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Chapter 6

The Positive and Negative Aspects of Reactive Oxygen Species in Sports Performance

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http://dx.doi.org/10.5772/53360

1. Introduction

Physical exercise, especially moderate physical exercise, can benefit health in a wide range of ways [1-3]. Evidence from different age groups, genders and races has revealed that regular physical exercise is associated with high levels of physical fitness and a reduced risk of mortality, while sedentary habits are related to low levels of physical fitness and an increased threat of all-cause mortality [1-8]. However, the physiological mechanism of physical exercise-induced physical fitness remains only partly understood.

During physical exercise, the metabolic rate increases greatly, as quantified by oxygen consumption and heat production, which results in an enhanced generation of reactive oxygen species (ROS). ROS describe both oxygen-centred free radicals and reactive non-radical derivatives of oxygen resulting from a sequential reduction of oxygen through the addition of electrons. Table 1 shows the representative ROS. The role of ROS in physical exercise is frequently misunderstood. Most people tend to either overemphasize the deleterious role of ROS by maintaining that any ROS generation in vivo during exercise would damage cellular constituents, or underemphasize the beneficial effect of exercise-induced ROS by assuming that the body has enough ROS in vivo that it needs. Two breakthroughs, the identification of ROS in redox regulation and findings on the role of antioxidant supplementation in preventing health-promoting effects of physical exercise, have led scientists to re-examine the role of ROS, especially their positive influence. The goal of this chapter is to outline the current evidence on the sites of ROS generation during exercise, the role of exercise-induced ROS, the effects of antioxidant supplementation on physical-exercise-induced physical fitness, and the mechanism of ROS in exercise-induced adaptation.

Oxygen-centred free radicals	Reactive non-radical derivatives of oxygen
superoxide anion ($O_2^{\cdot -}$)	hydrogen peroxide (H_2O_2)
hydroxyl radical ($HO^{\cdot}$)	singlet oxygen (1Δg)
peroxyl radical ($RO_2^{\cdot}$)	ozone (O_3)
alkoxyl radical ($RO^{\cdot}$)	

Table 1. Name (Radical depiction) of reactive oxygen species (ROS)

2. Evidence of ros generation in exercise

Exercise has been shown to alter oxidative stress in a wide range of body fluids, cells and/or tissues in human beings, rodents and other animals. These include commonly used model tissues, such as blood [9-11] and skeletal muscle [9, 12-14], along with many other models less often used for laboratory research, such as neutrophils [15-17], lymphocytes [18-20], the diaphragm [21, 22], liver [23-25], heart [23, 26-28], lung [22, 29], brain [30-32], kidney [33, 34], spleen [35, 36], and thymus [35, 37, 38], as well as urine [39-41] and exhaled breath [42, 43].

Although oxidative stress is a common response of cells or tissues to exercise, this does not suggest that all models respond in a similar way to the same exercise. In fact, the levels of ROS generation are different across tissues and/or cells even at rest, let alone during exercise. There is some good evidence that the basal rate of superoxide anion production within the liver of the sperm whale is the highest, more than fourfold higher than that in the brain, about threefold higher than in the heart and muscle, and twofold higher than in the kidney [44]. Another indirect piece of evidence indicates that the heart contains about a tenfold higher level of lipid peroxide than the liver in rats [45]. Moreover, different forms of exercise result in different levels of oxidative stress depending on organ or tissue types. The responses to oxidative stress in the heart and muscle caused by eight-week treadmill running (chronic exercise) or treadmill running to exhaustion (acute exercise) are quite different from those in the brain and liver of rats [46]. This is possibly due to the differences in mitochondrial biogenesis and the occurrence of oxidant-induced degeneration.

The following sections therefore present the evidence on ROS generation during exercise in different tissues or organs.

2.1. Muscle

To explore the relationships between oxidative stress and sports medicine, the majority of researchers have focused on muscles for the reason that their contractions are primarily responsible for all force production and movement, as well as maintenance of and changes in posture.

ROS are hard to be detected because they are highly unstable and short-lived. In early studies, due to the limitations in the analytical techniques and approaches available to detect ROS directly, the levels of ROS are commonly evaluated through indirect and nonspecific methods,

http://dx.doi.org/10.5772/53360

such as the analysis of thiobarbituric acid reactive substances (TBARS) or end products of lipid peroxidation [47, 48]. As indicated by these indirect methods, a significant number of studies suggest an increase of ROS during exercise, especially during bouts of intensive exercise [47-49]. Some studies have found that, in comparison to sedentary control, the muscular malondialdehyde (MDA) levels of muscle homogenates in rats exposed to periods of exhaustive exercise increased by more than 100% [47]. The administration of vitamin E can reduce the damage to skeletal muscle [50-52], and muscles from vitamin-E-deficient mice or rats are more likely to be damaged during contractile activity [47, 53]. Based on these early studies, some researchers have suggested that mitochondria are the predominant site for generating ROS during exercise [47], and that the generating rate is related to mitochondrial oxygen consumption [54, 55].

Confusingly, some studies have found little or no change in muscular TBARS or MDA levels after exercise. The results from Alessio et al. have demonstrated that the levels of TBARS do not increase significantly with exhaustive aerobic or nonaerobic isometric exercise [56]. Other studies also show that moderate-intensity resistance exercise had no effects on serum MDA concentration in both resistance-trained and untrained subjects [57], and graded exercise to fatigue did not promote an increase in MDA levels [58]. Though the exact reason is still unclear, the methodical variation between studies, the nonspecific nature of TBARS assay [59, 60], the reactivity of MDA and other aldehydes [61], or even the rapid clearance of TBARS from plasma [62], may account for this issue.

Still, it cannot be concluded that exercise does not alter the levels of ROS even if the TBARS or MDA levels do not change. In fact, there is much evidence for oxidative stress after exhaustive exercise, although the levels of TBARS do not increase [56]. Therefore, if the direct evidence that indicates increasing ROS levels during exercise is lacking, it is difficult to conclude that the damage incurred during contractile activity is mediated by ROS.

The emergence of new technologies, especially electron spin resonance/electron paramagnetic resonance (ESR or EPR) spectroscopy, has made the direct detection of free radicals *in vivo* possible. To our knowledge, though EPR/ESR is not sensitive to the concentrations of free radicals typically found in biological systems, it is the only direct method to assay free radicals. In 1982, Davies and collaborators provided the first direct proof that high-intensity exercise enhances free radical production as indicated by a heightened ESR signal (around g=2.004) in muscle and liver homogenates [47]. Other studies have provided further evidence to suggest that exercise promotes ROS generation. Intriguingly, the increase of ROS seems to play some roles in muscle damage caused by extensive muscular activity, as 30 minutes of excessive contractile activity of rat hind-limb muscles shows an average 70% increase in the amplitude of the major ESR signal, and also a leakage of intracellular creatine kinase enzyme into the blood plasma [63].

These observations have prompted researchers to look for more details on the kinds of ROS that are formed in muscles during or after exercise. Based on ESR/EPR signals, Davies and collaborators have found that the concentration of two ubisemiquinone free radicals (presumably Qi and Qo) is very high in exercised animals [64]. A result from extracellular fluid by

microdialysis has also shown that a 15-min protocol of 180 isometric contractions can induce a rapid increase in superoxide anion concentrations and hydroxyl radical activity [65].

Based on the well-characterized *in vitro* models of single isolated muscles or cultured myotubes, researchers have identified a series of ROS and provided evidence that muscles are under considerable oxidative stress after contractile activities, especially lengthening contractile activities. Reid and colleagues have shown that muscular contraction increases intracellular levels of superoxide anion radicals and hydrogen peroxide (H_2O_2), and these ROS promote low-frequency fatigue [66]. Subsequent data from the same group also identify superoxide anion in the extracellular space of diaphragm muscle fibres, and the level is enhanced by fatiguing muscular contractions [67]. When the cultured myotubes are stimulated to contract with different frequencies of electrical stimulation, there is a release of superoxide anion and nitric oxide (NO) into the extracellular medium and an increase in extracellular hydroxyl radical activity [68]. Through loading fluorescein probes with single intact muscle fibres, other studies have developed a method to measure the intracellular ROS generation *in situ* by real-time fluorescence microscopy and illustrated a net increase of ROS by contractions of isolated fibres [69]. It is now possible to analyse different ROS by using different fluorescein probes. The intracellular NO production is visualized in real time using the fluorescent NO probe 4-amino-5-methylamino-2',7'-difluorofluorescein diacetate [70]. With the use of 2',7'-dichlorodihydrofluorescein as an intracellular probe, researchers have confirmed the dynamic changes of ROS levels during contractile activity in skeletal muscle myotubes [71]. The rate of ROS generation does not change significantly over 30 min in resting myotubes, but it is increased approximately fourfold during 10 min of repetitive contractile activities [71], and the superoxide scavenger Tiron can effectively negate the rise in intracellular fluorescence [71]. Recently, several other probes have also been developed, which permit the monitoring of different ROS in specific cells or organelles [69-74], and will provide more detailed evidence for the exercise-induced increase of ROS. Of note is that, since there are limitations to the most widely used fluorescent probes for detecting and measuring ROS, researchers should be cautious with regard to the optimal use of selected fluorescent probes and interpretation of results [75].

Despite the challenges of detection and the inconsistent results from different methods or models, significant studies have provided evidence for exhaustive exercise promoting extensive ROS formation in muscles (for reviews, see [76-78]).

2.2. Liver

A great deal of research has detected an alteration of ROS in the liver during or after exercise. When Davies *et al*. provided the first direct evidence for ROS generation in muscles after exhaustive exercise, they also found a rise of free radicals in liver homogenates [47]. TBARS, an indicator of lipid peroxidation, has also been reported to increase in the liver and muscles subsequent to exercise, and dietary vitamin E supplementation can reduce (but not eliminate) the increase of TBARS in the liver [79]. Endurance training shows a decreased level of MDA and protein carbonylation, and a significant increase in the activity of superoxide dismutase in mice [80]. Consistent with the effects of exercise on oxidative stress in muscles, most of the other available studies have also suggested that acute exercise, especially intensive or exhaus-

http://dx.doi.org/10.5772/53360

tive acute exercise, indiscriminately induces oxidative stress in the liver, while endurance or long-term training shows a beneficial role in ameliorating oxidative stress.

Important to note is that the liver is distinct from muscles that directly participate in contractile activity or produce forces to support movement. It is logical to consider that the impact of exercise on hepatic oxidative stress should not be the same as the impact on muscles. Results from acute sprint exercise in mice have confirmed this concept. Although the exercise causes an increase in TBARS levels in skeletal muscle, there is no change in the liver [81]. Furthermore, exercise training appears to have little effect on hepatic or myocardial enzyme systems, but can cause adaptive effects in skeletal muscle antioxidant enzymes [82]. A study to investigate the responses to oxidative stress induced by chronic or acute exercise in the brain, liver, heart, kidney, and muscles of rats has also shown that the responses from the brain and liver to oxidative stress are quite different from those in the heart and muscles, and the difference may be attributed to the organ or tissue types and endogenous antioxidant levels [46].

Although the potential mechanism for generating ROS induced by exercise in muscles has been explored in depth, the related mechanism in the liver has not been extensively studied. Based on the above evidence, the mechanism for ROS production in the liver should be greatly different from that in muscles. Further research is needed to reveal the detailed mechanisms, and the energy stress and hepatic ischemia reperfusion should be given particular attention.

2.3. Brain

Exercise has been reported to benefit the brain or nervous system in a wide range of ways, while oxidative stress is involved in the pathogenesis of several age-related nervous diseases. Therefore, the links between exercise-induced alteration of ROS generation in the brain and the potential beneficial effects of exercise on the brain have attracted great attention from researchers in recent years.

