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REVIEW ARTICLE

Free radicals and exercise: implication in health and fitness

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Abstract

Generation of oxygen free radicals and other reactive oxygen species underlies the mechanism for the exercise-induced oxidative damage. Enzymatic and nonenzymatic antioxidants play a vital role in protecting tissues from excessive oxidative damage during strenuous exercise, certain pathogenesis and aging. The purpose of this communication is to present several lines of research evidence that support the notion that cellular antioxidant defense capacity can be enhanced by (1) exercise-elicited signal transduction of antioxidant enzymes; (2) chronic exercise training in conjunction with antioxidant supplementation; and (3) dietary supplementation of phytochemical antioxidants.

Keywords: Antioxidant, exercise, Free radical, Glutathione, Oxidative stress, Phytochemical, Signal transduction

Introduction

Strenuous physical exercise and sports are associated with a dramatic increase in oxygen uptake both at the whole body and cell levels, especially in the skeletal muscle and heart. Most of the oxygen is utilized in the mitochondria for oxidative phosphorylation and reduced to water. However, a small fraction of oxygen (~2-5%) is converted to superoxide radical ($O_2^{-}\bullet$), hydrogen peroxide (H_2O_2) and hydroxyl radicals ($OH\bullet$) (Halliwell & Gutteridge 1989). $O_2^{-}\bullet$ and $OH\bullet$, along with several carbon or nitrogen-centered derivatives are free radicals by definition since they contain an unpaired electron in their atomic structure. H_2O_2 and other peroxides are not radicals but are highly reactive. Collectively, they are classified as the reactive oxygen species (ROS). In the past two decades, increasing evidence has accumulated indicating that the production of ROS may be involved in numerous biochemical and physiological events leading to cell and tissue damage, certain diseases, and aging (Finkel & Holbrook 2000, Harman 1956). Since strenuous exercise promotes ROS production, considerable concerns have been raised among exercise physiologists and health workers regarding the consequences of and defense strategies against ROS (Ji 1995, Jenkins 1988).

The body is equipped with a sophisticated antioxidant system to deal with the production of ROS. The system includes antioxidant vitamins, i.e. α-tocopherol (vitamin E), ascorbic acid (vitamin C), β-carotene (vitamin A precursor), thiol-containing compounds, e.g. glutathione (GSH), and antioxidant enzymes (Ji 1995). Each of these antioxidants plays a unique role in the cell and complements each other functionally. These antioxidant defense systems preserve homeostasis for normal cell functions at rest and under normal physiological conditions. However, during heavy exercise, pathogenic processes and aging, ROS production may overwhelm antioxidant defense capacity causing cell and tissue damage. Also, if antioxidant defense is severely hampered by nutritional deficiency and pharmacological intervention, the body can become more susceptible to ROS. In either situation, the body is said under oxidative stress. Thus, we should carefully evaluate the impacts of diet, drugs, and lifestyle on the health of people actively participating in sports and exercise. However, this concern should not be extrapolated to a conclusion that exercise has an adverse effect to health of the general population. Recent research has demonstrated that increased ROS during exercise can activate cell signal transduction pathways that lead to elevated antioxidant defense, mainly by upregulation of antioxidant gene expression (Ji, 2002). The purpose of this communication is to present several lines of research evidence from our laboratory and other researchers that support the notion that cellular antioxidant defenses capacity can be enhanced by (1) exercise-elicited signal transduction of antioxidant enzymes; (2) chronic exercise training in conjunction

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with antioxidant supplementation; and (3) dietary supplementation of phytochemical antioxidants.

