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Oxidative stress and skeletal muscle in exercise

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Summary

Reactive oxygen species (ROSs) are often associated with damage to cellular functions. ROSs production is indicatives of oxidative stress during physical exercise. Oxidative stress occurs in those circumstances in which free radicals determine a tissue damage or production of toxic and dangerous compounds for tissues. In a relaxation state, antioxidant defense of body may hold under control free radicals. Physical activity promotes specific adaptations in relation to type, intensity and duration of physical exercise performed, and a cytoprotective response in skeletal muscle is the increased production of heat shock proteins (HSPs).
In ageing, skeletal muscle shows a series of deteriorations, and numerous data suggest that redox processes may play an important role in ageing processes.

Key words

Reactive oxygen species; physical exercise.

Introduction

A free radical is an atom with, at least, an unpaired electron in the most outside shell; it is highly reactive. Free radicals in which oxygen is involved are named reactive oxygen species (ROSs), such as superoxide anion, hydroxyl radical, singlet oxygen and hydrogen peroxide. ROSs are often associated with damage to cellular functions and the kind of damage depends on nature of ROSs; furthermore damages induced by oxidative stress have cumulative effects connected with various diseases. ROSs contribute to a number of human pathologies, and so the question arises if exercise-induced oxidative stress contributes to the development of these pathologies.

Production of ROSs is a normal process in aerobic life but it is also indicative of oxidative stress during physical exercise, in fact during a muscular performance oxygen intake increases a lot, due to the increased muscular work. Physical exercise causes an increase in ROSs production, but physical activity also promotes very specific adaptations in relation to type, intensity and duration of physical exercise performed, to defend the body and improve exercise performance. In relation to physical activity, a cytoprotective response in skeletal muscle is an increased production of heat shock proteins (HSPs). Increased content of HSPs, as a result of stress, is believed to provide remarkable protection against subsequent periods of stress damage and to facilitate a rapid recovery and remodeling if damage occurs. In ageing,

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skeletal muscle shows a series of deteriorations in dimension, structure and function; in this condition oxidative stress level in muscle is influenced by two fundamental biological processes: increased ROSs production and changes in antioxidant defense. Several data suggest the possibility that redox processes may play an important role in ageing processes.

Oxidative stress and its effects

It's known that free radicals, including ROSs, remove electrons from lipid membrane, leading to a chain of reactions called "lipid peroxidation". During physical exercise, free radicals may exceed those removed and so they can cause lipid peroxidation. Peroxidation products have been detected in blood after an extreme exercise (Ilhan *et al.,* 2004), and extension of lipid peroxidation depends on intensity of exercise; in addition to lipid peroxidation, ROSs cause oxidative modifications in proteins (enzymes) and nucleic acids, as it has been observed in athletes after a marathon in whom DNA damage increased (Banerjee *et al.,* 2003; Preta *et al.,* 2010).

In relax, antioxidant defenses of body may hold under control free radicals. If free radicals are not under control, muscle tissue might be damaged. This damage could inhibit performance and induce fatigue. Athletes in condition of excessive training have high levels of lipid peroxidation, indicating that this excess of training deteriotates antioxidant defenses (Schneider *et al.,* 2005). Also moderate exercise may lead to oxidative stress, a condition in which ROSs production exceeds antioxidant defenses, inducing damage of lipids, proteins and DNA (Sen, 2001). Oxidative damage of proteins may determine their aggregation and denaturation, and so a loss of their essential biological functions. Oxidative injury related to exercise is implied in muscle damage and diminishes muscular performance (Kinnunen *et al.,* 2005). A metabolic response to stress is muscular catabolism with release of amino acids by muscle itself (Wolfe, 2005; Pasiakos *et al.,* 2010). Glutamine is the most abundant amino acid in muscle and blood and it is used for cell division, nucleotide biosynthesis and satisfaction of energetic needs. During several catabolic states, like prolonged exercise, glutamine steady state is under stress and its level falls. Furthermore during physical activity glutamine availability to leucocytes is altered and this may influence immune function (Walsh *et al.,* 2000).