Intense physical training can significantly increase TBARS levels and decrease the levels of the brain-derived neurotrophic factors (BDNF) in the brain cortex of mice, which promotes brain mitochondrial dysfunction [83]. Acute and exhaustive swimming exercise has also been reported to elevate the lipid peroxidation and ROS formation in the brain tissue of rats [84, 85], while long-term dietary restriction or selenium supplementation protects against the oxidative stress [84, 85]. Vitamin E deficiency may promote mitochondrial H_2O_2 generation, lipid peroxidation and protein oxidation in the brain [86]. However, vitamin C supplementation has been shown to offer no protection against exercise-induced oxidative damage in brain tissue [87]. Swimming does not significantly influence the oxidative damage, nor is it reflected in the carbonyl content [88], and even over-training does not significantly change the levels of TBARS, 8-hydroxydeoxyguanosine or other biomarkers of oxidative stress in rat brains significantly [89]. Aerobic exercise does not affect lipid peroxidation of the brain, but a diabetic condition improves the activities of several antioxidant enzymes [90]. Though different brain regions of rats react differentially in response to acute exercise-induced oxidative stress, as reported by Somani *et al.* [91, 92], and this may explain some of the discrepancies, differences in the type of exercise, the analytic technique and the age, sex and strain of animals should be the key issues.

Under conditions of aging or stress, or pathological conditions, the oxidative stress in the brain increases rapidly. Exercise may improve these conditions through strengthening the function of antioxidant defence systems and/or decreasing oxidative stress. Habitual exercise has been reported to overcome the age-related deficit in antioxidant enzymes and prevent oxidative damage in aged brain [93, 94]. There is considerable evidence for physical exercise playing an important preventive and therapeutic role in oxidative stress-associated diseases, such as in reducing oxidative stress after traumatic brain injury [32], increasing thioredoxin-1 levels [95] and the activities of antioxidant enzymes [90] in diabetic brains, and restoring the antioxidant system in the brain of hyperphenylalaninemic rats [96]. Furthermore, exercise-induced modulation of the redox state is an important means to withstand oxidative stress under stress conditions. It has been suggested that exercise may promote mitochondrial function, expressions of mitofusin and antioxidant enzymes against chronic unpredictable mild stress in the brain [97], and reverse the decrease in BDNF and the increase in ROS induced by consuming a high-fat diet [98].

In summary, the effect of exercise on the brain is complex. Although the current data on exercise-induced redox alternation in the brain is still conflicted, there is overwhelming evidence that habitual and regular exercise is an important way to improve brain function by enhancing resistance against oxidative stress and facilitating recovery from oxidative stress. Further investigation is needed to identify the biological basis for the association of exercise, ROS and brain functions.

2.4. Others

Muscular contractile activity has been proven to promote the generation of ROS, and the redox status in the brain and liver may also be altered after physical exercise. However, the effect of exercise on the oxidative stress of other tissues or cells is not consistent. This discrepancy in the findings may be attributed to the differences in exercise type, duration and intensity across protocols, as well as the differences in cells and/or tissues.

Oxidative damage occurs in lymphoid tissues after exhaustive exercise [35], and vigorous exercise has also been reported to result in a transient increase of oxidative stress in lymphocytes [18]. For cigarette smokers, maximal exercise induces pulmonary oxidative stress and leads to oxidative damage in the lungs [42], while in normal lungs exercise neither leads to significant oxidative stress, nor alters mitochondrial respiration [22]. For trained men, even strenuous bouts of exercise do not cause a significant increase in blood oxidative stress, which may be related to the attenuation in ROS production as an adaptation to chronic exercise training [11].

Intriguingly, in rat kidneys exercise training has been noted to prevent oxidative stress and inflammation and to preserve antioxidant status, which mediates the effects of chronic exercise on preserving renal haemodynamics and structure [33, 34]. In rat hearts, prolonged exercise could upregulate the mRNA expression and activity of uncoupling protein 2 (UCP2), which may reduce cross-membrane potential and thus ROS production [27]. However, endurance training can blunt exercise-induced UCP2 activation, and increase removal of ROS [27]. In

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white blood cells, exercise results in substantial improvements in markers of DNA and RNA damage [39].

The impacts of gender on exercise-induced oxidative stress should not be ignored. Females seem to be more protected against oxidative stress induced by swimming. H_2O_2 is mainly produced in males, which subsequently leads to the increase of MnSOD gene expression and activity [20].

3. Sites of ROS generation in exercise

3.1. ROS generation by mitochondria

Mitochondria have often been cited as the major site of ROS generation in tissues. Based on the classic works by Chance and his collaborators, when mitochondria are in state 4, about 2% of total oxygen consumed by mitochondria is converted into H_2O_2 and other ROS [99, 100]. As oxygen consumption increases greatly during exercise, many researchers have assumed that mitochondria should be a key site of ROS formation, and the extent of ROS generation may be related to the oxygen consumption by mitochondria [54, 55]. When Davies and colleagues found the first direct evidence for exercise-induced ROS formation, they also suggested mitochondria as the predominant source [47]. This hypothesis seems to be confirmed by subsequent data. Davies and Hochstein did identify two free radicals, that is, two forms of semistabilized mitochondrial ubisemiquinone (presumably Qi and Qo) [64]. They found that the concentration of the two free radicals was obviously higher in exercised animals than in control animals, which has actually provided the first evidence for the mitochondrial generation of free radicals induced by exercise *in vivo* [64]. Other EPR signal studies also supported the importance of mitochondria in ROS production [63, 101].

In vitro experiments have indicated that mitochondrial ROS generation is lower in state 3 than in state 4 respiration [100]. There is considerable evidence that muscular mitochondria are predominant in state 3 rather than in state 4 during aerobic contractile activity, which would limit the ROS formation during contractions [102, 103]. This has led other researchers to support the above hypothesis of mitochondria as a main site of ROS generation. To explore the specific site of exercise associated with ROS production, Puente-Maestu *et al.* isolated mitochondria from skeletal muscle of chronic obstructive pulmonary disease (COPD) patients at rest and after exercise, and analysed mitochondrial oxygen consumption and ROS production [49]. Then, they related the *in vitro* ROS production during the state 3 respiration with skeletal muscle oxidative stress after exercise [49]. They found that mitochondrial complex III was the main site of producing H_2O_2 in mitochondria of skeletal muscle, and the mitochondrial production of H_2O_2 in the state 3 respiration contributed to exercise-induced muscle oxidative damage [49].

Another argument regards the semiquinone radicals. McArdle and his colleagues assayed the effects of repeated lengthening contractions on semiquinone-derived free radical signal, oxidation of protein thiols and glutathione, and lipid peroxidation in the extensor digitorum

longus muscles of rats. Although they found the oxidation of protein thiols and glutathione was enhanced after contractions, the magnitude of the semiquinone-derived free radical signal observed by ESR was the same in exercised and non-exercised skeletal muscles [104]. To further explore the site of ROS generation during exercise, another study [65] isolated the gastrocnemius muscles from MnSOD knockout heterozygous ($Sod2^{+/-}$) and wild-type ($Sod2^{+/+}$) mice, and measured the concentrations of superoxide anions and hydroxyl radical activity in the extracellular space by microdialysis. They found that isometric contractions induced a rapid, equivalent increase in superoxide anion concentrations in the extracellular space of both $Sod2^{+/-}$ and $Sod2^{+/+}$ mice, whereas hydroxyl radical activity increased only in the extracellular space of muscles of $Sod2^{+/+}$ mice [65]. In other words, a reduction in MnSOD activity did not change the concentration of superoxide anions in the extracellular space, but decreased the concentration of hydroxyl radicals in the extracellular space. Considering that MnSOD is located in the mitochondrial matrix, these results suggest that mitochondria are the key sites in converting superoxide anions to hydroxyl radicals. Furthermore, mice with skeletal-muscle-specific deficiency of MnSOD (muscle-$Sod2^{-/-}$) also demonstrated a severe disturbance in exercise activity, increased oxidative damage and reduced ATP content in their muscle tissue, while a single administration of the antioxidant EUK-8 significantly improved the exercise activity and ATP level [14]. These findings indicate that even if the mitochondrion is not the major site, it is at least an important site in generating superoxide anions in muscles during exercise.

In light of the above observations, the electron transport associated with the mitochondrial respiratory chain is considered the central process leading to ROS production during exercise.

3.2. ROS generation by xanthine oxidase

Another possible site for ROS generation during exercise, especially intensive or exhaustive exercise, is xanthine oxidase (XO). As an intensive or exhaustive exercise can result in ischemia or hypoxia in certain regions of the body, massive ATP depletion occurs and ATP will be converted to adenosine diphosphate, adenosine monophosphate, inosine, and finally hypoxanthine. Under normal physiological conditions, xanthine dehydrogenase is the dominant form of XO, which can catalyse the oxidation of hypoxanthine to xanthine or further the oxidation of xanthine to uric acid by using NAD^+ as an electron acceptor. However, under ischemia conditions, the xanthine dehydrogenase can be converted to XO by reversible sulfhydryl oxidation or by irreversible proteolytic modification [105, 106], and XO can no longer utilize NAD^+ as the electron acceptor, instead using molecular oxygen as the electron acceptor and yielding four units of superoxide anions per unit of transformed substrate. As a result, under reperfusion conditions, a burst of superoxide anions and H_2O_2 can result [107].

XO has been thought to be responsible for the production of ROS and tissue damage during or after intensive exercise, and the inhibition of XO by allopurinol or oxypurinol can reduce the production of ROS. Ryan and collaborators measured XO activity, H_2O_2 levels, lipid peroxidation, the activities of antioxidant enzymes, and skeletal muscle function in aged mice with or without administration of allopurinol. In addition to finding inhibition of XO by allopurinol treatment, they found the treatment could prevent the increase of catalase and

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CuZnSOD activities, reduce oxidative stress and improve skeletal muscle function in response to electrically stimulated isometric contractions [108]. In most cases in other animals, evidence has also been provided for the beneficial effects of allopurinol or oxypurinol in inhibiting XO and thus attenuating the generation of ROS. Lipid hydroperoxides, GSSG and the formation of ROS during exercise are reduced significantly in an allopurinol-treated horse [109]. Exercise could cause an increase in blood XO activity in rats, and inhibiting XO with allopurinol could prevent exercise-induced oxidation of glutathione in both rats and human beings [110]. Furthermore, allopurinol has also been shown to decrease oxidative stress and ameliorate the morbidity and mortality of congestive heart failure patients (for reviews, see [111]). In the light of these observations, some researchers have suggested that XO may play a more important role in generating ROS than mitochondria do [112].

However, results from Capecchi *et al.* have shown that allopurinol has no effect on superoxide anion generation or enzyme release from neutrophils stimulated *in vitro* with formyl-methionyl-leucyl-phenylalanine [113]. Nor do more recent observations support the critical role of XO in generating ROS during intensive exercise. Olek and colleagues tested the effects of allopurinol ingestion on the slow component of VO_2 kinetics (the dynamic behaviour of O_2 uptake in the transition from rest to exercise) and the alternations of plasma oxidative stress markers during severe intensity exercise. They found short-term intensive exercise could induce oxidative stress, and although allopurinol intake might cause an increase in resting xanthine and hypoxanthine plasma concentrations (supporting XO inhibition by allopurinol), it neither modified the kinetics of oxygen consumption nor altered ROS overproduction [114].

Gomez-Cabrera *et al.* [115] examined the effects of allopurinol on the inhibition of ROS production and on the activation of nuclear factor kappaB (NFκB) in rats subjected to exhaustive exercise. They found that exercise did result in considerably more glutathione oxidation in the control rat than in the rat administered with allopurinol before exercise. However, the administration of allopurinol could also negate the exercise-induced activation of NFκB, which is an important signalling pathway involved in upregulating the expression of important enzymes for cell defence (superoxide dismutase) and adaptation to exercise. That is to say, at the same time as allopurinol decreases XO-mediated oxidative stress, it also prevents useful cellular adaptations to exercise in rats.

3.3. Other sites and current understanding

Except for mitochondria and XO, there should be other sites of ROS production during and after exercise. When tissue damage has occurred, several cells in the immune system (including macrophages/monocytes, eosinohpils and neutrophils) may also generate large quantities of ROS [116]. For example, circulating neutrophils has been reported to produce ROS due to the facilitation of myeloperoxidase degranulation after exhaustive exercise [17]. Although more investigation is needed to fully elucidate the mechanism and site of ROS formation in exercise, at the present time mitochondria and XO are still worth focusing on.

4. Role of ROS in exercise: Foe or friend?

Sedentary habits are associated with low levels of cardiorespiratory fitness and an increased threat of all-cause mortality, while physically active habits are associated with fitness improvement and reduced mortality risk [1, 7, 117]. However, the detailed mechanism of physical activity-induced physical fitness remains only partly understood.

