INFLUENCE OF FREE RADICALS ON MUSCLE FUNCTION AND ADAPTATION IN EXERCISE

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SUMMARY

The first suggestion that physical exercise results in free radical-mediated damage appeared in 1978, and since that time the sources of oxidant production during exercise continue to be debated. Many researchers focused on the damaging effects of oxidants in muscle (oxidative damage of proteins and lipids), but the examination of cell-signaling effects of free radicals on muscle activity became today's main issue. Free radicals can modulate a number of cell signaling pathways and regulate the expression of multiple genes, contributing to the muscle adaptation on exercise and improving the muscle force production. Those effects are provided by changes in calcium handling by muscle cells or changing in the sensitivity of myofilaments to calcium. As a conclusion we can say that low and physiological levels of free radicals are required for normal force production in skeletal muscle and antioxidant adaptation, while high levels of free radicals promote contractile dysfunction resulting in muscle weakness and fatigue.

Keywords: Free radicals, exercise, antioxidants, adaptation, muscle force.

INTRODUCTION

The first serious studies about free radical generation and its role during exercise date from the 1970's. Since that time a great deal of researches has been undertaken in effort to understand the nature and sources of free radicals, the factors influencing their generation, effects on muscle and other cells, and how those effects might be manipulated [1]. Free radicals are defined as an atom/molecule containing one or more unpaired electrons and are capable for independent existence.

There is a number of potential pathways included in exercise induced free radical production. Mitochondrial respiration (electron leakage from electron transport chain and subsequent production of the superoxide radical), prostanoid metabolism, autoxidation of catecholamines and oxidase enzyme activity (NADPH-oxidase, xanthine oxidase) are considered as dominant free radical generation pathways. Additional, secondary free radical generation induce phagocyte respiratory burst, a loss of calcium homeostasis and/or the destruction of iron-containing proteins [2]. These mechanisms can act synergistically where different types of exercise, including the mode (aerobic/anaerobic), intensity and duration of exercise, involve different mechanism of free radical production. During contraction, superoxide and nitric oxide represent a primary species produced by skeletal muscle, but they are also the precursor for secondary species formation, such as hydrogen peroxide, hydroxyl radical or peroxynitrite. Contracting skeletal muscle fibers are a major source of free radicals as well as one's main targets [3]. It has been noticed that exercise performance increases blood temperature and concentration of lactate and decreases blood pH level and oxygen partial pressure. All these exercise-associated homeostasis disruptions are able to modify blood redox status so it is reasonable to assume that there is a bidirectional movement of free radicals from the muscle to the blood and vice versa, until equilibrium is reached [4].

Numerous studies indicate that prolonged or high-intensity exercise results in oxidative damage of macromolecules in both blood and skeletal muscle, leading to state known as oxidative stress [5, 6]. This state represents an imbalance between oxidants and antioxidants in favor to the oxidants, causing a disruption of redox signaling and control, and/or molecular damage.

Body antioxidant system can prevent oxidative stress at 'normal' level of free radical production by controlling the level of free radicals rather when eliminating them completely. Free radicals have numerous physiological functions so their elimination should effect normal body functioning [7]. This process can be described by the concept of hormesis, a dose-response relationship in which a low dose of substance is stimulatory or beneficial and a high dose is inhibitory or toxic [8]. Stimulatory effects of free radicals evoke specific adaptation such as an increased antioxidant damage-repairing enzyme activity, increased resistance to oxidative stress and lower levels of oxidative damage. Those effects seems to be systemic [9]. The two end-points of the hormesis curve are inactivity and overtraining, and both result in decreased physiological function.

During last two decades many researchers have pointed the damaging effects of oxidants, but today's main issue become the examination of cell-signaling effects of free radicals on muscle activity.

THE ROLE OF FREE RADICALS IN ANTIOXIDANT ADAPTATION

There is a growing evidence from numerous researchers confirming that presence of a small stimulus, such as a low concentration of free radicals, is able to influence the expression of antioxidant enzymes causing the systemic adaptation of antioxidant system. It has also been confirmed that exercise provoke free radicals generation, who are playing an important physiological function in the regulation of exercise induced antioxidant adaptation [10]. The ability of free radicals to activate redox-sensitive transcription factors and cellular signaling cascades, make them important intracellular messengers. The main cellular components sensitive to redox changes are nuclear factor-kappa beta (NF-kB), activator protein-1 (AP-1), mitogen-activated protein kinases (MAPKs) and heat shock transcription factor 1 (HSF1) [11]. Most antioxidant enzyme genes contain regulatory sequences in their promoter regions that can interact with redox-sensitive transcription factors [12]. Major mechanisms by whom redox-signaling controls gene expression is via the phosphorylation status of transcription activating factors.