Exercise activates antioxidant signaling

Several strategies have been employed to enhance endogenous antioxidant levels such as dietary restriction, transgenic animal model, dietary antioxidant supplementation, and use of pharmaceutical antioxidant mimetics. None of the above strategies to this date has been shown to successfully boost antioxidant defense in skeletal muscle. In a recent review, Finkel and Holbrook (2000) elegantly stated that the best strategy to enhance endogenous antioxidant levels may actually be oxidative stress itself, based on the classical physiological concept of Hormesis. Hormesis is a Greek word meaning a sublethal dose of toxin can increase the tolerance of the organism to withstand higher doses of toxins. Exercise at high intensity is a form of oxidative stress due to the generation of ROS that exceeds the defense capacity in skeletal muscle (McArdle et al. 2001). However, it has been consistently observed that individuals undergoing exercise training have high levels of antioxidant enzymes and certain non-enzymatic antioxidants in muscle and demonstrate greater resistance to exercise-induced or imposed oxidative stress (Ji 1995, Sen 1995, Jenkins, 1988). Presumably, these adaptations result from cumulative effects of repeated exercise bouts on the gene expression of antioxidant enzymes. The question arises as to how exercise could trigger cellular mechanisms to increase antioxidant defense, i.e. signal transduction.

Mammalian cells are endowed with several signaling pathways that can be activated by oxidative stress. Those include NF-κB, heat-shock transcriptional factor 1 (HSF-1), and P53 pathways, as well as mitogen-activated protein kinase (MAPK) and PI(3)K/Art that regulate the first three pathways through phosphorylation (Finkel & Holbrook 2000). Recent evidence suggests that a single bout of muscular contraction, especially eccentric contraction, can activate MAPK pathway in human skeletal muscle (Aronson et al 1997). Sixty min after an acute bout of one-leg cycling activity of MAPK-activated protein kinase 2 (MAPKAPK2) was increased by 300% (Krook et al 2000). Furthermore, Extracellular signal-regulated kinase (ERK) and p38 MAPK activity was increased in rat slow- and fast-twitch skeletal muscle after electrically stimulated contraction (Wretman et al 2000). Also, ERK and p38 were activated in rat soleus and tibialis muscles immediately after an acute bout of treadmill running (Nader & Esser 2001). Activation of various kinases involved in MAPK pathway can lead to the sequential phosphorylation of a series of proteins, resulting in increased expression of c-Jun, a subunit of the transcription factor activator protein-1 (AP-1) (Pulverer et al 1991). Alternatively, it may phosphorylate downstream kinases such as p90 ribosomal S6 kinase (p90rsk), which activity was found to increase up to 25 fold in human muscle after exercise (Krook et al 2000). Although cause of exercise-activated MAPK pathway has not been identified and so far no data has linked MAPK to antioxidant gene expression, oxidative stress is a well-established mechanism for increasing AP-1 binding to target genes, including antioxidant enzymes. Furthermore, activation of the kinases involved in AP-1 pathway may phosphorylate enzymes having critical roles in other oxidative stress-sensitive signaling pathways (Finkel & Holbrook 2000).

Mechanism of NFκB-induced signaling in response to oxidative stress is well-defined (Allen & Tresini 2000). ROS have been shown to activate several kinases that phosphorylate serine residue19 and 23 on the inhibitory subunit (IκB) of NF-κB, causing its ubiquitination and release from the NFκB complex. The p50 and p65 dimer subsequently translocates into the nucleus and binds to the κB domain of the target gene promoter, leading to transcriptional activation. Cellular redox status influences NF-κB activation profoundly (Flohe et al 1997). Although ROS and other prooxidant cytokines such as TNF-α initiate IκB dissociation, binding of activated and traslocated p50 and p65 dimer to DNA sequence requires a reduced cellular milieu with possible participation of GPX and thioredoxin.