Since 1982, when Davies *et al.* provided the first direct proof that high-intensity exercise enhances free radical production [47], further evidence has emerged for exercise promoting ROS formation. Besides mitochondria, XO and phagocytes in skeletal muscle have also been reported to be potentially responsible for generating ROS in response to exercise [77]. Here, it is necessary to substantiate the role of ROS in sports medicine and in exercise-induced effects.

4.1. Harmful effect of ROS in exercise

ROS form as a natural by-product of normal energy metabolism. They have been considered as toxic molecules due to their high reactivity to most of the biological macromolecules, which generally include DNA damage, oxidations of polyunsaturated fatty acids and amino acids, and oxidative inactivation of specific enzymes.

As aerobic exercise will undoubtedly increase the metabolic rate in the body, the harmful effects of exercise and exercise-induced ROS are well documented. Exercise localized to a peripheral muscle group in COPD patients has been shown to induce systemic oxidative stress [118]. Acute exercise-induced oxidative stress contributes to post-exercise proteinuria in untrained rats [119]. A maximal bicycle exercise results in DNA strand breaks and oxidative DNA damage [120]. High-competition swimming imposes high and sustained oxidative and proteolytic stress on adolescents, which may increase potential risk of cardiovascular disease in the future [121]. A run-to-exhaustion exercise leads to an increase in oxidative damage of lymphoid tissues in rats [122].

In summary, strenuous exercise under conditions of disease or overtraining would significantly elevate respiration rate, lead to a dramatic and sustained increase in ROS that is more than the antioxidant defence system can scavenge, and eventually result in oxidative stress and damage to physiological functions. Therefore, though regular exercise is important to improve cardiorespiratory fitness, extreme or exhaustive physical activities should be avoided, especially under certain disease conditions.

4.2. Beneficial role of ROS in exercise

4.2.1. Oxidative stress and beneficial effect of exercise

There is growing evidence for the healthy role of exercise. Some studies indicate its beneficial effect is associated with the attenuation of oxidative stress. It is reported that regular training can ameliorate ethanol-induced oxidative injury in the liver [123], endurance training may attenuate exercise-induced oxidative stress [25], and chronic exercise can improve antioxidant status and induce a reduction in arterial hypertension development in rats [124]. Athletes

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participating in regular and adequate training would enhance antioxidant capacity and bring about improvement in both peripheral resistance to insulin and all the functional metabolic interchanges in cellular membranes [125]. Intriguingly, leisure time, moderate occupational or household physical activities are also positively related to total antioxidant capacity, and can decrease the risk of cardiovascular disease [126].

In particular conditions, however, although exercise prevents some pathologic processes, it increases oxidative stress. As illustrated in elderly people, sustained exercise enhances cardiorespiratory function and reduces the risk of cardiovascular disease, but it also significantly enhances some biomarkers of oxidative stress [127]. This is also the case in atherogenic mice. Exercise lowered plasma cholesterol and atherosclerotic lesions, with a concomitant increase in oxidative stress and endothelial NO synthase [128]. In this condition, though vitamin E supplementation can decrease the exercise-induced oxidative stress, it also counteracts the beneficial effects of exercise on atherosclerosis and hinders the induction of arterial antioxidant response [128]. These findings have led to researchers beginning to consider the positive effects of ROS themselves.

4.2.2. Beneficial role of ROS in exercise

Early studies in this area have focused on the oxidative damage induced by augmented formation of ROS. Subsequent data, however, have shown that ROS also participate in redox regulation, and it has been widely accepted that the moderate concentrations of ROS *in vivo* function as regulatory mediators in signalling processes and as initiators in re-establishing ''redox homeostasis'' [129, 130]. There are now a significant number of studies suggesting that regular exercise can enhance the capacity of antioxidant defence systems to lower oxidative stress or the levels of ROS. In this context, some researchers have begun to speculate a positive role of a transient high level of ROS induced by exercise. This hypothesis has been confirmed in a rat diaphragm. In this study, fibre bundles from a rat diaphragm were incubated with exogenous catalase or SOD to decrease the tissue level of ROS, and then the peak twitch stress, time-to-peak tension and half-relaxation time were measured. The results showed that either selective removal of H_2O_2 with catalase or selective removal of superoxide anions with SOD depressed submaximal contractile activities in a dose-dependent way [131]. These findings indicate the ROS present in non-fatigued muscle can promote excitation-contraction coupling and are responsible for optimal contractile function [131]. Subsequently, many studies have documented a role of ROS as second messengers responsible for the prevention of diseases by stimulating antioxidant response [128], or other adaptations to exercise by activating useful cellular redox signalling pathways including peroxisome proliferator-activated receptor-gamma coactivator-1alpha [132], mitogen-activated protein kinase and NFκB [115, 133].

Moreover, it is now clear that ROS not only play an important role in regulating muscle contractile activity, but are also involved in promoting muscle regeneration in recovery from muscle damage [134], improving insulin sensitivity [135], and mediating the vasodilatory response during exercise [136]. As a result, ROS generated in response to exercise and other physiological or pathological stimuli might be important signalling molecules rather than solely by-products of energy metabolism.

4.3. Current understanding

Thanks to evidence gathered over the last three decades, we now understand the effects of exercise and the role of exercise-induced ROS more clearly. During exercise, although oxygen consumption in the body increases more than tenfold, the intracellular H_2O_2 concentrations in skeletal muscle induced by contractile activities only increase by approximately 100 nM [78]. This modest increase of H_2O_2 can only be enough to assume the functions of the signalling molecule and to stimulate some of the adaptations of muscle to exercise. ROS are not only toxic but also involved in cell signalling and in regulating several redox-sensitive transcription factors [115, 132, 133]. An inhibition of ROS generation would also modify cellular redox signalling pathways associated with adaptations to exercise [115, 132, 133]. It is now clear that physical activities cause oxidative stress only when exhaustive. ROS induced by moderate exercise may serve as signalling molecules to increase the expression of cytoprotective proteins and to maintain some other normal functions. Habitual and regular exercise is a useful strategy for improving physical fitness and reducing mortality risk.

5. Antioxidant supplementation in exercise: Beneficial or detrimental?

ROS are unavoidable by-products of energy metabolism, and cells continuously generate ROS in metabolic processes. High metabolic rates during exercise have led to the assumption that exercise leads to excessive production of ROS in skeletal muscle, which is associated with muscle damage and impaired muscle function. As a result, the supplementation of antioxidants may offer some protection against exercise-induced oxidative damage, and improve muscle function and physical performance. In this context, numerous antioxidants are marketed, and antioxidant supplementation has become very common with athletes or other physically active individuals. However, there is not enough scientific evidence to support their efficacy and long-term safety.

5.1. Antioxidant supplementation and oxidative stress

The majority of studies have illustrated that antioxidants attenuate the oxidative stress induced by exercise, although oxidative stress is estimated through measuring its indirect outcomes, such as by-products of lipid peroxidation, protein oxidation and DNA damage. A study by Alessio *et al.* tested the effects of vitamin C supplementation for one day and two weeks on oxidative stress in subjects with or without exercise. When the subjects were at rest, they found that vitamin C supplementations did not affect the levels of TBARS or oxygen radical absorbance capacity, but with the same subjects after 30 minutes of exercise, the supplementation did prevent the increase of oxidative stress [137]. Oral ingestion of vitamin C has been reported to effectively prevent exercise-induced lipid peroxidation in patients with type 1 diabetes mellitus [138]. The supplementation of vitamin E can diminish the increase of lipid hydroperoxides and TBARS in the plasma and muscle fibres of rats following aerobic exercise [139]. The combined administration of vitamin E and C improves indices of oxidative stress associated with repetitive loading exercise and aging, and ameliorates the positive work output of

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muscles in aged rodents [140]. Although the most widely studied antioxidants are vitamin E and ascorbic acid (vitamin C), the effects on suppressing exercise-induced oxidative stress have also demonstrated in other antioxidants, including β-carotene [141], N-acetylcysteine (NAC) [142], L-arginine [143], coenzyme Q [144], α-lipoic acid [145], resveratrol [146], several other compounds [147, 148], selenium [149], teas [150], and concentrates from fruit, berry and vegetable [151].

However, many studies show that the administration of antioxidants, alone or in combination, does not significantly affect exercise-induced oxidative stress [134, 152-157]. Several observations even indicate an increase of oxidative stress following antioxidant supplementation pre- or post-exercise, especially with high doses [158-162]. Moreover, some investigations that have confirmed the beneficial effects of antioxidants on oxidative stress did not demonstrate a significant improvement in performance [163] or the functions related to pain and muscle damage [151]. Therefore, the health-promoting effects of antioxidants should be explored in more detail.

5.2. Antioxidant supplementation and fatigue

The role of antioxidant supplementation in protecting against fatigue remains highly controversial. One reason for this controversy is the lack of strong evidence for oxidative stress involved in muscle fatigue. Some studies have displayed an association between oxidative stress and muscle fatigue [164, 165], and the anabolic androgenic steroid stanozolol, a drug used in sport to enhance muscle mass and strength and to increase muscle fatigue resistance, can protect against acute exercise-induced oxidative stress by reducing mitochondrial ROS production [13]. However, the association has been challenged by other observations that suggest that graded exercise to fatigue does not promote an increase in oxidative stress in the blood of exercise-trained heart transplant recipients [58], and an enhanced running time to exhaustion does not lead to attenuation of lipid peroxidation [166]. As a result, although NAC supplementation has been reported to improve muscle fatigue in rats [167], it does not affect the time to fatigue in a group of untrained men [168], or in those participating in submaximal cycling exercises [169].

5.3. Antioxidant supplementation and muscle damage

The processes of force production during repetitive eccentric exercise have been widely accepted to result in muscle damage, which is specifically the case when the exercise is unaccustomed. Given that high levels of ROS generated during contractile activities may contribute to the muscle damage (for reviews, see [170, 171]), and antioxidants may scavenge ROS, the potential preventive effects of antioxidant supplementation on muscle damage have been explored in depth, with variations in dosage, timing and duration of administration. Most of the research has focused on the effects of vitamin C and E. Some studies do find some protecting role of the two antioxidants against oxidative stress, while there is no strong evidence for their role in preventing muscle damage (for reviews, see[172]). However, some findings do not support a major role for antioxidant supplementation to reduce markers of oxidative stress [134, 152, 173, 174]. There appears to be no independent or combined effect of

vitamin C, vitamin E and other antioxidants supplementation on facilitating recovery of muscle function after exercise-induced muscle damage [152], protecting against the delayed onset of muscle soreness and markers of muscle damage [173], or attenuating muscular damage induced by exhaustive exercise such as a marathon run [174]. On the contrary, a number of investigations suggest that the administration of antioxidants may promote cellular damage [161], transiently increase tissue damage [162], and hinder the recovery of muscle damage [134]. Therefore, recent studies have cast doubt on the benign effects of antioxidant supplementation.

5.4. Antioxidant supplementation and exercise performance

Similar to equivocal effects of antioxidant administration on muscle damage, present results regarding the role of antioxidant supplementation in exercise performance are inconsistent. There is some evidence to display that the supplementation of antioxidant can benefit exercise performance, while the majority of studies do not support it. Even the combined supplementation of vitamins E, C, NAC, coenzyme Q10, polyprenols and other antioxidants in different subject populations and exercise protocols fails to improve exercise performance. Moreover, there is increasing evidence suggesting a deleterious effect of antioxidant supplementation on exercise performance. For more details on this issue, readers are recommended to read an excellent recently published review by Peternelj and Coombes [136].

5.5. Current understanding

ROS formation during exercise may have dual effects. High levels of ROS produced during strenuous exercise may be related to oxidative damage and impaired muscle function. However, the moderate or transient high levels of ROS induced by exercise may act as signalling molecules to stimulate adaptive responses through redox-sensitive signalling pathways to maintain cellular redox homeostasis during exercise. This scenario explains why subjects involved in exercise training have shown an increase of resistance to oxidative stress under a wide range of physiological and pathological stresses.

Although the majority of studies on the supplementation of antioxidants have supported their beneficial effects on attenuating exercise-induced oxidative stress, there is limited evidence for antioxidant treatment offering any protection against exercise-induced muscular function damage or exercise performance. A plausible explanation is that the attenuation of ROS by antioxidant supplementation may block some useful cell signalling pathways and gene expression involved in adaptations to exercise, which may preclude the health-promoting effects of exercise in subjects.

