REVIEW

ACUTE EXERCISE INDUCED OXIDATIVE STRESS AND ANTIOXIDANT CHANGES

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Generation of reactive oxygen species (ROS) is a normal process. Under physiological conditions, these deleterious species are mostly removed by the cellular antioxidant systems, which include antioxidant vitamins, protein and non-protein thiols, and antioxidant enzymes. An acute bout of exercise at sufficient intensity has been shown to stimulate activities of antioxidant enzymes. This could be considered as a defensive mechanism of the cell under oxidative stress. However, we still have insufficient knowledge about the interaction between exercise and antioxidants, which are important in assessing the adequacy of protection against oxidative damage and about the necessity of dietary manipulation and/or supplementation. This review concerns effects of acute exercise on various oxidative stress parameters and antioxidant defense system.

Keywords: Acute exercise, Oxidative stress, Antioxidant status, Lipid peroxidation, Antioxidant supplementation.

INTRODUCTION

Cells continuously produce free radicals and ROS as part of metabolic processes. These free radicals are neutralized by an elaborate antioxidant defense system consisting of enzymes such as catalase, superoxide dismutase, glutathione peroxidase, and numerous non-enzymatic antioxidants, including vitamins A, E and C, glutathione, ubiquinone, and flavonoids. Exercise can cause an imbalance between ROS and antioxidants, which is referred to as oxidative stress (1).

While regular exercise training is associated with numerous health benefits, it can be viewed as an intense physical stressor leading to increased oxidative cellular damage, likely due to enhanced production of ROS (2).

A single bout of exercise can result in activation of several distinct systems of radical generation and may be separated into both primary (e.g., electron leakage through the mitochondria during aerobic respiration, prostanoid metabolism, catecholamines, and the enzymes xanthine oxidase and NADPH oxidase), as well as secondary sources (e.g., phagocytic cells, disruption of iron containing proteins, and excessive calcium accumulation) (2).

Many studies have reported that acute aerobic exercise contributes to oxidative stress, especially when performed at high intensity levels. Two mechanisms linking acute aerobic exercise and oxidative stress are 1) increased pro-oxidant activity via a mass action effect when VO_2 is elevated 10- to 15-fold above rest, and 2) inadequate antioxidant activity relative to pro-oxidants (3).

ACUTE EXERCISE INDUCED OXIDATIVE STRESS

Acute exercise-induced oxidative stress has been well documented over the last decade. A single bout of physical exercise has been shown to induce formation of ROS and nitrogen species and the related oxidative damage. On the other hand, regular training is known to increase the resistance against ROS induced lipid peroxidation, and to decrease the accumulation of oxidative protein and DNA damage (4). Previous studies have identified elevations in blood oxidative

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stress markers after acute exercise, indicating that oxidative stress is not limited to the cellular compartment. Furthermore, very high intensity exercise appears to exaggerate the blood oxidative stress response (5). A number of potential pathways exist for exercise-related oxidant production (6):

1. Oxygen consumption increases several-fold with exercise. Electron leak from the mitochondrial electron transfer chain results in the production of superoxide anions. Free radical production measured by electron spin resonance spectroscopy correlates strongly with maximal oxygen consumption.

2. Xanthine dehydrogenase oxidizes hypoxanthine to xanthine and xanthine to uric acid using NAD^+ as the electron acceptor forming NADH. During ischemia, in active muscles xanthine is formed via anaerobic metabolism of ATP and xanthine dehydrogenase is converted to xanthine oxidase. During reperfusion, with the resulting increase in oxygen load, xanthine oxidase still converts hypoxanthine to uric acid, but utilizes oxygen as the electron acceptor forming superoxide.

3. Tissue damage resulting from exercise may induce the activation of inflammatory cells such as neutrophils, with the subsequent production of free radicals by NADPH oxidase.

4. Catecholamine concentrations are increased during exercise, and ROS can result from their auto-oxidation.

5. Muscle mitochondria undergo increased uncoupling and superoxide generation with increasing temperatures. Therefore, exercise-induced hyperthermia may cause oxidative stress.

6. Auto-oxidation of oxyhemoglobin to methemoglobin results in the production of superoxide and the rate of formation of methemoglobin can increase with exercise.

Aerobic–anaerobic exercises result in a higher degree of oxidative stress and females are able to tolerate oxidative stress more effectively than males (7). One explanation for the observed gender difference is a higher metabolic rate in men leading to increased mitochondrial flux and increased production of ROS, the female hormone estrogen, another possible explanation, is known to exhibit antioxidant properties (8).

Alessio et al (3) found that after exhaustive aerobic (AE) and isometric exercise (IE) protein carbonyls increased 67% immediately and 1 h after AE, and 12% immediately after IE and returned to baseline 1 h after IE. Malondialdahyde (MDA) did not increase significantly with either treatment. Lipid hydroperoxides increased 36% above rest during IE compared with 24% during AE. ORAC (Oxygen Radical Absorbance Capacity) increased 25% after AE, compared with 9% after IE (3).