Several antioxidant enzymes contain NFκB and AP-1binding sites in their gene promoter region, such as Mn SOD and γ-glumatylcysteine synthetase (GCS) (Allen & Tresini 2000). Therefore, they are potential targets for exercise-activated upregulation via NFκB signaling pathway. Hollander et al (2001) investigated the time course after an acute bout of treadmill running on Mn SOD gene expression in rat skeletal muscle. In both type 2a (DVL) and 2b (SVL), NFκB binding was significantly increased ~2 h after the acute exercise bout. This finding was confirmed in our recent experiment wherein NFκB binding reached the peak at 2 h after exercise but gradually returned to resting level at 48 h. AP-1 binding in these two muscle types were also dramatically increased by acute exercise reaching peak at 30 min, but returned to resting levels within a few hours. Furthermore, mRNA abundance for MnSOD in DVL was increased during the post-exercise recovery period (Fig. 1), whereas an increases in MnSOD protein level was observed only after 48 h. These data suggest that an acute bout of exercise may represent a sufficiently large oxidative stress to activate MnSOD gene transcription via NFκB signaling. Recently, we

reported that increased NFκB binding to nuclear extracts from DVL muscle at 1-2 hour post exercise was accompanied by an elevated P65 content (Ji et al 2003). Cytosolic content of IκB, the inhibitory subunit of NFκB complex, was decreased, whereas phosphor-IκB content increased at 0, 1 and 2 h post-exercise. Furthermore, activity of IκB kinase (IKK), the enzyme that phosphorylates IκB, was elevated, as revealed by increased phospho-IKK content in DVL homogenate of E rats. Based on these observations, it is likely that rigorous exercise can activate IKK, leading to IκB phosphorylation and dissociation, and subsequent NFκB nuclear translocation. This cascade may explain the transcriptional activation and eventual training adaptation of MnSOD reported in our previous studies (Hollander et al 2001, 1999).

Training and antioxidant supplementation attenuated ischemic-reperfuion injury

While exercise training and antioxidant supplementation may independently increase endogenous antioxidant reserve and protect against oxidative injury, the combination of the two regimens may provide additional benefits. This is because (a) endurance training improves skeletal muscle and myocardial microperfusion status due to adaptation of angiogenesis that facilitates the transport and incorporation of certain antioxidants into the tissues; and (b) key enzymes controlling the biosynthesis of some antioxidants may be activated or induced by acute and/or chronic exercise. Creditable evidence

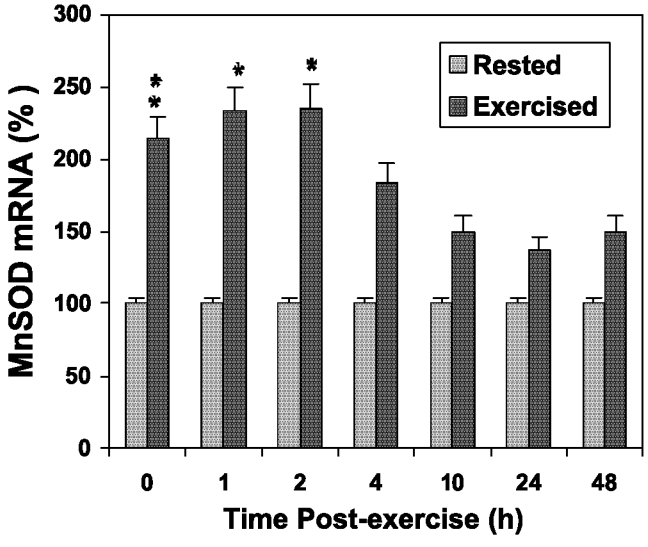

Fig. 1 Relative abundance of MnSOD mRNA in rat DVL muscle. Each data point represents the mean (±SEM) from 6 rats, derived from autoradiographic signals mRNA normalized with 18S. $^{**}P$ <0.01; $^{*}P$ <0.05, Exercised vs. Rested. (Hollander et al. 2001)

that illustrates this potential benefit of exercise is GSH homeostasis in heart ischemia-reperfusion (I-R).