6. The mechanism of ROS for exercise-induced physical fitness

Despite great progress made in sports medicine, the mechanism of exercise-induced physical fitness remains only partly understood. Combined with the hormetic characteristic of physical activity and the property of allostasis, we have assumed that hormesis-induced allostatic

http://dx.doi.org/10.5772/53360

buffering capacity enhancement is a physiological mechanism to explain exercise-induced physical fitness [130]. This hypothesis seems to be a good framework to illustrate the role of ROS in exercise-induced physical fitness.

6.1. Exercise, ROS and hormesis

Hormesis is basically characterized by biphasic dose-response –low-dose stimulation and high-dose inhibition [175-177]. This is often used to refer to the beneficial effects of low doses of potentially harmful substances [175-177]. As described in section 2, exercise is associated with the increased generation of ROS. This may be the reason for early studies considering aerobic exercise as a mild oxidative stressor [139, 178]. Indeed, sustained high doses of ROS are unquestionably deleterious, whereas a large amount of evidence emerging in recent years has suggested that a mild increase of ROS may evoke a cellular adaptive response to exercise. Therefore, ROS-induced response has the typical bi-phasic features of hormesis.

6.2. ROS-induced enhancement of allostatic buffering capacity

6.2.1. ROS and allostatic buffering capacity

More than two decades ago, Sterling and Eyer coined the term allostasis from the Greek "allo" meaning "variable", and "stasis" meaning "stable". Thus, allostasis means "remaining stable by being variable" [179], that is, maintaining stability through a multi-point. Since in organisms, especially in higher animals, the stability of the internal milieu is associated with many rhythms, such as daily rhythm of body temperature, daily rhythmic secretion of serotonin, melatonin and other hormones, and many other rhythms, allostasis should be a more accurate concept than homeostasis (remaining stable by staying the same). Although there is no evidence at present to show that redox *in vivo* remains stable by being variable, numerous studies have suggested that the increased formation of ROS, whether induced by aging, exercise, or other stress conditions, is initiated to re-establish "redox homeostasis" (for review, see [129]). From a rigorous scientific point of view, the term "redox homeostasis" used here should be replaced by "redox allostasis".

Based on the multi-point property of allostasis, we have postulated the allostatic system as a special "buffering system": it has a basal level and certain buffering capacity that can maintain dynamic stability. Therefore, we have coined the term "allostatic buffering capacity (ABC)" with five components: basal level, peak level, buffering range, increase rate and recovery rate, to give a good picture of the capacity of an allostatic system to maintain dynamic stability. The action model of exercise on ABC has also been addressed. For more details, readers are recommended to read our review published in 2009 [130].

6.2.2. Present evidence of exercise-induced ROS to enhance redox ABC

Regular exercise can promote mitochondrial biogenesis and enhance muscle oxidative capacity [180, 181], and the molecular signals are mainly the increased ROS, such as H_2O_2 [180, 181]. In addition, exercise training has been reported to decrease ROS production through

reducing the electronic leakage with better-regulated mitochondrial electron-transport chain [182] and a larger pool of functional mitochondria [183], which is critical to maintain health and delay the onset and progressive course of some diseases [184]. Moreover, the SOD activity has consistently been shown to increase with exercise in an intensity-dependent manner [185]. Long-term athletic training can increase the activity of proteasome complexes, which increase the degradation and turnover rate of oxidative modified proteins [186].

These findings indicate that regular exercise can enhance the redox ABC through: (a) lowering the basal ROS level by reducing ROS production, decreasing resting respiration rate and re-establishing redox allostasis, (b) increasing the peak level and oxidative buffering range by promoting mitochondrial biogenesis, and (c) decreasing the oxidative stress rate and increasing recovery rate by re-establishing redox allostasis and enhancing the antioxidant defensive system and damage repair system. In contrast, intense and prolonged exercise may damage redox ABC.

7. Summary and perspectives

Most currently available evidence clearly demonstrates that physical activity is associated with an increase of ROS generation in almost all studied cells, tissues and organs. There are many sites for producing ROS during or after exercise (Figure 1]. During moderate aerobic exercise, mitochondria are the predominant site for generating ROS. When energy depletion or ischemia-reperfusion occurs, especially during or after exhaustive exercise, XO may be an important site for ROS production. Macrophages, eosinophils, neutrophils and other cells in the immune system may also contribute to the ROS formation after exercise when tissue damage occurs. With the advance of analytical methods and techniques for assaying ROS *in situ*, more evidence would be produced to fully elucidate the mechanism and site of ROS formation during or after exercise.

ROS formation during exercise has dual effects. Based on the free radical theory of aging, ROS are toxic molecules due to their high reactivity to most biological macromolecules. Supplementation with antioxidants should offer some preventive effects against exercise-induced oxidative damage, and improve muscular function and physical performance. However, growing evidence shows that exercise-induced ROS may act as signalling molecules to mediate useful cellular adaption to exercise, mainly through regulating the expression of cytoprotective proteins and/or several redox-sensitive transcription factors. Although the supplementation of antioxidants may attenuate exercise-induced oxidative stress, there is insufficient evidence that it protects against exercise-induced muscular function damage or exercise performance.

Combined with the hormetic characteristic of exercise-induced ROS and the property of allostasis, hormesis-induced ABC enhancement should be a physiological mechanism to explain ROS-induced physical fitness (Figure 1). Different intensities or types of physical exercise would cause different levels of ROS generation. Too-small or too-large ROS will introduce too-weak eustress (“good stress”) or too-strong distress (“bad stress”) and result in allostasis load through weakening ABC or damaging ABC, respectively. However, moderate

http://dx.doi.org/10.5772/53360

and transient high levels of ROS induced by physical exercise will introduce eustress *in vivo* and contribute to the hormesis-induced ABC enhancement, which benefits physical fitness. Further work is needed to substantiate the exact mechanisms of ROS in physical fitness.

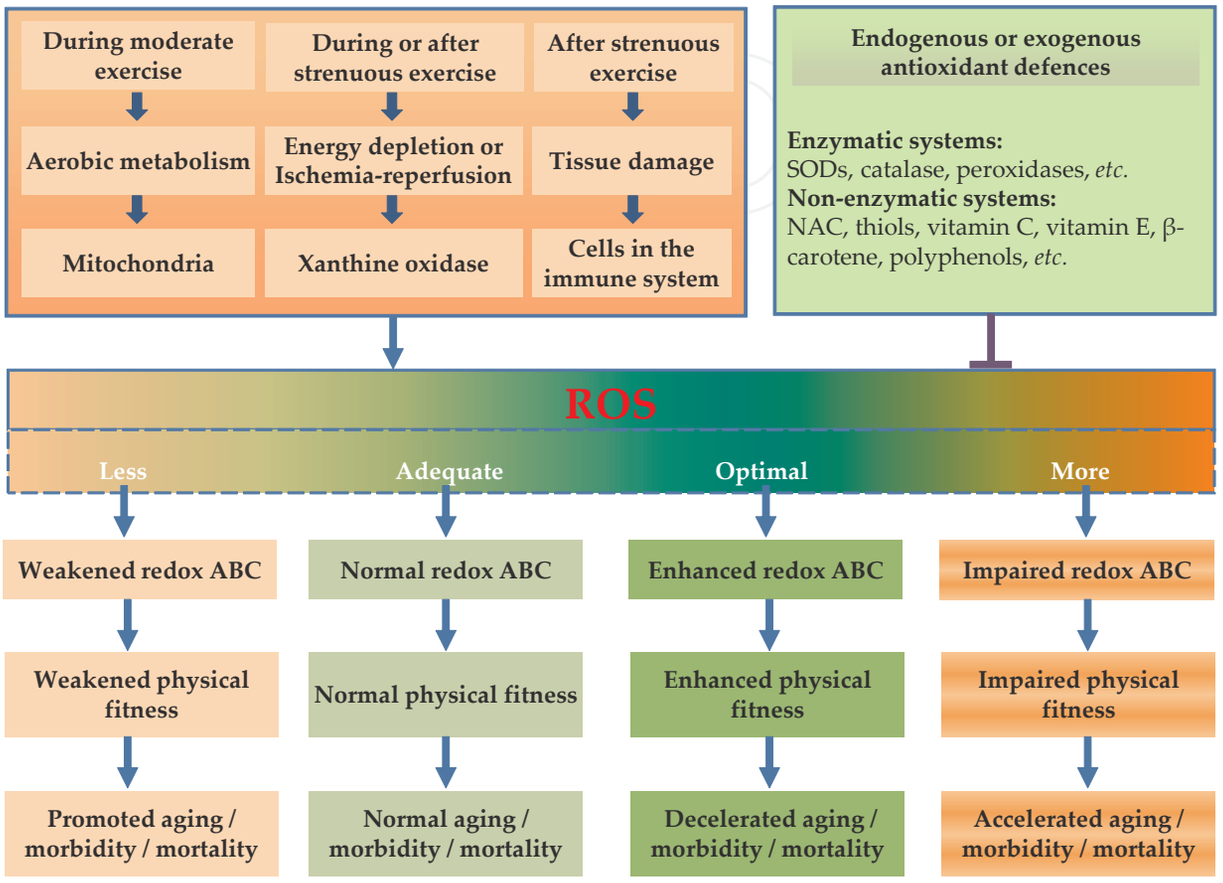

Figure 1. The sources and potential effects of reactive oxygen species (ROS). During or after exercise, ROS are generated as a result of aerobic metabolism in mitochondria, as well as from the activation of xanthine oxidase (XO). In addition, a variety of cells in the immune system can contribute to ROS production. A sophisticated enzymatic and non-enzymatic antioxidant defence system regulates overall ROS levels. Adequate ROS levels are necessary to maintain redox allostatic buffering capacity (ABC). Optimal higher levels of ROS can enhance redox ABC, which improves physical fitness and subsequently delays the aging process and reduces morbidity or mortality of all-cause diseases. Lowering ROS levels below the allostatic set point may interrupt the physiological role of ROS in maintaining redox ABC and cellular adaption to exercise. Similarly, an excessive rise in ROS levels may also constitute a stress signal that damages redox ABC, and ultimately accelerate the aging process and age-related diseases.

Acknowledgements

Very grateful to Dr. Dazhong Yin and Ms. Fang Lei for their constructive suggestions during preparation of the paper. This work has been supported by National Science Funds of China (30800207, 31271257) and Scientific Research Funds of Hunan Provincial Education Department.

List of abbreviations

ROS: reactive oxygen species

TBARS: thiobarbituric acid reactive substances

MDA: malondialdehyde

ESR: electron spin resonance

EPR: electron paramagnetic resonance

NO: nitric oxide

BDNF: brain-derived neurotrophic factor

UCP2: uncoupling protein 2

COPD: chronic obstructive pulmonary disease

ATP: adenosine triphosphate

XO: xanthine oxidase

NFκB: nuclear factor kappaB

NAC: N-acetylcysteine

ABC: allostatic buffering capacity

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References

[1] Blair SN, Kohl HW, III, Barlow CE, Paffenbarger RS, Jr., Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. JAMA: The Journal of the American Medical Association. 1995;273(14):1093-8.

[2] Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmeno-

pausal women with elevated blood pressure: a randomized controlled trial. JAMA: The Journal of the American Medical Association. 2007;297(19):2081-91.

[3] Kokkinos P, Myers J, Kokkinos JP, Pittaras A, Narayan P, Manolis A, et al. Exercise capacity and mortality in black and white men. Circulation. 2008;117(5):614-22.

[4] Blair SN, Kampert JB, Kohl HW, III, Barlow CE, Macera CA, Paffenbarger RS, Jr., et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA: The Journal of the American Medical Association. 1996;276(3):205-10.

[5] Ekelund LG, Haskell WL, Johnson JL, Whaley FS, Criqui MH, Sheps DS. Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men. The Lipid Research Clinics Mortality Follow-up Study. NEnglJ Med. 1988;319(21):1379-84.

[6] Lee IM. Dose-response relation between physical activity and fitness: even a little is good; more is better. JAMA: The Journal of the American Medical Association. 2007;297(19):2137-9.

[7] Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. NEnglJ Med. 2002;346(11): 793-801.

[8] Paffenbarger RS, Jr., Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. NEnglJ Med. 1986;314(10):605-13.