MAPKs has an important role in the regulation of cell signals conversion into cellular responses, while NF-kB pathway is required for skeletal muscle adaptation both for exercise and inactivity-induced atrophy (NF-kB regulates the expression of over 130 genes) [12].

Hollander et al [13] were the first who reported that an acute bout of treadmill running activated MnSOD gene expression in rat skeletal muscle, along with enhanced NF-kB binding in muscle nuclear in samples extracted 2h after exercise. Activation of MAPKs in rats gastrocnemius muscle, caused by exercise, has been also noticed by Gomez-Cabrera and Vina [14]. This in turn activated NF-kB pathway and consequently the expression of important enzymes involved in defense against free radicals. The same authors reported that all these changes were abolished after administration of alopurinol (free radical production inhibitor).

Mechanism involving in antioxidant adaptive response to exercise is shown on Fig. 1. This whole process was summarized by Fisher-Wellman and Bloomer [15] who pointed that exercise induced free radicals serve as the 'signal' needed for the activation of MAPKs, resulting in further activation of NF-kB, via activation of IkB kinase (IKK) which then phosphorylates IkB (the inhibitory subunit of NF-kB). Degradation of IkB leads to releasing of NF-kB and its migration into the nucleus. Several antioxidant enzymes (MnSOD, NOs, GCS) contain NF-kB binding sites in their gene promoter region and these are potential targets for exercise-induced upregulation via the NF-kB signaling pathway. It is clear that antioxidant supplementation in this case can blunt the adaptive increase in antioxidant defense.

THE ROLE OF FREE RADICALS IN MUSCLE FORCE PRODUCTION

It is well established that there is a great influence of free radicals on muscle force production. Raid et al. [16] developed a theoretical model to describe the relationship between muscle redox balance and isometric force production (Fig. 2.).

Figure 1. Antioxidat adaptive response to exercise (redrawn from [15])

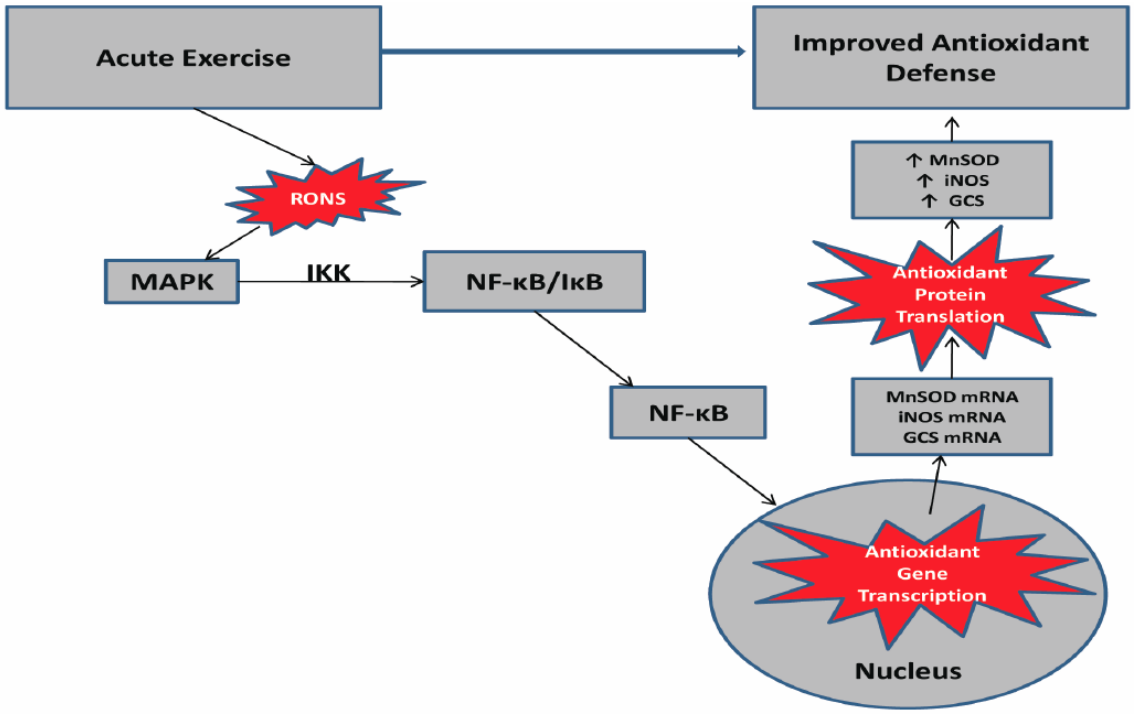
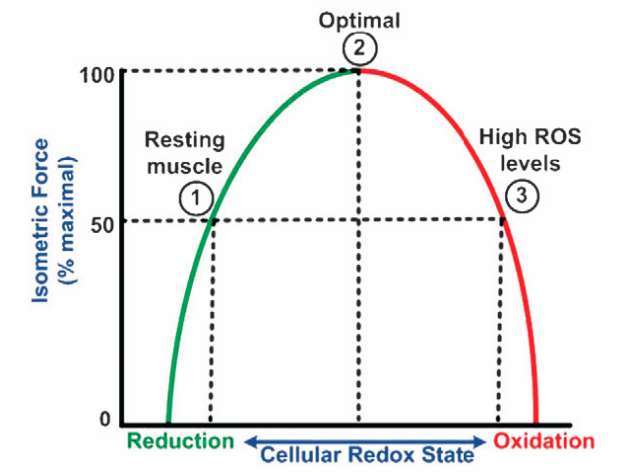