GSH is a major non-enzymatic antioxidant and has been reported to play an important role in protecting the skeletal muscle from exercise-induced oxidative injury and fatigue (Sen & Packer 2000, Ji & Leeuwenburgh 1995). In the heart GSH serves as a critical antioxidant as the levels of antioxidant enzymes and vitamin E are relatively low compared to myocardial oxidative potential. The role of GSH is clearly demonstrated in the antioxidant protection against myocardial I-R injury (Ceconi et al 1988). Depletion of endogenous GSH has been shown to intensify oxidative damage induced by I-R (Leichtweis & Ji 2001, Blaustein et al 1989). However, supplementation of exogenous GSH by intraperitoneal or intravenous injection has demonstrated limited and controversial effect on increasing tissue GSH levels and improving functional performance in a postischemic heart. A major obstacle is that high plasma GSH concentration resulting from exogenous supplementation can pose a strong feedback inhibition on the rate-limiting enzyme GCS and impair operation of the γ-glutamyl cycle. Oral GSH ingestion, on the other hand, has been advocated as a more effective method to increase tissue GSH (Hagen 1990). Since previous studies in our laboratory and others have shown that endurance training could increase γ-glutamyl transpeptidase (GGT) and GCS activity in the myocardium and skeletal muscle (Leichtweis et al 1997, Sen et al 1992), we hypothesized that this important adaptation may facilitate GSH cross-membrane transport and resynthesis, resulting in increased GSH level in the cardiomyocytes for better protection against I-R.

To test this hypothesis, an open-chest *in situ* rat heart model was employed wherein the main coronary artery was surgically occluded for 45 min followed by 30-min reperfusion, or sham operation (Ramires & Ji 2001). Prior to surgery rats were either trained by running on a treadmill on progressive workload for 10 weeks or remained sedentary. Half of each group of rats was fed a GSH supplemented diet at the dose of 5g/kg during the final 17 days of training. The other half group received a control diet. The results showed that GSH supplementation alone only had marginal improvement on cardiovascular function and did not change myocardial antioxidant capacity or susceptibility to I-R injury. GSH supplemented and trained (T/GSH) rats demonstrated 18% (P <0.05) higher left ventricle peak systolic pressure (LVSP) and 29% (P <0.05) greater postischemic contractility (+dP/dt), compared to controls (Fig. 2). T/GSH hearts had 15% (P <0.05) higher GSH reserve and 32% higher GSH:GSSG ratio (P <0.05) than untrained

controls after I-R. I-R induced myocardial lipid peroxidation (measured by MDA content) and lesion (measured LDH release to plasma) were significantly reduced with T/GSH-S treatment. Although myocardial antioxidant enzyme SOD GPX and GR activities were increased with training in both dietary groups, training alone had limited protection against I-R induced functional deterioration, lipid peroxidation or lesion. Hepatic GCS activity and myocardial GGT activity were elevated in the trained rats (Ramires & Ji 2001). Moreover, GSH contents in the liver and plasma were increased in T/GSH-S rats in response to ischemic insult. These data indicate that training enhances the efficacy of GSH supplementation due to adaptation of myocardial and hepatic enzymes in the γ-glutamyl cycle. Several other studies using a similar model of I-R as ours have also demonstrated that exercise in conjunction with antioxidant treatment, such as vitamin E and a-lipoic acid yielded desirable effect in protecting against I-R injury [Coombes et al 2000a, 2000b).

Phytochemicals protects age- and exercise-associated oxidative stress

Nature offers an abundance of resources of antioxidants, most of which are present in fruits and vegetables known as phytochemicals (Hertog 1996). We have become very interested in exploring this promising field that has great potential in providing effective protection against aging- and exercise-associated oxidative damage. Ginseng and oats are two examples of our recent efforts.

As one of the most popular dietary supplements, ginsengs (*Panax C. A. Meyer* or Asian ginseng, and *Panax quinquefolius L.* or North American ginseng) have drawn attention worldwide for their broad and invaluable medicinal potential (Kitts & Hu 2000). Although the mechanism for ginseng's health-promoting effects is complex and largely unknown, it is believed that the primary active ingredients are composed of a mixture of saponin glycosides, known as ginsenosides. Furthermore, higher ginsenoside content is found in *Panax quinquefolius* (Chan et al 2000, Wang et al 1999).