[9] Rodriguez DA, Kalko S, Puig-Vilanova E, Perez-Olabarria M, Falciani F, Gea J, et al. Muscle and blood redox status after exercise training in severe COPD patients. Free radical biology & medicine. 2012 Jan 1;52(1):88-94. PubMed PMID: 22064359. Epub 2011/11/09. eng.

[10] Nikolaidis MG, Kyparos A, Dipla K, Zafeiridis A, Sambanis M, Grivas GV, et al. Exercise as a model to study redox homeostasis in blood: the effect of protocol and sampling point. Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals. 2012 Feb;17(1):28-35. PubMed PMID: 22288504. Epub 2012/02/01. eng.

[11] Farney TM, McCarthy CG, Canale RE, Schilling BK, Whitehead PN, Bloomer RJ. Absence of blood oxidative stress in trained men following strenuous exercise. Medicine and science in sports and exercise. 2012 Apr 19. PubMed PMID: 22525774. Epub 2012/04/25. Eng.

[12] Smuder AJ, Kavazis AN, Min K, Powers SK. Exercise protects against doxorubicin-induced oxidative stress and proteolysis in skeletal muscle. Journal of applied physiology (Bethesda, Md : 1985). 2011 Apr;110(4):935-42. PubMed PMID: 21310889. Pubmed Central PMCID: 3075128. Epub 2011/02/12. eng.

[13] Saborido A, Naudi A, Portero-Otin M, Pamplona R, Megias A. Stanozolol treatment decreases the mitochondrial ROS generation and oxidative stress induced by acute

exercise in rat skeletal muscle. Journal of applied physiology (Bethesda, Md : 1985). 2011 Mar;110(3):661-9. PubMed PMID: 21164155. Epub 2010/12/18. eng.

[14] Kuwahara H, Horie T, Ishikawa S, Tsuda C, Kawakami S, Noda Y, et al. Oxidative stress in skeletal muscle causes severe disturbance of exercise activity without muscle atrophy. Free radical biology & medicine. 2010 May 1;48(9):1252-62. PubMed PMID: 20156551. Epub 2010/02/17. eng.

[15] Syu GD, Chen HI, Jen CJ. Severe exercise and exercise training exert opposite effects on human neutrophil apoptosis via altering the redox status. PloS one. 2011;6(9):e24385. PubMed PMID: 21931703. Pubmed Central PMCID: 3170310. Epub 2011/09/21. eng.

[16] Tauler P, Aguilo A, Gimeno I, Noguera A, Agusti A, Tur JA, et al. Differential response of lymphocytes and neutrophils to high intensity physical activity and to vitamin C diet supplementation. Free radical research. 2003 Sep;37(9):931-8. PubMed PMID: 14670000. Epub 2003/12/13. eng.

[17] Suzuki K, Sato H, Kikuchi T, Abe T, Nakaji S, Sugawara K, et al. Capacity of circulating neutrophils to produce reactive oxygen species after exhaustive exercise. Journal of applied physiology (Bethesda, Md : 1985). 1996 Sep;81(3):1213-22. PubMed PMID: 8889756. Epub 1996/09/01. eng.

[18] Turner JE, Bosch JA, Drayson MT, Aldred S. Assessment of oxidative stress in lymphocytes with exercise. Journal of applied physiology (Bethesda, Md : 1985). 2011 Jul; 111(1):206-11. PubMed PMID: 21493722. Epub 2011/04/16. eng.

[19] Fisher G, Schwartz DD, Quindry J, Barberio MD, Foster EB, Jones KW, et al. Lymphocyte enzymatic antioxidant responses to oxidative stress following high-intensity interval exercise. Journal of applied physiology (Bethesda, Md : 1985). 2011 Mar; 110(3):730-7. PubMed PMID: 21127208. Epub 2010/12/04. eng.

[20] Sureda A, Ferrer MD, Tauler P, Tur JA, Pons A. Lymphocyte antioxidant response and H2O2 production after a swimming session: gender differences. Free radical research. 2008 Apr;42(4):312-9. PubMed PMID: 18404530. Epub 2008/04/12. eng.

[21] Smuder AJ, Min K, Hudson MB, Kavazis AN, Kwon OS, Nelson WB, et al. Endurance exercise attenuates ventilator-induced diaphragm dysfunction. Journal of applied physiology (Bethesda, Md : 1985). 2012 Feb;112(3):501-10. PubMed PMID: 22074717. Epub 2011/11/15. eng.

[22] Caillaud C, Py G, Eydoux N, Legros P, Prefaut C, Mercier J. Antioxidants and mitochondrial respiration in lung, diaphragm, and locomotor muscles: effect of exercise. Free radical biology & medicine. 1999 May;26(9-10):1292-9. PubMed PMID: 10381202. Epub 1999/06/25. eng.

[23] Salo DC, Donovan CM, Davies KJ. HSP70 and other possible heat shock or oxidative stress proteins are induced in skeletal muscle, heart, and liver during exercise. Free

radical biology & medicine. 1991;11(3):239-46. PubMed PMID: 1937141. Epub 1991/01/01. eng.

[24] Hoene M, Franken H, Fritsche L, Lehmann R, Pohl AK, Haring HU, et al. Activation of the mitogen-activated protein kinase (MAPK) signalling pathway in the liver of mice is related to plasma glucose levels after acute exercise. Diabetologia. 2010 Jun; 53(6):1131-41. PubMed PMID: 20195842. Epub 2010/03/03. eng.

[25] Taysi S, Oztasan N, Efe H, Polat MF, Gumustekin K, Siktar E, et al. Endurance training attenuates the oxidative stress due to acute exhaustive exercise in rat liver. Acta physiologica Hungarica. 2008 Dec;95(4):337-47. PubMed PMID: 19009910. Epub 2008/11/18. eng.

[26] Frasier CR, Sloan RC, Bostian PA, Gonzon MD, Kurowicki J, Lopresto SJ, et al. Short-term exercise preserves myocardial glutathione and decreases arrhythmias after thiol oxidation and ischemia in isolated rat hearts. Journal of applied physiology (Bethesda, Md : 1985). 2011 Dec;111(6):1751-9. PubMed PMID: 21940849. Epub 2011/09/24. eng.

[27] Bo H, Jiang N, Ma G, Qu J, Zhang G, Cao D, et al. Regulation of mitochondrial uncoupling respiration during exercise in rat heart: role of reactive oxygen species (ROS) and uncoupling protein 2. Free radical biology & medicine. 2008 Apr 1;44(7): 1373-81. PubMed PMID: 18226608. Epub 2008/01/30. eng.

[28] Nie J, Close G, George KP, Tong TK, Shi Q. Temporal association of elevations in serum cardiac troponin T and myocardial oxidative stress after prolonged exercise in rats. European journal of applied physiology. 2010 Dec;110(6):1299-303. PubMed PMID: 20711602. Epub 2010/08/17. eng.

[29] Prigol M, Luchese C, Nogueira CW. Antioxidant effect of diphenyl diselenide on oxidative stress caused by acute physical exercise in skeletal muscle and lungs of mice. Cell biochemistry and function. 2009 Jun;27(4):216-22. PubMed PMID: 19382129. Epub 2009/04/22. eng.

[30] Falone S, D'Alessandro A, Mirabilio A, Petruccelli G, Cacchio M, Di Ilio C, et al. Long term running biphasically improves methylglyoxal-related metabolism, redox homeostasis and neurotrophic support within adult mouse brain cortex. PloS one. 2012;7(2):e31401. PubMed PMID: 22347470. Pubmed Central PMCID: 3275619. Epub 2012/02/22. eng.

[31] Lima FD, Oliveira MS, Furian AF, Souza MA, Rambo LM, Ribeiro LR, et al. Adaptation to oxidative challenge induced by chronic physical exercise prevents Na+,K+-ATPase activity inhibition after traumatic brain injury. Brain research. 2009 Jul 7;1279:147-55. PubMed PMID: 19422810. Epub 2009/05/09. eng.

[32] Griesbach GS, Hovda DA, Gomez-Pinilla F, Sutton RL. Voluntary exercise or amphetamine treatment, but not the combination, increases hippocampal brain-derived neurotrophic factor and synapsin I following cortical contusion injury in rats. Neuro-

science. 2008 Jun 23;154(2):530-40. PubMed PMID: 18479829. Pubmed Central PMCID: 2441485. Epub 2008/05/16. eng.

[33] Agarwal D, Elks CM, Reed SD, Mariappan N, Majid DS, Francis J. Chronic exercise preserves renal structure and hemodynamics in spontaneously hypertensive rats. Antioxidants & redox signaling. 2012 Jan 15;16(2):139-52. PubMed PMID: 21895524. Pubmed Central PMCID: 3222098. Epub 2011/09/08. eng.

[34] George L, Lokhandwala MF, Asghar M. Exercise activates redox-sensitive transcription factors and restores renal D1 receptor function in old rats. American journal of physiology Renal physiology. 2009 Nov;297(5):F1174-80. PubMed PMID: 19759268. Pubmed Central PMCID: 2781333. Epub 2009/09/18. eng.

[35] Azenabor AA, Hoffman-Goetz L. Intrathymic and intrasplenic oxidative stress mediates thymocyte and splenocyte damage in acutely exercised mice. Journal of applied physiology (Bethesda, Md : 1985). 1999 Jun;86(6):1823-7. PubMed PMID: 10368344. Epub 1999/06/16. eng.

[36] Kruger K, Frost S, Most E, Volker K, Pallauf J, Mooren FC. Exercise affects tissue lymphocyte apoptosis via redox-sensitive and Fas-dependent signaling pathways. American journal of physiology Regulatory, integrative and comparative physiology. 2009 May;296(5):R1518-27. PubMed PMID: 19261913. Epub 2009/03/06. eng.

[37] Quadrilatero J, Hoffman-Goetz L. Mouse thymocyte apoptosis and cell loss in response to exercise and antioxidant administration. Brain, behavior, and immunity. 2005 Sep;19(5):436-44. PubMed PMID: 16061151. Epub 2005/08/03. eng.

[38] Moraska A, Deak T, Spencer RL, Roth D, Fleshner M. Treadmill running produces both positive and negative physiological adaptations in Sprague-Dawley rats. American journal of physiology Regulatory, integrative and comparative physiology. 2000 Oct;279(4):R1321-9. PubMed PMID: 11004000. Epub 2000/09/27. eng.

[39] Hofer T, Fontana L, Anton SD, Weiss EP, Villareal D, Malayappan B, et al. Long-term effects of caloric restriction or exercise on DNA and RNA oxidation levels in white blood cells and urine in humans. Rejuvenation research. 2008 Aug;11(4):793-9. PubMed PMID: 18729811. Pubmed Central PMCID: 2724865. Epub 2008/08/30. eng.

[40] Radak Z, Pucsuk J, Boros S, Josfai L, Taylor AW. Changes in urine 8-hydroxydeoxyguanosine levels of super-marathon runners during a four-day race period. Life sciences. 2000 Mar 24;66(18):1763-7. PubMed PMID: 10809173. Epub 2000/05/16. eng.

[41] McAnulty SR, Nieman DC, Fox-Rabinovich M, Duran V, McAnulty LS, Henson DA, et al. Effect of n-3 fatty acids and antioxidants on oxidative stress after exercise. Medicine and science in sports and exercise. 2010 Sep;42(9):1704-11. PubMed PMID: 20164809. Epub 2010/02/19. eng.

[42] Taito S, Sekikawa K, Domen S, Konishi K, Kimura T, Takahashi M, et al. Pulmonary oxidative stress is induced by maximal exercise in young cigarette smokers. Nicotine

& tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2012 Feb;14(2):243-7. PubMed PMID: 22080589. Epub 2011/11/15. eng.

[43] Font-Ribera L, Kogevinas M, Zock JP, Gomez FP, Barreiro E, Nieuwenhuijsen MJ, et al. Short-term changes in respiratory biomarkers after swimming in a chlorinated pool. Environmental health perspectives. 2010 Nov;118(11):1538-44. PubMed PMID: 20833607. Pubmed Central PMCID: 2974690. Epub 2010/09/14. eng.

