise, its intensity, duration, and training status of the individual. The eccentric exercise, which imposes additional load on the sarcolemma and cytoskeletal network, elicits higher levels of oxidative damage and inflammation than concentric exercise [3,11]. The intensive and exhaustive aerobic exercises increase lipid and protein oxidation products more significantly than submaximal aerobic exercises, especially when the rest interval between exercise sessions is short [11]. On the other hand, trained individuals have a higher antioxidant capacity and increased efficiency of mitochondria as a result of which there is less net production of oxidative damage markers for an absolute work volume compared with the untrained individuals [2]. The above mentioned phenomena illustrate that regular exercise is more beneficial to develop the adaptive phenotype than a single intensive exercise.

6. Antioxidant Supplementation: Benefit or Interference?

Since too much ROS causes harmful effects, antioxidant vitamin supplementation (especially vitamin C and E supplementation) has been commonly practiced among athletes with the intention of avoiding oxidative stress and enhancing recovery. However, it has been proven from various studies that the chronic high-dose supplementation of antioxidant vitamin is counterproductive to training-induced physiological changes. Oral vitamin C intake has been proven to inhibit the training-induced increase of mitochondria production and also impair the endurance performance improvement in rodents and humans [8]. Additionally, vitamin C and E supplementation is seen to prevent the improvement of insulin sensitivity brought about by the exercise [9]. It has also been proven using proteomic analysis that antioxidant supplementations can limit the training-induced upregulation of the proteins in mitochondria [12]. Consequently, it is advised that the chronic high-dose supplementations of antioxidants be done carefully by those athletes who are under training in order to achieve the maximum adaptation, whereas acute supplementations could still be valuable in certain circumstances such as multi-day competitions [10].

7. Practical and Clinical Implications

The biphasic response to training in terms of oxidative stress has significant physiological relevance in practical settings. In terms of athletes and coaches, this research suggests that antioxidant taken at high dosages without specific cause during training cycles would negate the adaptive processes of training. In terms of the clinical setting or rehab population, where oxidative stress may be too much and can lead to muscle loss, myopathy, and reduced exercise tolerance, the implementation of graded exercise programs appears to be a more appropriate approach compared to pharmacological antioxidant suppression for correcting the oxidative stress imbalance [4,5]. Measurement of oxidative stress markers together with performance and recovery can assist in determining the training load, especially in those with redox imbalance.

8. Conclusion

Exercise creates a great amount of multiple source oxidative stress in skeletal muscle cells, creating ROS and RNS via mitochondrial, enzymatic, and inflammatory sources. These oxidants do not have an entirely negative effect on the body since, depending on their concentration, they either cause oxidative damage to lipids, proteins, and DNA, disrupt the excitation contraction coupling, fatigue, and even injuries of muscles or function as physiological signals for mitochondrial biogenesis and upregulation of antioxidant enzymes in case of physiological concentrations. Based on this hormetic model of the response, it is possible to conclude that the total prevention of exercise-induced ROS production via high doses of antioxidant supplementation is not always helpful for athletes who wish to get maximal benefits from training sessions. Further research should focus on determining the optimal dosages, modes, and populations for which the shift between adaptive and pathological oxidative stress occurs.

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Physiol. 2025