Recent research indicates that ginseng has powerful antioxidant properties which may explain its anti-aging and anti-neoplastic effects (Kitts et al 2000). Treatment of ginseng extract and dietary supplementation of ginseng have shown a variety of protective effects against oxidative damage in vitro and in vivo, ranging from isolated low-density lipoprotein (LDL) oxidation, ischemic neuron dysfunction, to heart reperfusion injury and physical exercise (Jiang et al 2000, Lim et al 1997, Zhang et al 1996). While a primary function of ginsenosides appears to be related to its free radical scavenging activity, some ginsenoside fractions have been shown

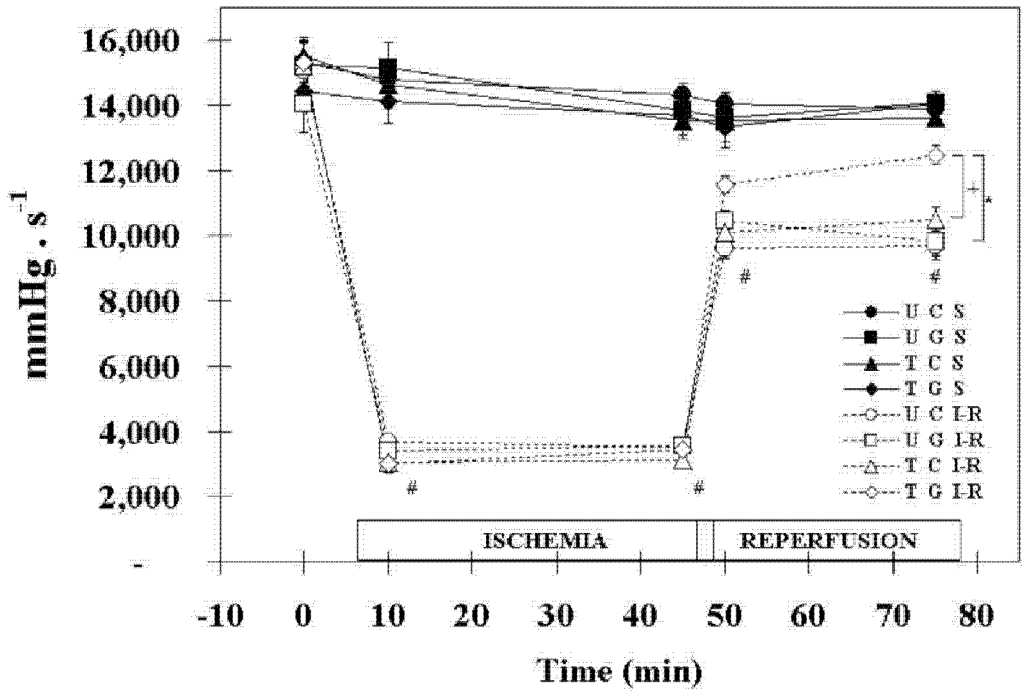

Fig. 2 Response of left ventricle contractility (+dP/dt) to ischemia-reperfusion (I-R) and sham surgery (S) in trained (T) and untrained (U) rats fed either a control (C) or GSH-supplemented diet (G). # P <0.01, I-R vs. Sham in a given time point. *P <0.05, T/G vs. U/G or U/C. + P <0.05, T/G vs. T/C. (Ramires and Ji 2001)