Reid and coworkers (Reid and Durham, 2002; Moylan and Reid, 2007; Reid, 2008) observed that, during muscular contraction, superoxides are produced intracellularly in muscle cells and then released in the extracellular medium; hydrogen peroxide, produced in muscle cells, crosses cellular membrane in order to catch up extracellular medium where it contributes to production of hydroxyl radicals. In this way, relatively little harmful ROSs such as superoxide and hydrogen peroxide may be release from cells in order to produce more dangerous hydroxyl radicals. Diaz *et al.* (1993) observed that hydroxyl radical, powerful oxidant, is generated by muscular hard work. Barclay *et al.* (2003) showed that superoxide radicals attenuate contracting function and amplify fatigue rate of muscle in contraction. ROSs contribute to a number of human pathologies, and so the question arises if exercise-induced oxidative stress contributes to development of these pathologies. This is particularly important for persons having a high risk to develop health disorders that could be caused by oxidative stress (Atalay *et al.,* 2006).

Eccentric exercise

Contraction can be concentric (when activated muscle shortens), eccentric (when activated muscle lengthens) or isometric (when activated muscle remains of the same length). In human, exercise-induced muscle damage often occurs after an unusual exercise, particularly if this exercise involves a great number of eccentric contractions. Direct signs of muscle damage include cellular and subcellular disturbances, particularly in the Z-line. Other markers of exercise-induced muscle damage include: decrease in force production, increase in inflammatory response both in muscle tissue and blood, increase of muscle proteins in blood and muscle soreness. Initially damage is due to a mechanical distruption of fibers, subsequently it is linked to inflammatory response and to changes in excitation-contraction coupling in muscle (Harmon *et al.,* 2010). Eccentric contraction-induced damage has a characteristic time course. Initially, microscopic lesions occur with distruption of myofibrillar banding; after 2-4 days, secondary changes may be observed including invasion by phagocytic cells and degeneration of cellular structures; after 4-6 days, regeneration of muscle occurs by muscle stem cells or satellite cells. These cells migrate in damaged area, differentiate in myoblast and fuse in order to form multinucleated myotubes, into mature skeletal muscle. It is clear that invasion of macrophages, necessary in order to prepare tissue for regeneration, follows injury to muscle fibers. These phagocytic cells release large amounts of oxidant radicals in order to favour the degeneration of necrotic tissue (Palomero and Jackson, 2010). Muscle slowly regenerates and its function is restored. Harmful effects of increased free radicals production, following a period of lengthening contraction, are supported by studies of Vasilaki *et al.* (2006). It's clear that during exercise there is an increased free radical activity (McArdle *et al.,* 2002). ROSs play an important role in regulating intracellular redox balance, influencing the activity of several transcription factors and signalling molecules (Jackson and McArdle, 2011).

Anaerobic exercise

Little is known about oxidative alterations induced by anaerobic exercise. There are indications that an intense anaerobic work involves same oxidative alterations of aerobic exercise, both in skeletal muscle and in blood (Bloomer, 2008; Fisher-Wellman and Bloomer, 2009; El Abed *et al.,* 2011). This kind of exercise has been associated with a substantial acidosis due to lactic acid both in blood and muscle, and also with a greater increment of plasma catecholamine levels. Moreover anaerobic exercise stimulates purine catabolism to xanthine and urate, as evidenced by plasma urate accumulation. It determines also a transitory and acute muscular deoxygenation, similar to the syndrome of ischaemia-reperfusion (Nioka *et al.,* 1998; Hoffman *et al.,* 2005). Both purine catabolism and ischaemia-reperfusion syndrome activate xanthine oxidase system (Groussard *et al.,* 2003; Machefer *et al.,* 2007). All these data lead to the hypothesis that short-duration intense anaerobic exercise could be a potential factor of oxidative stress. Groussard *et al.* (2003) have investigated, on humans, what is the effect of a short-duration intense anaerobic exercise on several markers of oxidative stress in blood. Wingate test was used for that study: subjects must cycle for 30 seconds as fast as possible, the speed is recorded and the power is calculated. This test