Alessio et al (3) and Ashton et al (9) have also found immediate postmaximal exercise rises in lipid hydroperoxides (42% and 20%, respectively) with no alteration in MDA levels.

Alessio et al (10) reported that 1 min high-intensity running (45 m/min) in rats resulted in 167% and 157% elevation of TBARS in red slow-twitch and white fast-twitch muscle, respectively. LH increased 34% and 31% in red slow-twitch and white fast-twitch muscle, respectively (10).

A study by Ortenblad et al (11) had subjects perform six bouts of 30-s strenuous jumping with 2-min rest between bouts. Biomarkers of lipid peroxidation did not increase significantly, but several key antioxidants (e.g. superoxide dismutase, glutathione peroxidase, and glutathione reductase) significantly increased (11).

Groussard et al (12) showed that short-term supramaximal anaerobic exercise (Wingate test of 30-s) induced an oxidative stress and that the plasma TBARS level was not a suitable marker during this type of exercise. Short-term supramaximal anaerobic exercise has been associated with a substantial lactic acidosis both in blood and muscle and also with a major increase in plasma catecholamine levels. Moreover, such exercise stimulates the catabolism of purines to xanthine and urate, as evidenced by plasma urate accumulation (12).

In rats, short intense exercise has been found to induce an increase in either lipid (10) or protein oxidation (13).

Thirty minutes of aerobic and anaerobic exercise performed by young, cross-trained males can increase protein and glutathione oxidation while having little impact on lipid or DNA oxidation; protein oxidation appears to be more greatly affected by anaerobic exercise and the magnitude of protein oxidation is greater following anaerobic compared with aerobic exercise; and glutathione oxidation appears to be more greatly affected by aerobic exercise (2).

Mastaloudis et al (14) reported that plasma F2-isoprostane levels increased significantly (57%) during the 50 km ultramarathon and returned to baseline at 24 h post-race.

In untrained humans and animals, one bout of intensive exercise may cause muscle damage, followed by activation of neutrophils in response to inflammation. The activated neutrophils produce ROS, such as superoxide and hydrogen peroxide, which damage the neighboring cells as well as the neutrophils themselves (15). Oh-ishi et al (16) reported that superoxide production by neutrophils was increased after intensive exercise in untrained but not in trained rats. These findings may indicate that intensive exercise induces oxidative DNA damage in muscle and blood cells not only by increased uptake of oxygen, but also by muscle damage. High neutrophil counts and neutrophil-generated superoxide levels immediately after maximal treadmill exercise suggests that exercise-induced neutrophilia may have contributed to the observed oxidative stress (5).

Liu et al (17) have found acute exercise induced increases in MDA content and decrease in glutamine synthetase activity in liver. Acute exercise did not induce any significant increase in protein carbonyl levels in any organs. For kidney contents, mean values of MDA, protein carbonyl, or glutamine synthetase activity did not change as a result of acute exercise. In the fast muscle, acute exercise induced some decrease in glutamine synthetase activity and vice versa for slow muscle. The differences among organs may be dependent on several factors, such as oxygen consumption, susceptibility to oxidants and to antioxidant enzyme activation, antioxidant levels, and other repair systems. Muscle and heart appear to respond to oxidative stress quite differently than other organs, such as brain and liver, possibly due to the difference in mitochondrial biogenesis and the occurrence of oxidant-induced degeneration (17).

Carbohydrate ingestion during exercise is associated with reduced levels of stress hormones, which may influence oxidative stress and plasma antioxidant potential. In contrast, McAnulty et al (18) have reported that exhaustive resistance exercise did not result in increased oxidative stress as measured by F2-isoprostanes. Furthermore, carbohydrate administration did not affect blood antioxidant capacity or result in differences in F2-isoprostane levels (18).

ANTIOXIDANT DEFENCE IN ACUTE EXERCISE

The antioxidant status showed quite different changes in direction and magnitude in different organs and by different types of exercise. Changes due to exercise are subtle, suggesting that there are active stress-strain relationships between oxidant formation and scavenging during exercise (17).

One bout of vigorous exercise did not change vitamin E concentration in exercised rats. However, in the exercised rats, the concentration of vitamin C in plasma was significantly higher at 2 h and tended to be lower at 24 h and 48 h than that in control rats. The concentrations of vitamin C in the plasma and adrenal glands showed a significant negative correlation (15).

The mountain cycling stage (171 km) increased catalase, glutathione reductase activities, oxidized glutathione and uric acid levels, decreased glutathione peroxidase activity. Plasma vitamin E was increased after the stage but dropped to below basal values after 3 h of recovery (19).

Alessio et al (20) showed that exhaustive exercise lowered glutathione/oxidized glutathione ratio in unlimited running wheel exercise and limited physical exercise rats fed ad libitum.

Quindry et al (5) reported that after maximal-intensity exercise ascorbic acid and uric acid levels decreased immediately. Camus et al (21) observed a decrease (~40%) in ascorbic acid immediately postexercise (35 min of downhill running at 60% VO_{2max}) followed by a return toward baseline after only 20 min of recovery (~17%).