to induce cytosolic superoxide dismutase (CuZn SOD) via enhanced nuclear protein binding to its promoter (Chang et al 1999, Kim et al 1996, Bittles et al 1979). Since the majority of research was performed in vitro, and using Asian ginseng, the antioxidant functions of North American ginseng in vivo and the mechanisms of protection are largely unknown. Recently, we have performed a study wherein female Fischer 344 rats at 4 (n=36) or 22 (n=24) month of age were randomly divided into three groups, fed either a control diet, or a diet containing 0.5 g/kg (low-dose) or 2.5 g/kg (high-dose) dry ginseng power for 4 months (Fu & Ji in press). Oxidant generation, measured with 2'7'-dichlorofluorescin (DCFH), was significantly lowered with ginseng feeding in the homogenates of heart, soleus, and the deep portion of DVL muscle. In the heart young and old rats fed high dose ginseng diet showed 18% and 38% (P <0.05) lower DCF formation compared to control rats, respectively (Fig. 3). In DVL muscle, high dose ginseng feeding decreased DCF formation by 18% in young rats and by 24% in old rats (not shown). Ginseng supplementation significantly increased antioxidant enzyme activities in rats. SOD activity was elevated in heart, DVL and soleus muscle. Glutathione peroxidase (GPX) activity in DVL and soleus muscle was also increased in ginseng-supplemented rats. In addition, citrate synthase activity in the heart of both age groups and DVL of young rats was elevated, suggesting mitochondrial oxidative capacity was elevated.

We measured protein carbonyl formation as a marker of oxidative damage in the various tissues. Protein oxidation was more than two-fold higher in the hearts and 65% higher (P <0.01) in the DVL, comparing old vs. young rats (Fu & Ji, in press). High-dose ginseng treatment attenuated carbonyl levels in the hearts and DVL muscle. This was confirmed by both chemical assays and Western blot analysis using antibody against protein carbonyl (Fig. 4). Taken together, it is clear that North American ginseng supplementation in rats can decrease oxidant production and age-related oxidative damage to protein in the heart and skeletal muscle. Elevated SOD and GPX activities may partially explain these protective effects.

Oats (*Avena sativa* L.) contain several families of phytochemicals that display antioxidant properties, such as tocotrienols, phenolic acids, flavonoids, sterols and phytic acid (Bratt et al 2002, Peterson 2001, Dimberg et al 1993, Collins 1989). Both animal studies and human clinical trials confirmed that oat antioxidants have the potential of reducing cardiovascular risks by lowering serum cholesterol, inhibiting LDL oxidation, and attenuating platelet

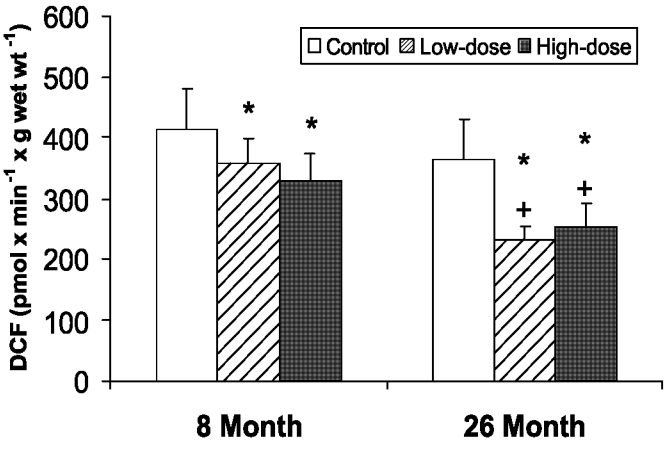

Fig. 3 Oxidation rate of dichlorofluorescin (DCFH) to dichlorofluorescein (DCF) in the homogenate of rat heart. The assay buffer contained 130 mM KCl, 5 mM $MgCl_2$, 20 mM NaH_2PO_4, 20 mM Tris-HCl, and 30 mM glucose (pH 7.4) with 5 μM DCFH-diacetate dissolved in 1.25 mM methanol. Each bar represents mean ± SEM with number of rats in each group specified in Table 2. * P <0.05, Low-dose or High-dose ginseng vs. Control. ^{+}P <0.05, main age effect; ^{++}P <0.01, 26 month vs. 8 month old rats. (Fu and Ji. 2003)