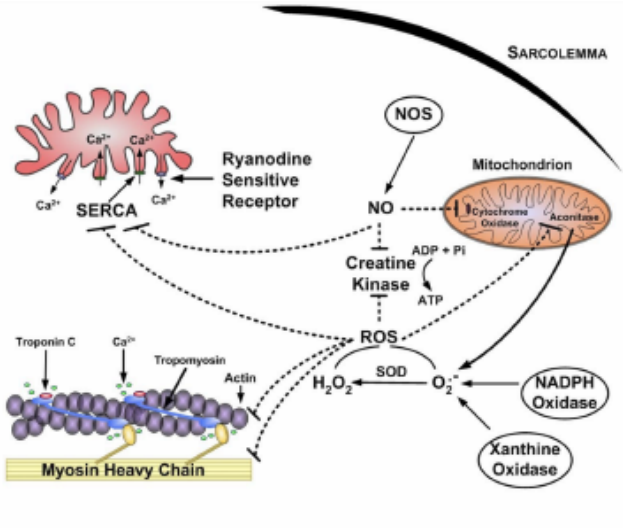
Figure 2. A theoretical model of a biphasic effects of free radicals on skeletal muscle force production (Redrawn from [18])



The basic principle of this model is that muscle redox state is a physiologically regulated variable that is balanced by matching the rate of free radical production with cellular antioxidant buffering capacity. As a consequence, a deviation from the optimal redox balance leads to loss of force production [17]. The low levels of free radicals in skeletal muscle during basal condition is necessary for normal force production, so any depletion of ROS (antioxidant supplementation) can decrease it. At high free radical concentration, their positive effect is reversed and force production decreases in dose-dependent manner (antioxidant supplementation is benefit) [18].

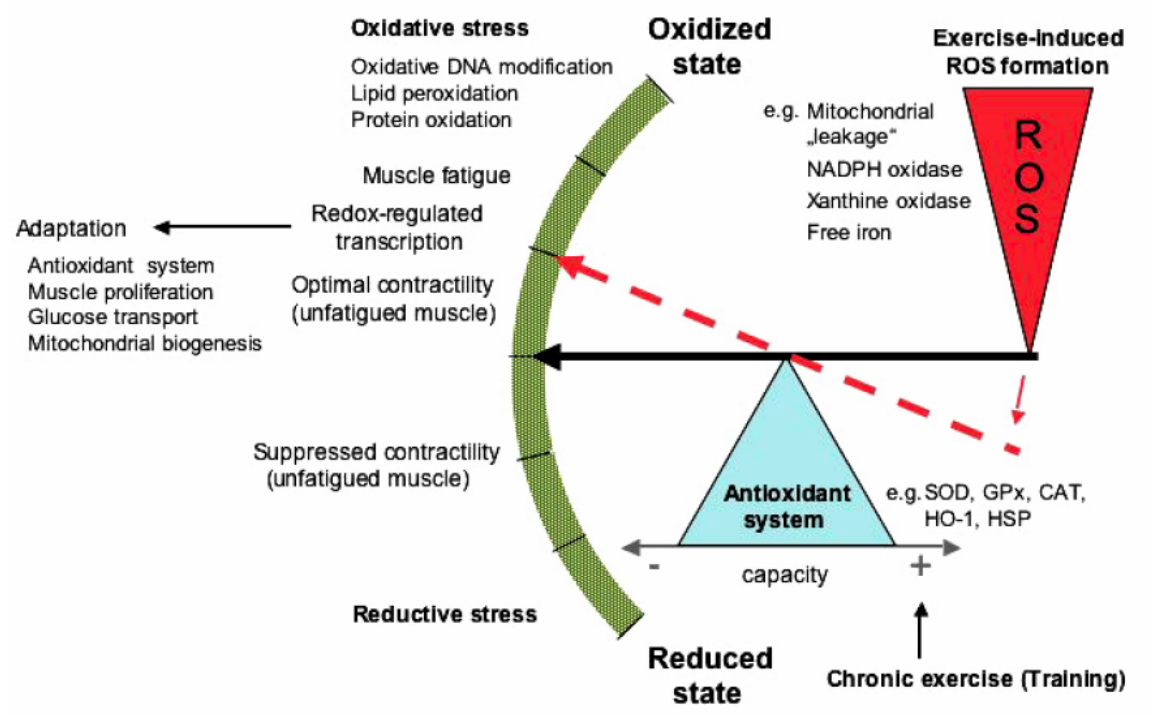
The mechanisms by whom free radicals effect contractile force in skeletal muscle are still only partly understood. It seems that the explanation of free radical influence on muscle force production is closely connected with calcium homeostasis (Fig. 3.) [18].