Acute exercise induced a significant decrease in ubiquinone in the brain, a decrease in cysteine and cystine in the liver, an increase in ascorbic acid and GSH in the heart, and a decrease in ascorbic acid in the slow muscle (17).

Somani et al (22) showed that, acute exercise results in a larger increase in antioxidant enzyme activities than does chronic exercise in rat heart. This difference was proposed to be a result of a compensatory mechanism to cope with the enhanced production of superoxide and oxyradicals during exhaustive exercise.

While the maximal test increased the circulating number of lymphocytes, the activities of catalase and glutathione peroxidase were decreased. No changes were observed in lymphocyte number or in lymphocyte antioxidant enzyme activities after the submaximal test. The circulating number of neutrophils increased significantly after the submaximal test. Maximal and submaximal tests decreased the activities of

neutrophil glutathione dependent antioxidant enzymes (glutathione peroxidase and glutathione reductase), but no changes in catalase or superoxide dismutase activities after either test (23).

In professional cyclists participating in a mountain stage, catalase and glutathione peroxidase activities decreased (40% and 50%, respectively) and myeloperoxidase (MPO) increased (39%) in neutrophils after the cycling stage, while glutathione peroxidase increased (87%) in lymphocytes (24). Plasma MDA directly correlated with neutrophil MPO activity and erythrocytes MDA. Sureda et al (24) suggest that intense exercise induces oxidative damage in erythrocytes and lymphocytes, but not in neutrophils. Swimming exercise lasting 1 h resulted in significant increases in the activity levels of catalase in liver, heart, kidney and lung tissues in both male and female rats. Increases were 462% for liver, 302% for heart, 598% for kidney and 253% for lung in male rats compared to 436% for liver, 251% for heart, 760% for kidney and 271% for lung in female rats (25).

Basal iNOS levels and SOD activity were similar in neutrophils and lymphocytes, iNOS levels and SOD activity dropped in neutrophils and rose in lymphocytes, arginase activity rose only in lymphocytes, neutrophil nitrite was correlated with SOD activity and iNOS levels, but not in lymphocytes after a mountain cycling stage (26).

Normally, the largest proportion of fat soluble antioxidant is transported in various lipoproteins, e.g. HDL and LDL, which have been reported to increase directly after exercise, which could also increase fat soluble antioxidant in plasma (27).

The elevated levels of blood antioxidant markers during recovery has three possible explanations: 1) the slowing of oxidant production with the cessation of exercise giving antioxidant defenses an opportunity to return to resting levels, 2) the upregulation of endogenous antioxidants, and/or 3) the mobilization of antioxidants from tissue stores to blood as a result of oxidant increase during exercise (28).

EFFECTS OF ANTIOXIDANT RESTRICTION AND SUPPLEMENTATION

Antioxidant restriction has been reported to impair exercise performance in animals. In a study comparing vitamin E-deficient rats with vitamin E-sufficient animals, exercise capacity was reduced by 40% (29).

F2-isoprostane concentration (a marker of oxidative stress) was significantly higher after submaximal exercise (38%), exhaustion (45%), and 1 h of recovery (31%) when following the restricted antioxidant diet compared with the habitual antioxidant diet (28).

Rats deprived of dietary vitamin E up to 16 week (resulting in tissue vitamin E depletion >90%). No difference was noted between untrained rats deprived of vitamin E and untrained rats undeprived of vitamin E in post exercise blood indices such as TBARS, creatine kinase, hematocrit, hemoglobin and lactate (30).

Six weeks of vitamin E and C supplementation prevented endurance exercise-induced lipid peroxidation but had no effect on inflammatory markers (8).

McBride et al (31) studied the interactive effects of resistance training and vitamin E supplementation on MDA. Subjects completed heavy resistance exercise that consisted of three sets of 10 maximal repetitions for each of eight different exercises, allowing 2-min rest between sets. MDA increased up to three-fold above resting levels immediately, 6, and 24 h after one bout of these resistance exercises. Vitamin E supplementation attenuated MDA increase and was associated with return of MDA to resting levels within 6 h post resistance exercise (31).

With two months of vitamin E supplementation, plasma F2-isoprostanes increased 181% versus 97% during the race and lipid hydroperoxides were significantly elevated, plasma antioxidant potential was significantly higher 1.5 h postrace in vitamin E supplemented group (32). In rats consuming a moderate fat diet, short-term moderate intensity exercise increases Mn-SOD activity and oxidative stress in skeletal muscle (33).

CONCLUSION

The development of free radicals and oxidative stress during exercise is an important consideration for optimal performance, recovery, and health. Two widespread dogmas in the exercise science literature are that: (i) exercise increases free radical production; and (ii) this is a negative side effect that needs to be prevented (34).

In summary, acute exercise increases oxidant levels and oxidative stress in untrained subjects, but long-term exercise

may counter this effect by increasing the activity of antioxidant enzymes and reducing oxidant production. These defenses may be critical for preventing chronic oxidative damage to muscle during exercise and even at rest (35).

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