[44] Cantu-Medellin N, Byrd B, Hohn A, Vazquez-Medina JP, Zenteno-Savin T. Differential antioxidant protection in tissues from marine mammals with distinct diving capacities. Shallow/short vs. deep/long divers. Comparative biochemistry and physiology Part A, Molecular & integrative physiology. 2011 Apr;158(4):438-43. PubMed PMID: 21147244. Epub 2010/12/15. eng.

[45] Arguelles S, Garcia S, Maldonado M, Machado A, Ayala A. Do the serum oxidative stress biomarkers provide a reasonable index of the general oxidative stress status? Biochimica et biophysica acta. 2004 Nov 1;1674(3):251-9. PubMed PMID: 15541294. Epub 2004/11/16. eng.

[46] Liu J, Yeo HC, Overvik-Douki E, Hagen T, Doniger SJ, Chyu DW, et al. Chronically and acutely exercised rats: biomarkers of oxidative stress and endogenous antioxidants. Journal of applied physiology (Bethesda, Md : 1985). 2000 Jul;89(1):21-8. PubMed PMID: 10904031. Epub 2000/07/25. eng.

[47] Davies KJ, Quintanilha AT, Brooks GA, Packer L. Free radicals and tissue damage produced by exercise. Biochemical and biophysical research communications. 1982 Aug 31;107(4):1198-205. PubMed PMID: 6291524. Epub 1982/08/31. eng.

[48] Jackson MJ, Jones DA, Edwards RH. Vitamin E and skeletal muscle. Ciba Foundation symposium. 1983;101:224-39. PubMed PMID: 6557905. Epub 1983/01/01. eng.

[49] Puente-Maestu L, Tejedor A, Lazaro A, de Miguel J, Alvarez-Sala L, Gonzalez-Aragoneses F, et al. Site of Mitochondrial ROS Production in Skeletal Muscle of COPD and its Relationship with Exercise Oxidative Stress. American journal of respiratory cell and molecular biology. 2012 Apr 5. PubMed PMID: 22493009. Epub 2012/04/12. Eng.

[50] Phoenix J, Edwards RH, Jackson MJ. The effect of vitamin E analogues and long hydrocarbon chain compounds on calcium-induced muscle damage. A novel role for alpha-tocopherol? Biochimica et biophysica acta. 1991 Oct 21;1097(3):212-8. PubMed PMID: 1932145. Epub 1991/10/21. eng.

[51] Phoenix J, Edwards RH, Jackson MJ. Effects of calcium ionophore on vitamin E-deficient rat muscle. The British journal of nutrition. 1990 Jul;64(1):245-56. PubMed PMID: 2119221. Epub 1990/07/01. eng.

[52] Phoenix J, Edwards RH, Jackson MJ. Inhibition of Ca2+-induced cytosolic enzyme efflux from skeletal muscle by vitamin E and related compounds. The Biochemical

journal. 1989 Jan 1;257(1):207-13. PubMed PMID: 2493242. Pubmed Central PMCID: 1135557. Epub 1989/01/01. eng.

[53] Quintanilha AT, Packer L. Vitamin E, physical exercise and tissue oxidative damage. Ciba Foundation symposium. 1983;101:56-69. PubMed PMID: 6557908. Epub 1983/01/01. eng.

[54] Boveris A, Chance B. The mitochondrial generation of hydrogen peroxide. General properties and effect of hyperbaric oxygen. The Biochemical journal. 1973 Jul;134(3): 707-16. PubMed PMID: 4749271. Pubmed Central PMCID: 1177867. Epub 1973/07/01. eng.

[55] Loschen G, Azzi A, Richter C, Flohe L. Superoxide radicals as precursors of mitochondrial hydrogen peroxide. FEBS letters. 1974 May 15;42(1):68-72. PubMed PMID: 4859511. Epub 1974/05/15. eng.

[56] Alessio HM, Hagerman AE, Fulkerson BK, Ambrose J, Rice RE, Wiley RL. Generation of reactive oxygen species after exhaustive aerobic and isometric exercise. Medicine and science in sports and exercise. 2000 Sep;32(9):1576-81. PubMed PMID: 10994907. Epub 2000/09/20. eng.

[57] Dixon CB, Robertson RJ, Goss FL, Timmer JM, Nagle EF, Evans RW. The effect of acute resistance exercise on serum malondialdehyde in resistance-trained and untrained collegiate men. Journal of strength and conditioning research / National Strength & Conditioning Association. 2006 Aug;20(3):693-8. PubMed PMID: 16937984. Epub 2006/08/30. eng.

[58] Jimenez L, Lefevre G, Richard R, Duvallet A, Rieu M. Exercise does not induce oxidative stress in trained heart transplant recipients. Medicine and science in sports and exercise. 2000 Dec;32(12):2018-23. PubMed PMID: 11128845. Epub 2000/12/29. eng.

[59] Halliwell B, Chirico S. Lipid peroxidation: its mechanism, measurement, and significance. Am J Clin Nutr. 1993 May;57(5 Suppl):715S-24S; discussion 24S-25S. PubMed PMID: 8475889. Epub 1993/05/01. eng.

[60] Gutteridge JM, Halliwell B. The measurement and mechanism of lipid peroxidation in biological systems. Trends in biochemical sciences. 1990 Apr;15(4):129-35. PubMed PMID: 2187293. Epub 1990/04/01. eng.

[61] Li G, Liu L, Hu H, Zhao Q, Xie F, Chen K, et al. Age-related carbonyl stress and erythrocyte membrane protein carbonylation. Clinical hemorheology and microcirculation. 2010 2010/12/28;46(4):305-11. PubMed PMID: 21187579. Epub 2010/12/29. eng.

[62] Jenkins RR. Exercise and oxidative stress methodology: a critique. Am J Clin Nutr. 2000 Aug;72(2 Suppl):670S-4S. PubMed PMID: 10919973. Epub 2000/08/02. eng.

[63] Jackson MJ, Edwards RH, Symons MC. Electron spin resonance studies of intact mammalian skeletal muscle. Biochimica et biophysica acta. 1985 Nov 20;847(2): 185-90. PubMed PMID: 2998478. Epub 1985/11/20. eng.

[64] Davies KJ, Hochstein P. Ubisemiquinone radicals in liver: implications for a mitochondrial Q cycle in vivo. Biochemical and biophysical research communications. 1982 Aug 31;107(4):1292-9. PubMed PMID: 6291526. Epub 1982/08/31. eng.

[65] McArdle A, van der Meulen J, Close GL, Pattwell D, Van Remmen H, Huang TT, et al. Role of mitochondrial superoxide dismutase in contraction-induced generation of reactive oxygen species in skeletal muscle extracellular space. American journal of physiology Cell physiology. 2004 May;286(5):C1152-8. PubMed PMID: 15075214. Epub 2004/04/13. eng.

[66] Reid MB, Haack KE, Franchek KM, Valberg PA, Kobzik L, West MS. Reactive oxygen in skeletal muscle. I. Intracellular oxidant kinetics and fatigue in vitro. Journal of applied physiology (Bethesda, Md : 1985). 1992 Nov;73(5):1797-804. PubMed PMID: 1474054. Epub 1992/11/01. eng.

[67] Reid MB, Shoji T, Moody MR, Entman ML. Reactive oxygen in skeletal muscle. II. Extracellular release of free radicals. Journal of applied physiology (Bethesda, Md : 1985). 1992 Nov;73(5):1805-9. PubMed PMID: 1335453. Epub 1992/11/01. eng.

[68] Pattwell DM, McArdle A, Morgan JE, Patridge TA, Jackson MJ. Release of reactive oxygen and nitrogen species from contracting skeletal muscle cells. Free radical biology & medicine. 2004 Oct 1;37(7):1064-72. PubMed PMID: 15336322. Epub 2004/09/01. eng.

[69] Palomero J, Pye D, Kabayo T, Spiller DG, Jackson MJ. In situ detection and measurement of intracellular reactive oxygen species in single isolated mature skeletal muscle fibers by real time fluorescence microscopy. Antioxidants & redox signaling. 2008 Aug;10(8):1463-74. PubMed PMID: 18407749. Pubmed Central PMCID: 2536563. Epub 2008/04/15. eng.

[70] Pye D, Palomero J, Kabayo T, Jackson MJ. Real-time measurement of nitric oxide in single mature mouse skeletal muscle fibres during contractions. The Journal of physiology. 2007 May 15;581(Pt 1):309-18. PubMed PMID: 17331997. Pubmed Central PMCID: 2075220. Epub 2007/03/03. eng.

[71] McArdle F, Pattwell DM, Vasilaki A, McArdle A, Jackson MJ. Intracellular generation of reactive oxygen species by contracting skeletal muscle cells. Free radical biology & medicine. 2005 Sep 1;39(5):651-7. PubMed PMID: 16085183. Epub 2005/08/09. eng.

[72] Belousov VV, Fradkov AF, Lukyanov KA, Staroverov DB, Shakhbazov KS, Terskikh AV, et al. Genetically encoded fluorescent indicator for intracellular hydrogen peroxide. Nature methods. 2006 Apr;3(4):281-6. PubMed PMID: 16554833. Epub 2006/03/24. eng.

[73] Zuo L, Christofi FL, Wright VP, Liu CY, Merola AJ, Berliner LJ, et al. Intra- and extracellular measurement of reactive oxygen species produced during heat stress in

diaphragm muscle. American journal of physiology Cell physiology. 2000 Oct; 279(4):C1058-66. PubMed PMID: 11003586. Epub 2000/09/26. eng.

[74] Robinson KM, Janes MS, Pehar M, Monette JS, Ross MF, Hagen TM, et al. Selective fluorescent imaging of superoxide in vivo using ethidium-based probes. Proceedings of the National Academy of Sciences. 2006 Oct 10;103(41):15038-43. PubMed PMID: 17015830. Pubmed Central PMCID: 1586181. Epub 2006/10/04. eng.

[75] Kalyanaraman B, Darley-Usmar V, Davies KJ, Dennery PA, Forman HJ, Grisham MB, et al. Measuring reactive oxygen and nitrogen species with fluorescent probes: challenges and limitations. Free radical biology & medicine. 2012 Jan 1;52(1):1-6. PubMed PMID: 22027063. Epub 2011/10/27. eng.

[76] Powers SK, Jackson MJ. Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. Physiol Rev. 2008 Oct;88(4):1243-76. PubMed PMID: 18923182. Pubmed Central PMCID: 2909187. Epub 2008/10/17. eng.

[77] Jackson MJ. Free radicals generated by contracting muscle: by-products of metabolism or key regulators of muscle function? Free RadicBiolMed. 2008;44(2):132-41.

[78] Jackson MJ. Control of reactive oxygen species production in contracting skeletal muscle. Antioxidants & redox signaling. 2011 Nov 1;15(9):2477-86. PubMed PMID: 21699411. Pubmed Central PMCID: 3176346. Epub 2011/06/28. eng.

[79] Brady PS, Brady LJ, Ullrey DE. Selenium, vitamin E and the response to swimming stress in the rat. The Journal of nutrition. 1979 Jun;109(6):1103-9. PubMed PMID: 448449. Epub 1979/06/01. eng.

[80] da Silva LA, Pinho CA, Rocha LG, Tuon T, Silveira PC, Pinho RA. Effect of different models of physical exercise on oxidative stress markers in mouse liver. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme. 2009 Feb;34(1):60-5. PubMed PMID: 19234586. Epub 2009/02/24. eng.

[81] Kayatekin BM, Gonenc S, Acikgoz O, Uysal N, Dayi A. Effects of sprint exercise on oxidative stress in skeletal muscle and liver. European journal of applied physiology. 2002 Jun;87(2):141-4. PubMed PMID: 12070624. Epub 2002/06/19. eng.

[82] Ji LL. Antioxidant enzyme response to exercise and aging. Medicine and science in sports and exercise. 1993 Feb;25(2):225-31. PubMed PMID: 8450725. Epub 1993/02/01. eng.

[83] Aguiar AS, Jr., Tuon T, Pinho CA, Silva LA, Andreazza AC, Kapczinski F, et al. Intense exercise induces mitochondrial dysfunction in mice brain. Neurochemical research. 2008 Jan;33(1):51-8. PubMed PMID: 17619145. Epub 2007/07/10. eng.

[84] Akil M, Bicer M, Menevse E, Baltaci AK, Mogulkoc R. Selenium supplementation prevents lipid peroxidation caused by arduous exercise in rat brain tissue. Bratislavske lekarske listy. 2011;112(6):314-7. PubMed PMID: 21692404. Epub 2011/06/23. eng.

