OXIDATIVE STRESS, STRESS PROTEINS AND ANTIOXIDANTS IN EXERCISE

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Exercise appears to increase reactive oxygen species (ROS), which can result in damage to cells. Potencial sources of ROS in skeletal muscle fibers during exercise include the mitochondrial respiratory chain, xantine oxidase production of superoxide, enzymatic arachidonic acid oxygenation, nitric oxide synthesis, catecholamine oxidation, and neutrophil-induced oxidative burts. Stress proteins (SPs) represent one of the general molecular protective mechanisms that enable cell and whole organisms to survive stress. The exact relationship between exercise, ROS and SPs remains unclear. Antioxidant supplements have been touted by manufacturers as a means for athletes to perform better, recover more quickly and fully from endurance exercise, or allow them to train more strenuously. At present, data are insufficient to recommend antioxidant supplements for athletes or other persons who exercise regularly. However, no one questions the importance of ingesting a diet rich in antioxidants for all who exercise and train regularly. *Acta Medica Medianae 2004; 43(4): 45–47.*

***Key words**: exercise, antioxidant, oxidative stress, stress protein, skeletal muscle*

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Introduction

Skeletal muscle is a complex organ, which in man forms approximately 40% of total body mass. Also, striated muscle is one of the most plastic and dynamic organs in body (1). Among the components that allow muscle to meet its many and varied tasks is a group of intracellular proteins know as stress proteins (SPs) or heat shock proteins (HSPs). Stress proteins represent one of the general molecular protective mechanisms that enable cell and whole organisms to survive stress. The major HSPs found in striated muscle are: small HSPs (17-27 kDa molecular weight), HSP32 (or HO-1), HSP47, HSP70 family and HSP90 family. The physiological stress asociated with endurance exercise training results in a rapid induction of several isoforms of SPs (2). This induction of cellular SPs is associated with cellular protection from a variety of stresses (e.g. oxidative stress). To date, the exact relationship between exercise, reactive oxygen species (ROS) and SPs remains unclear. Potencial sources of ROS in skeletal muscle fibers during exercise include the mitochondrial respiratory chain, xantine oxidase production of superoxide, enzymatic arachidonic acid oxygenation, nitric oxide synthesis, catecholamine oxidation, and neutrophil-induced oxidative burts (2,3). The relative contributions of each of these pathways during exercise is at this time far from understood.

Ros effects on muscle contraction

ROS have biphasic effects on the contractile function of unfatigued skeletal muscle (4). The low ROS levels present under basal conditions are essential for normal force production. Selective depletion of ROS from unfatigued muscle by use of superoxide dismutase (SOD) or catalase causes force to fall. Conversely, modest ROS supplementation causes force to increase. This positive effect is reversed at higher ROS concentrations; force production falls in a time- and dose-dependent manner. These negative effects can be inhibited by pretreating muscles with antioxidants or can be reversed by post hoc administration of reducing agents (5). The rise in ROS production that occurs during strenuous exercise contributes to the development of acute muscle fatigue. Muscle-derived ROS are generated faster than they can be buffered by endogenous antioxidants. As ROS accumulate in the working muscle, they inhibit force production. This is analogous to the drop in force that occurs when unfatigued muscle is exposed to high levels of exogenous ROS. As in unfatigued muscle, ROS effects in fatiguing muscle can be blunted by pretreatment with selected antioxidants and can be partially reversed by post hoc exposure to reducing agents. Other factors may also increase ROS activity in muscle. Aging appears to increase the oxidant load to which muscles

are exposed. Muscle injury, e.g., due to reperfusion or stretch, also results in oxidative stress that is linked to loss of function (6). Finally, muscles may experience oxidative stress in inflammatory disease processes, including hyperthyroid myopathy, sepsis, malignant hyperthermia, and heart failure (2,5).

Adaptation to exercise

ROS production are linked to muscle activity and are known to influence gene expression (7,8). Accordingly, there is considerable interest in the potential of these mediators to regulate muscle adaptation to exercise (9,10). This is one of the oldest postulates in the field, dating back to the suggestion by Davies and co-workers in 1982 (11) that free radicals produced in exercising muscle might stimulate mitochondrial biogenesis. A growing body of evidence supports the prospect that muscle gene expression is redox sensitive. Muscles adapt to exercise by up regulating the expression of genes for antioxidant enzymes, including SOD, catalase, and glutathione peroxidase (GPX) (12). Stress proteins are also upregulated in response to exercise (13).

Ros and stress proteins

The cellular toxicity associated with ROS is largery reflective of their rapid participation in damaging reaction with celular components. The damage resulting from these reactions includes lipid peroxidation, protein oxidation, and DNA damage. During hypoxia-reoxygenation injury, for example, cellular proteins, membrane lipids, and DNA are particularly vulnerable to oxidative damage. Damaged proteins and by products of degradation may serve as important triggers for SPs production (14). Proposed relationship between SPs and ROS is simplistically illustrated in Figure 1.