was chosen because it stimulates glycolytic systems and activates purine catabolism and lactic acid production. Moreover Wingate test determines an increase in plasma catecholamine levels (Vincent *et al.*, 2003; Jacob *et al.*, 2004). Many factors could contribute to oxidative stress induced by this exercise: proton accumulation due to acidosis by lactic acid, that is a powerful pro-oxidant factor; catecholamine autoxidation might contribute to short-duration intense anaerobic exercise-induced oxidative stress, since elevated levels of catecholamines have been found after this type of exercise (Vincent *et al.*, 2003; Jacob *et al.*, 2004); a last and perhaps most important factor might be the activation of xanthine oxidase system (Groussard *et al.*, 2003; Machefer *et al.*, 2007). Nioka *et al.* (1998) have demonstrated, during Wingate test, an immediated deoxygenation in activated muscle followed by reoxygenation, and these transitory but severe changes can activate xanhtine oxidase system in blood.

Adaptative responses to oxidative stress

A cytoprotective response in skeletal muscle is the increased production of HSPs (McArdle *et al.*, 2002). HSPs are named in relation to their molecular weight and they include small HSPs such as α- β-crystallin, HSP10, HSP60, HSP70 and the larger HSPs such as HSP90 and HSP110 (McArdle *et al.*, 2002; Kayani *et al.*, 2010). HSPs are normally present in cells. Increased content of HSPs, as a result of stress, is believed to provide protection against subsequent periods of stress damage and to facilitate a rapid recovery and remodelling if damage occurs. All HSPs act to preserve cellular integrity (McArdle *et al.*, 2002). HSP70 has ability to repair many proteins. HSP60 is primarily located in mitochondria. HSP60 synthesis is induced in a great number of tissues by a great number of stress conditions, including in skeletal muscle by exercise (Jackson, 2009; Khassaf *et al.*, 2001). HSP60 and HSP10 are believed to be capable to save proteins that denature spontaneously within mitochondria. HSPs are involved also in intracellular degradation. It seems that cytoplasmic HSP70, mitochondrial HSP60 and HSP10 are associated with short-life proteins and they promote their degradation by ATP-dependent protease (McArdle *et al.*, 2002).

Skeletal muscle of adult and young mammalians quickly adapts to sequential periods of exercise, so that muscle is protect against subsequent periods of physical exercise. This cytoprotection is associated with several changes in gene expression, upregulation of cellular protective mechanisms and remodelling of muscle structure, including also mitochondrial biogenesis (McArdle *et al.*, 2002). HSP expression is considered an adaptive mechanism and a marker of some types of cell injury, including exercise-induced oxidative stress (Demirel *et al.*, 2003; Staib *et al.*, 2007; Staib *et al.*, 2009). Understanding role and expression of HSPs and their association with oxidative injury could give important information on the mechanisms of cellular protection and could help to reduce deleterious effects of physical exercise (Kinnunen *et al.*, 2005). HSPs expression varies a lot among different species (Liu *et al.*, 2004). HSP70 induction depends on exercise intensity in humans (Liu *et al.*, 2006). It seems that HSPs induction differs in relation to type of muscular fibers, suggesting that HSPs expression is specific for every type of muscular fiber (Liu *et al.*, 2004).