[85] Aydin C, Sonat F, Sahin SK, Cangul IT, Ozkaya G. Long term dietary restriction ameliorates swimming exercise-induced oxidative stress in brain and lung of middle-aged rat. Indian journal of experimental biology. 2009 Jan;47(1):24-31. PubMed PMID: 19317348. Epub 2009/03/26. eng.

[86] Jolitha AB, Subramanyam MV, Asha Devi S. Modification by vitamin E and exercise of oxidative stress in regions of aging rat brain: studies on superoxide dismutase isoenzymes and protein oxidation status. Experimental gerontology. 2006 Aug;41(8): 753-63. PubMed PMID: 16843630. Epub 2006/07/18. eng.

[87] Coskun S, Gonul B, Guzel NA, Balabanli B. The effects of vitamin C supplementation on oxidative stress and antioxidant content in the brains of chronically exercised rats. Molecular and cellular biochemistry. 2005 Dec;280(1-2):135-8. PubMed PMID: 16311914. Epub 2005/11/29. eng.

[88] Toldy A, Stadler K, Sasvari M, Jakus J, Jung KJ, Chung HY, et al. The effect of exercise and nettle supplementation on oxidative stress markers in the rat brain. Brain Res Bull. 2005 May 30;65(6):487-93. PubMed PMID: 15862920. Epub 2005/05/03. eng.

[89] Ogonovszky H, Berkes I, Kumagai S, Kaneko T, Tahara S, Goto S, et al. The effects of moderate-, strenuous- and over-training on oxidative stress markers, DNA repair, and memory, in rat brain. Neurochemistry international. 2005 Jun;46(8):635-40. PubMed PMID: 15863241. Epub 2005/05/03. eng.

[90] Ozkaya YG, Agar A, Yargicoglu P, Hacioglu G, Bilmen-Sarikcioglu S, Ozen I, et al. The effect of exercise on brain antioxidant status of diabetic rats. Diabetes & metabolism. 2002 Nov;28(5):377-84. PubMed PMID: 12461474. Epub 2002/12/04. eng.

[91] Somani SM, Husain K, Diaz-Phillips L, Lanzotti DJ, Kareti KR, Trammell GL. Interaction of exercise and ethanol on antioxidant enzymes in brain regions of the rat. Alcohol (Fayetteville, NY). 1996 Nov-Dec;13(6):603-10. PubMed PMID: 8949956. Epub 1996/11/01. eng.

[92] Somani SM, Ravi R, Rybak LP. Effect of exercise training on antioxidant system in brain regions of rat. Pharmacology, biochemistry, and behavior. 1995 Apr;50(4):635-9. PubMed PMID: 7617712. Epub 1995/04/01. eng.

[93] Devi SA, Kiran TR. Regional responses in antioxidant system to exercise training and dietary vitamin E in aging rat brain. Neurobiology of aging. 2004 Apr;25(4):501-8. PubMed PMID: 15013571. Epub 2004/03/12. eng.

[94] Asha Devi S. Aging brain: prevention of oxidative stress by vitamin E and exercise. TheScientificWorldJournal. 2009;9:366-72. PubMed PMID: 19468659. Epub 2009/05/27. eng.

[95] Lappalainen Z, Lappalainen J, Oksala NK, Laaksonen DE, Khanna S, Sen CK, et al. Diabetes impairs exercise training-associated thioredoxin response and glutathione

status in rat brain. Journal of applied physiology (Bethesda, Md : 1985). 2009 Feb; 106(2):461-7. PubMed PMID: 19074570. Epub 2008/12/17. eng.

[96] Mazzola PN, Terra M, Rosa AP, Mescka CP, Moraes TB, Piccoli B, et al. Regular exercise prevents oxidative stress in the brain of hyperphenylalaninemic rats. Metabolic brain disease. 2011 Dec;26(4):291-7. PubMed PMID: 21947687. Epub 2011/09/29. eng.

[97] Liu W, Zhou C. Corticosterone reduces brain mitochondrial function and expression of mitofusin, BDNF in depression-like rodents regardless of exercise preconditioning. Psychoneuroendocrinology. 2012 Jan 12;37(7):1057-70. PubMed PMID: 22244747. Epub 2012/01/17. Eng.

[98] Molteni R, Wu A, Vaynman S, Ying Z, Barnard RJ, Gomez-Pinilla F. Exercise reverses the harmful effects of consumption of a high-fat diet on synaptic and behavioral plasticity associated to the action of brain-derived neurotrophic factor. Neuroscience. 2004;123(2):429-40. PubMed PMID: 14698750. Epub 2003/12/31. eng.

[99] Chance B, Sies H, Boveris A. Hydroperoxide metabolism in mammalian organs. Physiol Rev. 1979 Jul;59(3):527-605. PubMed PMID: 37532. Epub 1979/07/01. eng.

[100] Boveris A, Oshino N, Chance B. The cellular production of hydrogen peroxide. The Biochemical journal. 1972 Jul;128(3):617-30. PubMed PMID: 4404507. Pubmed Central PMCID: 1173814. Epub 1972/07/01. eng.

[101] Richardson RS, Donato AJ, Uberoi A, Wray DW, Lawrenson L, Nishiyama S, et al. Exercise-induced brachial artery vasodilation: role of free radicals. American journal of physiology Heart and circulatory physiology. 2007 Mar;292(3):H1516-22. PubMed PMID: 17114239. Epub 2006/11/23. eng.

[102] Herrero A, Barja G. ADP-regulation of mitochondrial free radical production is different with complex I- or complex II-linked substrates: implications for the exercise paradox and brain hypermetabolism. Journal of bioenergetics and biomembranes. 1997 Jun;29(3):241-9. PubMed PMID: 9298709. Epub 1997/06/01. eng.

[103] Di Meo S, Venditti P. Mitochondria in exercise-induced oxidative stress. Biological signals and receptors. 2001 Jan-Apr;10(1-2):125-40. PubMed PMID: 11223645. Epub 2001/02/27. eng.

[104] McArdle A, van der Meulen JH, Catapano M, Symons MC, Faulkner JA, Jackson MJ. Free radical activity following contraction-induced injury to the extensor digitorum longus muscles of rats. Free radical biology & medicine. 1999 May;26(9-10):1085-91. PubMed PMID: 10381177. Epub 1999/06/25. eng.

[105] Nishino T, Okamoto K, Kawaguchi Y, Hori H, Matsumura T, Eger BT, et al. Mechanism of the conversion of xanthine dehydrogenase to xanthine oxidase: identification of the two cysteine disulfide bonds and crystal structure of a non-convertible rat liver xanthine dehydrogenase mutant. The Journal of biological chemistry. 2005 Jul 1;280(26):24888-94. PubMed PMID: 15878860. Epub 2005/05/10. eng.

[106] Saksela M, Lapatto R, Raivio KO. Irreversible conversion of xanthine dehydrogenase into xanthine oxidase by a mitochondrial protease. FEBS letters. 1999 Jan 25;443(2): 117-20. PubMed PMID: 9989587. Epub 1999/02/16. eng.

[107] Engerson TD, McKelvey TG, Rhyne DB, Boggio EB, Snyder SJ, Jones HP. Conversion of xanthine dehydrogenase to oxidase in ischemic rat tissues. The Journal of clinical investigation. 1987 Jun;79(6):1564-70. PubMed PMID: 3294898. Pubmed Central PMCID: 424467. Epub 1987/06/01. eng.

[108] Ryan MJ, Jackson JR, Hao Y, Leonard SS, Alway SE. Inhibition of xanthine oxidase reduces oxidative stress and improves skeletal muscle function in response to electrically stimulated isometric contractions in aged mice. Free radical biology & medicine. 2011 Jul 1;51(1):38-52. PubMed PMID: 21530649. Epub 2011/05/03. eng.

[109] Mills PC, Smith NC, Harris RC, Harris P. Effect of allopurinol on the formation of reactive oxygen species during intense exercise in the horse. Research in veterinary science. 1997 Jan-Feb;62(1):11-6. PubMed PMID: 9160417. Epub 1997/01/01. eng.

[110] Vina J, Gimeno A, Sastre J, Desco C, Asensi M, Pallardo FV, et al. Mechanism of free radical production in exhaustive exercise in humans and rats; role of xanthine oxidase and protection by allopurinol. IUBMBLife. 2000;49(6):539-44.

[111] Kelkar A, Kuo A, Frishman WH. Allopurinol as a cardiovascular drug. Cardiology in review. 2011 Nov-Dec;19(6):265-71. PubMed PMID: 21983313. Epub 2011/10/11. eng.

[112] Vina J, Gomez-Cabrera MC, Lloret A, Marquez R, Minana JB, Pallardo FV, et al. Free radicals in exhaustive physical exercise: mechanism of production, and protection by antioxidants. IUBMB life. 2000 Oct-Nov;50(4-5):271-7. PubMed PMID: 11327321. Epub 2001/05/01. eng.

[113] Capecchi PL, Pasini FL, Pasqui AL, Orrico A, Ceccatelli L, Acciavatti A, et al. Allopurinol prevents ischaemia-dependent haemorheological changes. European journal of clinical pharmacology. 1988;35(5):475-81. PubMed PMID: 2853054. Epub 1988/01/01. eng.

[114] Olek RA, Safranow K, Jakubowska K, Olszewska M, Chlubek D, Laskowski R. Allopurinol intake does not modify the slow component of V(.)O(2) kinetics and oxidative stress induced by severe intensity exercise. Physiological research / Academia Scientiarum Bohemoslovaca. 2012 Mar 6;61(1):89-96. PubMed PMID: 22188105. Epub 2011/12/23. eng.

[115] Gomez-Cabrera MC, Borras C, Pallardo FV, Sastre J, Ji LL, Vina J. Decreasing xanthine oxidase-mediated oxidative stress prevents useful cellular adaptations to exercise in rats. The Journal of physiology. 2005 Aug 15;567(Pt 1):113-20. PubMed PMID: 15932896. Pubmed Central PMCID: 1474177. Epub 2005/06/04. eng.

[116] Malm C, Lenkei R, Sjodin B. Effects of eccentric exercise on the immune system in men. Journal of applied physiology (Bethesda, Md : 1985). 1999 Feb;86(2):461-8. PubMed PMID: 9931177. Epub 1999/02/04. eng.

[117] Gulati M, Pandey DK, Arnsdorf MF, Lauderdale DS, Thisted RA, Wicklund RH, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. Circulation. 2003 Sep 30;108(13):1554-9. PubMed PMID: 12975254. Epub 2003/09/17. eng.

[118] Couillard A, Koechlin C, Cristol JP, Varray A, Prefaut C. Evidence of local exercise-induced systemic oxidative stress in chronic obstructive pulmonary disease patients. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2002 Nov;20(5):1123-9. PubMed PMID: 12449164. Epub 2002/11/27. eng.

[119] Gunduz F, Senturk UK. The effect of reactive oxidant generation in acute exercise-induced proteinuria in trained and untrained rats. European journal of applied physiology. 2003 Nov;90(5-6):526-32. PubMed PMID: 12905046. Epub 2003/08/09. eng.

[120] Moller P, Loft S, Lundby C, Olsen NV. Acute hypoxia and hypoxic exercise induce DNA strand breaks and oxidative DNA damage in humans. The FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2001 May;15(7):1181-6. PubMed PMID: 11344086. Epub 2001/05/10. eng.

[121] Santos-Silva A, Rebelo MI, Castro EM, Belo L, Guerra A, Rego C, et al. Leukocyte activation, erythrocyte damage, lipid profile and oxidative stress imposed by high competition physical exercise in adolescents. Clinica chimica acta; international journal of clinical chemistry. 2001 Apr;306(1-2):119-26. PubMed PMID: 11282102. Epub 2001/04/03. eng.

[122] Watson TA, Callister R, Taylor R, Sibbritt D, MacDonald-Wicks LK, Garg ML. Antioxidant restricted diet increases oxidative stress during acute exhaustive exercise. Asia Pacific journal of clinical nutrition. 2003;12 Suppl:S9. PubMed PMID: 15023594. Epub 2004/03/17. eng.