Figure 3. Putative redox-sensitive targets in skeletal muscle that can influence force production (Redrawn from [17])



Sarcoplasmic reticulum (SR) represents an important redox-sensitive target in skeletal muscle. Increased free radical production is followed by increasing probability of opening the ryanodine-sensitive calcium-release channels. As a consequence it results in increased calcium release from the SR. The ryanodine receptor calcium release channel is containing sulfhydryl groups that are sensitive to oxidants. Free radicals may also affect the ability to develop action potentials required for muscle contraction through damaging ATPase pumps required for potassium influx back into skeletal muscle

Figure 4. Schematic model of exercise-related changes in the cellular redox balance in skeletal muscle (Redrawn from [11])



cells. Free radicals can also influence myofilament structure and function, probably by affecting their calcium sensitivity. Muscle contractile proteins (fast and slow myosin heavy chain) and mitochondrial enzymes required for energy provision (succinate dehydrogenase, cytochrome oxidase) appear to be susceptible to oxidative damage [7].

There is also preliminary data supporting the possibility that redox control is important in the regulation of cytokine and myokine synthesis and/or their release by skeletal muscle. The ability of muscle to product those anti-inflammatory cytokines has been used for justifying exercise as a potential health promoter in many chronic disorders [3].

CONCLUSION

Collectively, the mechanisms involved in the regulation of the effects of free radicals during exercise are shown in Fig. 4.

Strenuous exercise cause oxidative stress and cell damage so antioxidant supplementation is desirable. If physical activity is practice on moderate and regular way it increases the expression of antioxidant enzymes, improves the muscle force production and antioxidant supplementation might be harmful.

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SRPSKI

UTICAJ SLOBODNIH RADIKALA NA MIŠIĆNU FUNKCIJU I ADAPTACIJU PRI VEŽBANJU

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SAŽETAK
Prva saznanja da fizička aktivnost može da poveća stvaranje slobodnih radikala i dovede do oštećenja tkiva potiču iz 1978, pri čemu još uvek način i mesta njihovog stvaranja nisu potpuno razjašnjena. U prošlosti su se mnogi istraživači fokusirali na ispitivanje štetnog efekta slobodnih radikala na funkciju mišića (oksidativno oštećenje proteina i lipida), međutim danas se u fokusu interesovanja nalazi ispitivanje uloge slobodnih radikala u procesu prenošenja informacija unutar ćelija i uticaja na mišićnu aktivnost. Slobodni radikali mogu da utiču na brojne procese ćelijskog prenosa informacija i regulišu ekspresiju velikog broja gena, doprinoseći adaptaciji mišića na vežbanje i povećanju mišićne snage. Ovi efekti su posledica promene u aktivnosti kalcijuma u mišićnim ćelijama i promeni osetljivosti miofilamenata na kalcijum. Može se zaključiti da su nizak i fiziološki nivo slobodnih radikala neophodni za snagu skeletnih mišića, dok visok nivo slobodnih radikala dovodi do kontraktilne disfunkcije i posledične slabosti mišića ili oštećenja.

Ključne reči: slobodni radikali, vežbanje, antioksidanti, adaptacija, mišićna snaga.