It's clear that physical well-being of a person is improved by physical activity and nutrition diet. Moreover physical activity determines stress of various intensity

to several body systems and promotes various adaptations in relation to type, intensity and duration of exercise. For each individual, metabolic stress during physical activity is usually determined by the type of exercise and its intensity, by nutritional status and environmental conditions. Other conditions that influence individual metabolic stress during exercise include genetic background, age and sex (Joyner and Coyle, 2008). Physical activity may have positive consequences such as reduced risk of cardiac disease on the one hand and improved physical performance on the other. However physical activity may place tissues under acute stress condition. Training determines adaptations capable to attenuate harmful effects of ROSs (Schneider *et al.*, 2005). As previously said, eccentric contraction (muscle lengthening) causes muscle damage; this muscle damage may be repaired, an adaptation so that muscle is more resistant to subsequent damages induced by exercise. Adaptation also gives in this case a potent stimulus to muscle growth, more than what observed after concentric or isometric exercise (Kostek *et al.,* 2007). It's well established that a repeated bout of the same exercise determines much less damage symptoms than initial bout (McHugh and Pasiakos, 2004). This protective adaptation has been defined "repeated bout effect" (Nosaka and Clarkson, 1995; Peake *et al.,* 2005). It has been demonstrated both in animals and humans.

The mechanism of repeated bout effect has not been well understood (McHugh, 2003). Theories explaining adaptative phenomenon related to repeated bout exercise have been divided into three categories: 1. neural adaptations; 2. mechanical adaptations; 3. cellular adaptations.

Neural theory: Moritani *et al.* (1987) proposed that muscle damage results from high stress in a reduced number of active fibers during eccentric contraction. Fast-twitch fibers are more susceptible to distruption during eccentric contractions. It follows that a change in activation that reduces the stress to fibers could limit the subsequent myofibrillar distruption (McHugh, 2003). Nosaka and Clarkson (1995) suggested that neural adaptation "could better distribute work among fibers". However phenomenon of "repeated bout effect" can occur independently from neural adaptation (Nosaka *et al.,* 2011).

Mechanical theory: the damage induced by eccentric contraction is believed to begin with a mechanical distruption of myofibrils. Mechanical adaptation seems to depend on changes of not contractile elements of the muscleskeletal system, such as cytoskeletal proteins responsable for the structure of sarcomere; another protective effect has been attributed to increased intramuscular connective tissue that may dissipate myofibrillar stress (McHugh, 2003). Lapier *et al.* (1995) suggested that tissue repair after damage by eccentric exercise is characterized by an increase in intramuscular connective tissue capable to protect from repeated bouts.

Cellular theory: Morgan (1990) and Morgan and Proske (2004) have suggested that muscle damage is due to irreversible tension of sarcomeres during eccentric contraction. Based on this idea, they have suggested that repair processes result in an increased number of sarcomeres connected in series and this serves to reduce tension during repeated bouts and limit myofibrillar distruption. Lynn *et al.* (1998) supported the predictions of Morgan (1990), in fact they compared eccentric contraction training of muscles with concentric contraction training, and their data evidenced muscles with more sarcomeres connected in series and more resistant to damage from eccentric test contractions.

Ageing and stress

Maintenance of mobility is a critical element for the quality of life. In ageing, skeletal muscle undergoes deterioration in size, structure and function. It becomes smaller and weaker; moreover muscle is more susceptible to damage related to physical effort, damage restoration is impaired and muscle is incapable to adapt itself quickly to periods of exercise (McArdle *et al.,* 2002). Structural changes responsible for fall in muscle force, typical of ageing, are well documented; decline in muscle volume is due to both reduction in total number of muscle fibers and atrophy of individual fibers. Several data suggest the possibility that redox processes may play an important role in ageing processes. Several theories have been proposed on ageing and they support strongly a role of ROSs (McArdle *et al.,* 2002; Vasilaki *et al.,* 2006). Many studies have evidenced increased production of free radicals in aged skeletal muscle with an increased production of oxidized derivatives of proteins, lipids and DNA (Zainal *et al.,* 2000) Oxidized proteins don't work efficiently. Moreover several transcription factors have redox-sensitive sites that are particularly susceptible to damage (McArdle *et al.,* 2002). Studies on isolated mitochondria of skeletal muscle of aged rats have demonstrated that a great portion of free radicals are generated within mitochondria (Bejma *et al.,* 2000; Leichtweis *et al.,* 2001). Moreover, during ageing, abnormal mitochondria are accumulated. A pathological increment in free radical production results in accumulation of oxidation products and in accumulation of abnormal mitochondria which produce further increased amounts of free radicals; therefore inefficient function of mitochondria may have a significant role in physiological and structural changes in muscles of aged mammals (McArdle *et al.,* 2002).