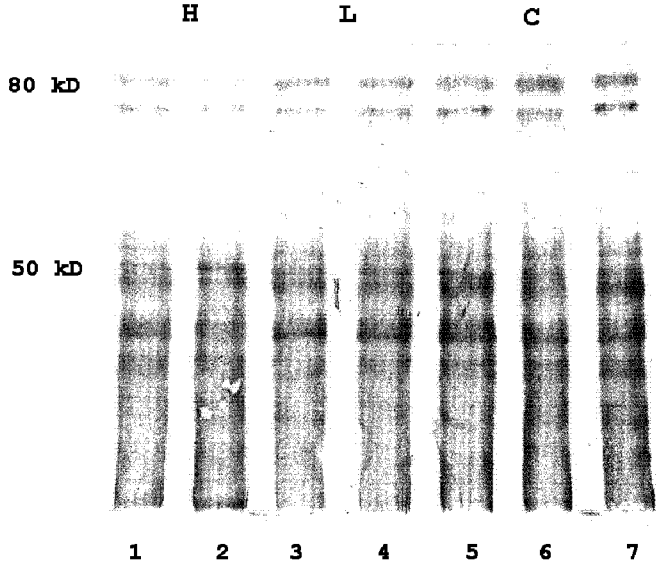

Fig. 4 Western blot analysis of Reactive carbonyl derivatives (RCD) in the heart of old rats. Samples are pooled from 5 rats randomly selected from each group. Lane 1-2, high-dose ginseng diet; lane 3-4, low-dose ginseng diet; 5-7, control diet. (Fu and Ji. 2003)

aggregation and peroxidation. In vivo animal studies also have shown that caffeic and ferulic acids process anti-carcinogenic properties. In addition to these well-characterized antioxidants, there is a small fraction of anionic, nitrogen-containing, covalently linked hydroxycinnamic acid compounds that have only been identified in oats, called avenanthramides (AVEN) (Peterson et al 2002). Among a group of several avenanthramides that differ in the substituents on the cinnamic acid and anthranilic acid rings, three are predominant in oat grain: Bp, Bf and Bc [*N*-(3',4'-dihydroxycinnamoyl)-5-hydroxyanthranilic acid].

In a recent study we examined whether dietary AVEN supplementation increases antioxidant capacity in the biological tissues, thereby reducing steady-state ROS formation and oxidative tissue damage (Ji et al in press). In order to reveal their potential protective effects, we subjected AVEN-fed rats to an acute bout of strenuous physical exercise, which is known to increase ROS generation in the heart and skeletal muscle. Female Sprague-Dawley rats (n=48, age 6-7 wk) were fed either an AIN-93 based control diet or the same diet containing 0.1 g/kg AVEN-Bc for 50 days. Each group was further divided into rested and exercised (treadmill running at 22.5 m/min, 10% grade for 1 hour) prior to killing. AVEN supplementation per se had no effect on ROS production (using DCFH method) in most tissues, except soleus muscle wherein ROS level was decreased. AVEN-fed rats had higher SOD activity in the DVL muscle, liver and kidney and higher GPX activity in the heart and DVL, compared to control rats. Exercise increased ROS production in the liver, DVL and soleus, and lipid peroxidation in the heart, liver and DVL. AVEN attenuated exercise-induced ROS in soleus and lipid peroxidation in the heart. These data suggest that AVEN can serve as a potential dietary antioxidant supplement to reduce exercise-induced oxidative stress.

Conclusion

Oxidative and antioxidantive balance underlies basis biological phenomena such as growth, development, disease, adaptation and death. Augmentation of cellular antioxidant defense is an important issue not only to researchers but also health workers including exercise physiologists and fitness promoters. Although the research cited in the current article was derived mostly from animal work, and whether or not the findings could be directly applied to human requires further investigation, we can still safely recommend the following: eat well, avoid harmful life styles (such as excessive alcohol drinking and smoking), and exercise regularly.

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