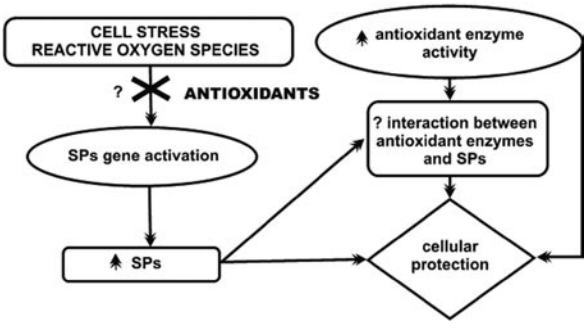

Figure 1. Relationship between SPs and ROS. (Adapted from Hamilton KL, Powers SK. Heat shock proteins and reactive oxygen species. In: Locke M. Noble EG. editors. Exercise and stress response 2002. Boca Raton: CRC Press; 2002. p. 124)

Cell stress, including stress mediated by ROS, leads to up-regulation of SPs and antioxidant enzyme activity and ultimately to protection againts subsequent cell stress. Exogenous antioxidants may interfere with activation of SPs genes, thus inhibiting SPs synthesis and related cell protection. SPs may or may not exert their cellular protective effects in concert with antioxidant enzymes.

The role of antioxidants in exercise

Cells have extensive endogenous and exogenous mechanisms for provoding protection against damage by ROS. Among the cells primary defences are both enzymatic antioxidans and nonenzymatic antioxidans. The enzymatic antioxidans include (a) superoxide dismutase, which dismutates the superoxide radical; (b) catalase, which decomposes hydrogen peroxide, and (c) glutathione peroxidase, which decomposes hydrogen peroxide with the assistance of the nonenzymatic antioxidant glutathione. Among the nonenzymatic antioxidant are vitamin E, vitamin C, carotenoids, glutathione, and flavonoids. Antioxidant work both independently and sinergistically to maintain a reduced cellular environment.

The oxidative stress caused by fatiguing exercise, muscle injury, or disease acts to shift the muscle rightward along this relationship, thereby depressing force. Under such conditions, antioxidants tend to increase force by returning cellular redox state toward optimal. Antioxidant supplements have been touted by manufacturers as a means for athletes to perform better, recover more quickly and fully from endurance exercise, or allow them to train more strenuously. However, the theoretical basis for why antioxidants should enhance performance is not clear. Studies have generally found that antioxidant supplements do not improve performance (15). The question remains as to whether athletes need supplements to prevent oxidative damage as a result of exercise or to help them recover from the damage. The results are equivocal in this regard. Furthermore, trained subjects generally show less evidence of damage than do untrained subjects. Thus, exercise may enhance the antioxidant defense system to offset the barrage of ROS generated during exercise. It is not known whether this enhanced defense system sufficiently balances the increase in exercise-induced ROS. However, data showing that trained athletes who ingest antioxidant supplements show evidence of reduced oxidative stress suggest the need for further research to fully document the efficacy and safety of long-term antioxidant supplement use (16). It should be noted that most studies that have assessed antioxidant changes after exercise or training have used as endpoints various antioxidants or oxidative byproducts (eg, glutathione disulfide – GSSG) in the blood. Increased or decreased blood concentrations do not necessarily reflect changes at the tissue level and may have minimal physiologic implications. Some researchers have suggested that megadoses and long-term use of antioxidants can be harmful (17,18). The high degree of variability in resting levels of some of these indicators and in their response to exercise underscores the tenuous nature of our understanding of the relationship between exercise, oxidative stress, and the generation of free radicals.

Conclusion

Research over the past decade has established the physiological importance of ROS as contractile modulators in skeletal muscle. Further studies about these mechanisms will provide a clearer picture of contractile regulation and will broaden our understanding of skeletal muscle function. At present, data are insufficient to recommend antioxidant supplements for athletes or other persons who exercise regularly. However, no one questions the importance of ingesting a diet rich in antioxidants for all who exercise and train regularly.

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OKSIDACIONI STRES, STRES PROTEINI I ANTIOKSIDANSI U VEŽBANJU

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Smatra se da vežbanje dovodi do povećanja stvaranja reaktivnih vrsta kiseonika što može dovesti do oštećenja ćelija. Potencijalni izvori reaktivnih vrsta kiseonika u vlaknima skeletnih mišića su: mitohondrijalni respiratorni lanac, stvaranje superoksida ksantinoksidazom, enzimska oksigenacija arahidonske kiseline, sinteza azotmonoksida, oksidacija kateholamina i oksidacioni prasak u neutrofilima. Stres proteini predstavljaju jedan od opštih zaštitnih mehanizama koji omogućavaju ćeliji i celom organizmu da preživi stres. Tačna povezanost vežbanja, stres proteina i reaktivnih vrsti kiseonika još uvek je nepoznata. Suplementacija antioksidansima se, od strane proizvođača, preporučuje sportistima kao sredstvo za poboljšanje učinka, brži oporavak i veću izdržljivost tokom napornih treninga. Do sada poznati podaci iz različitih istraživanja nedovoljni su da bi se suplementacija antioksidansima preporučivala sportistima ili fizičkim aktivnijim osobama. Međutim, takav stav ne dovodi u pitanje značaj dijete bogate antioksidansima za sve osobe koje vežbaju i treniraju redovno. *Acta Medica Medianae 2004; 43(4): 45–47.*

Ključne reči: *vežbanje, antioksidansi, oksidacioni stres, stres proteini, skeletni mišić*