The adaptation to exercise of aged mammal muscle is greatly impaired and so muscle remains susceptible to damage (Jackson, 2009); ability to induce HSPs is reduced in aged individuals and this loss of adaptation may have an important role in the general failure to adapt to stress (McArdle *et al.,* 2002).

Aged individuals, that are physically active, benefit of exercise-induced adaptation of cell antioxidant defense system. Physical activity renders them less vulnerable to acute damage and chronic inflammation (Ji *et al.,* 2010). Greater benefit of non-exhaustive exercise is to induce light stress stimulating some antioxidant enzymes expression. Ageing seems to attenuate antioxidant enzyme adaptation subsequent to training. It seems that although ROSs production increases, aged muscle has a diminished gene expression of antioxidant enzymes, possibly due to decreased ability for cell signaling. Therefore, for senescent muscle, training would have to be assisted with supplementation of exogenous antioxidants in order to achieve an optimal level of defense (Gomez-Cabrera *et al.,* 2009).

Discussion

The data reported in this brief review are in part contradictory and leave open questions especially in relation to the opportunity of using antioxidant supplements to the diet with particular regard to athletes.

Free radicals are produced during physical exercise; they induce transient lipid peroxidation and are then removed during the recovery phase (Schneider *et al.,*

2005). It is well known that the human body has adeguated antioxidant reserves in order to counteract ROSs production under physiological conditions. Each one of these antioxidants has a specific role in the cell and complement the others functionally. An intense or prolonged exercise can lead to an increase in free radicals production exceeding antioxidant defense, so that oxidative stress may have consequences on exercise performance (Cooper *et al.*, 2002). When ROSs production is excessive, as happens during prolonged aerobic exercise, antioxidant defense is overwhelmed by ROSs, leading to cell and tissue damage (Banerjee *et al.*, 2003). From the literature it is clear that the consequences of oxidative stress depend on tissue and/or species, membrane properties, content of endogenous antioxidants and ability to induce a response in antioxidant systems (Blokhina and Fagerstedt, 2010). It is commonly accepted that excessive free radical production is harmful for skeletal muscle and therefore its prevention should have beneficial effects.

On the other hand, some data suggest that an increased free radicals production may have beneficial adaptive effects and this would explain why, during some kinds of exercise, oxygen consumption is high but the risk of consequent damage is relatively low (Palomero and Jackson, 2010; Jackson, 2011). Other authors have shown that an habitual intense training, as is necessary for competitions, reduces lipid peroxidation products and prevents oxidative damage in tissues by activating antioxidant systems (Ilhan *et al.,* 2004).

It would seem reasonable to assume that if antioxidants may protect cells from oxidative stress, it should follow that an increase in intracellular antioxidant levels in muscle should offer greater protection against oxidative agents, which should in turn lead to reduced fatigue. Exogenous antioxidants of diet interact with endogenous ones and, as mentioned above, low ROSs levels seem necessary for optimal contractile muscle function (Strobel *et al.* 2011) Given these premises and the known effects of exercise on endogenous antioxidant defense, it remains unclear if regular and vigorous exercise increases the need for dietary antioxidant intake (Powers *et al.,* 2004).

In conclusion, it's difficult to give general indications on types and dosage of antioxidants to be given as dietary supplementation, and it remains an open question whether athletes need such a supplementation to prevent exercise-induced oxidative damage or to help the recovery phase. Some data demonstrate that training athletes have a reduced oxidative stress if administered antioxidant supplementation (Clarkson and Thompson, 2000). Therefore, the advantage of such a supplementation might depend on whether the practicing athlete is on training or already trained.

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