[123] Husain K, Somani SM. Interaction of exercise training and chronic ethanol ingestion on hepatic and plasma antioxidant system in rat. Journal of applied toxicology : JAT. 1997 May-Jun;17(3):189-94. PubMed PMID: 9250541. Epub 1997/05/01. eng.

[124] Bobillier Chaumont S, Maupoil V, Jacques Lahet J, Berthelot A. Effect of exercise training on metallothionein levels of hypertensive rats. Medicine and science in sports and exercise. 2001 May;33(5):724-8. PubMed PMID: 11323539. Epub 2001/04/27. eng.

[125] Cazzola R, Russo-Volpe S, Cervato G, Cestaro B. Biochemical assessments of oxidative stress, erythrocyte membrane fluidity and antioxidant status in professional soccer players and sedentary controls. European journal of clinical investigation. 2003 Oct;33(10):924-30. PubMed PMID: 14511366. Epub 2003/09/27. eng.

[126] Ma J, Liu Z, Ling W. Physical activity, diet and cardiovascular disease risks in Chinese women. Public health nutrition. 2003 Apr;6(2):139-46. PubMed PMID: 12675956. Epub 2003/04/05. eng.

[127] Galan AI, Palacios E, Ruiz F, Diez A, Arji M, Almar M, et al. Exercise, oxidative stress and risk of cardiovascular disease in the elderly. Protective role of antioxidant functional foods. BioFactors (Oxford, England). 2006;27(1-4):167-83. PubMed PMID: 17012773. Epub 2006/10/03. eng.

[128] Meilhac O, Ramachandran S, Chiang K, Santanam N, Parthasarathy S. Role of arterial wall antioxidant defense in beneficial effects of exercise on atherosclerosis in mice. Arteriosclerosis, thrombosis, and vascular biology. 2001 Oct;21(10):1681-8. PubMed PMID: 11597945. Epub 2001/10/13. eng.

[129] Droge W. Free Radicals in the Physiological Control of Cell Function. PhysiolRev. 2002;82(1):47-95.

[130] Li G, He H. Hormesis, allostatic buffering capacity and physiological mechanism of physical activity: a new theoretic framework. Medical hypotheses. 2009 May;72(5): 527-32. PubMed PMID: 19211194. Epub 2009/02/13. eng.

[131] Reid MB, Khawli FA, Moody MR. Reactive oxygen in skeletal muscle. III. Contractility of unfatigued muscle. Journal of applied physiology (Bethesda, Md : 1985). 1993 Sep;75(3):1081-7. PubMed PMID: 8226515. Epub 1993/09/01. eng.

[132] Kang C, O'Moore KM, Dickman JR, Ji LL. Exercise activation of muscle peroxisome proliferator-activated receptor-gamma coactivator-1alpha signaling is redox sensitive. Free radical biology & medicine. 2009 Nov 15;47(10):1394-400. PubMed PMID: 19686839. Epub 2009/08/19. eng.

[133] Ji LL. Antioxidant signaling in skeletal muscle: a brief review. Experimental gerontology. 2007 Jul;42(7):582-93. PubMed PMID: 17467943. Epub 2007/05/01. eng.

[134] Teixeira VH, Valente HF, Casal SI, Marques AF, Moreira PA. Antioxidants do not prevent postexercise peroxidation and may delay muscle recovery. Medicine and science in sports and exercise. 2009 Sep;41(9):1752-60. PubMed PMID: 19657294. Epub 2009/08/07. eng.

[135] Ristow M, Zarse K, Oberbach A, Kloting N, Birringer M, Kiehntopf M, et al. Antioxidants prevent health-promoting effects of physical exercise in humans. Proceedings of the National Academy of Sciences of the United States of America. 2009 May 26;106(21):8665-70. PubMed PMID: 19433800. Pubmed Central PMCID: 2680430. Epub 2009/05/13. eng.

[136] Peternelj TT, Coombes JS. Antioxidant supplementation during exercise training: beneficial or detrimental? Sports Med. 2011 Dec 1;41(12):1043-69. PubMed PMID: 22060178. Epub 2011/11/09. eng.

[137] Alessio HM, Goldfarb AH, Cao G. Exercise-induced oxidative stress before and after vitamin C supplementation. International journal of sport nutrition. 1997 Mar;7(1): 1-9. PubMed PMID: 9063760. Epub 1997/03/01. eng.

[138] Davison GW, Ashton T, George L, Young IS, McEneny J, Davies B, et al. Molecular detection of exercise-induced free radicals following ascorbate prophylaxis in type 1 diabetes mellitus: a randomised controlled trial. Diabetologia. 2008 Nov;51(11): 2049-59. PubMed PMID: 18769906. Epub 2008/09/05. eng.

[139] Goldfarb AH, McIntosh MK, Boyer BT, Fatouros J. Vitamin E effects on indexes of lipid peroxidation in muscle from DHEA-treated and exercised rats. Journal of applied physiology (Bethesda, Md : 1985). 1994 Apr;76(4):1630-5. PubMed PMID: 8045842. Epub 1994/04/01. eng.

[140] Ryan MJ, Dudash HJ, Docherty M, Geronilla KB, Baker BA, Haff GG, et al. Vitamin E and C supplementation reduces oxidative stress, improves antioxidant enzymes and positive muscle work in chronically loaded muscles of aged rats. Experimental gerontology. 2010 Nov;45(11):882-95. PubMed PMID: 20705127. Pubmed Central PMCID: 3104015. Epub 2010/08/14. eng.

[141] Vincent HK, Bourguignon CM, Vincent KR, Weltman AL, Bryant M, Taylor AG. Antioxidant supplementation lowers exercise-induced oxidative stress in young overweight adults. Obesity (Silver Spring, Md). 2006 Dec;14(12):2224-35. PubMed PMID: 17189550. Epub 2006/12/26. eng.

[142] Vassilakopoulos T, Karatza MH, Katsaounou P, Kollintza A, Zakynthinos S, Roussos C. Antioxidants attenuate the plasma cytokine response to exercise in humans. Journal of applied physiology (Bethesda, Md : 1985). 2003 Mar;94(3):1025-32. PubMed PMID: 12571133. Epub 2003/02/07. eng.

[143] Lucotti P, Setola E, Monti LD, Galluccio E, Costa S, Sandoli EP, et al. Beneficial effects of a long-term oral L-arginine treatment added to a hypocaloric diet and exercise training program in obese, insulin-resistant type 2 diabetic patients. American journal of physiology Endocrinology and metabolism. 2006 Nov;291(5):E906-12. PubMed PMID: 16772327. Epub 2006/06/15. eng.

[144] Tauler P, Ferrer MD, Sureda A, Pujol P, Drobnic F, Tur JA, et al. Supplementation with an antioxidant cocktail containing coenzyme Q prevents plasma oxidative damage induced by soccer. European journal of applied physiology. 2008 Nov;104(5): 777-85. PubMed PMID: 18665388. Epub 2008/07/31. eng.

[145] Williams CA, Hoffman RM, Kronfeld DS, Hess TM, Saker KE, Harris PA. Lipoic acid as an antioxidant in mature thoroughbred geldings: a preliminary study. The Journal of nutrition. 2002 Jun;132(6 Suppl 2):1628S-31S. PubMed PMID: 12042475. Epub 2002/06/04. eng.

[146] Ryan MJ, Jackson JR, Hao Y, Williamson CL, Dabkowski ER, Hollander JM, et al. Suppression of oxidative stress by resveratrol after isometric contractions in gastro-

cnemius muscles of aged mice. The journals of gerontology Series A, Biological sciences and medical sciences. 2010 Aug;65(8):815-31. PubMed PMID: 20507922. Pubmed Central PMCID: 2903786. Epub 2010/05/29. eng.

[147] Marquez R, Santangelo G, Sastre J, Goldschmidt P, Luyckx J, Pallardo FV, et al. Cyanoside chloride and chromocarbe diethylamine are more effective than vitamin C against exercise-induced oxidative stress. Pharmacology & toxicology. 2001 Nov; 89(5):255-8. PubMed PMID: 11881979. Epub 2002/03/08. eng.

[148] Maranon G, Munoz-Escassi B, Manley W, Garcia C, Cayado P, de la Muela MS, et al. The effect of methyl sulphonyl methane supplementation on biomarkers of oxidative stress in sport horses following jumping exercise. Acta veterinaria Scandinavica. 2008;50:45. PubMed PMID: 18992134. Pubmed Central PMCID: 2586020. Epub 2008/11/11. eng.

[149] Olinescu R, Talaban D, Nita S, Mihaescu G. Comparative study of the presence of oxidative stress in sportsmen in competition and aged people, as well as the preventive effect of selenium administration. Romanian journal of internal medicine = Revue roumaine de medecine interne. 1995 Jan-Jun;33(1-2):47-54. PubMed PMID: 8535352. Epub 1995/01/01. eng.

[150] Panza VS, Wazlawik E, Ricardo Schutz G, Comin L, Hecht KC, da Silva EL. Consumption of green tea favorably affects oxidative stress markers in weight-trained men. Nutrition (Burbank, Los Angeles County, Calif). 2008 May;24(5):433-42. PubMed PMID: 18337059. Epub 2008/03/14. eng.

[151] Goldfarb AH, Garten RS, Cho C, Chee PD, Chambers LA. Effects of a fruit/berry/vegetable supplement on muscle function and oxidative stress. Medicine and science in sports and exercise. 2011 Mar;43(3):501-8. PubMed PMID: 20689455. Epub 2010/08/07. eng.

[152] Bailey DM, Williams C, Betts JA, Thompson D, Hurst TL. Oxidative stress, inflammation and recovery of muscle function after damaging exercise: effect of 6-week mixed antioxidant supplementation. European journal of applied physiology. 2011 Jun; 111(6):925-36. PubMed PMID: 21069377. Epub 2010/11/12. eng.

[153] Bloomer RJ, Canale RE, Blankenship MM, Fisher-Wellman KH. Effect of Ambrotose AO(R) on resting and exercise-induced antioxidant capacity and oxidative stress in healthy adults. Nutrition journal. 2010;9:49. PubMed PMID: 21040582. Pubmed Central PMCID: 2987350. Epub 2010/11/03. eng.

[154] Bloomer RJ, Falvo MJ, Schilling BK, Smith WA. Prior exercise and antioxidant supplementation: effect on oxidative stress and muscle injury. Journal of the International Society of Sports Nutrition. 2007;4:9. PubMed PMID: 17915021. Pubmed Central PMCID: 2131751. Epub 2007/10/05. eng.

[155] Williams CA, Carlucci SA. Oral vitamin E supplementation on oxidative stress, vitamin and antioxidant status in intensely exercised horses. Equine veterinary journal Supplement. 2006 Aug(36):617-21. PubMed PMID: 17402493. Epub 2007/04/04. eng.

[156] Gaeini AA, Rahnama N, Hamedinia MR. Effects of vitamin E supplementation on oxidative stress at rest and after exercise to exhaustion in athletic students. The Journal of sports medicine and physical fitness. 2006 Sep;46(3):458-61. PubMed PMID: 16998452. Epub 2006/09/26. eng.

[157] Viitala PE, Newhouse IJ, LaVoie N, Gottardo C. The effects of antioxidant vitamin supplementation on resistance exercise induced lipid peroxidation in trained and untrained participants. Lipids in health and disease. 2004 Jun 22;3:14. PubMed PMID: 15212697. Pubmed Central PMCID: 479696. Epub 2004/06/24. eng.

[158] Lamprecht M, Hofmann P, Greilberger JF, Schwaberger G. Increased lipid peroxidation in trained men after 2 weeks of antioxidant supplementation. International journal of sport nutrition and exercise metabolism. 2009 Aug;19(4):385-99. PubMed PMID: 19827463. Epub 2009/10/16. eng.

[159] McAnulty SR, McAnulty LS, Nieman DC, Morrow JD, Shooter LA, Holmes S, et al. Effect of alpha-tocopherol supplementation on plasma homocysteine and oxidative stress in highly trained athletes before and after exhaustive exercise. The Journal of nutritional biochemistry. 2005 Sep;16(9):530-7. PubMed PMID: 16115541. Epub 2005/08/24. eng.

[160] Nieman DC, Henson DA, McAnulty SR, McAnulty LS, Morrow JD, Ahmed A, et al. Vitamin E and immunity after the Kona Triathlon World Championship. Medicine and science in sports and exercise. 2004 Aug;36(8):1328-35. PubMed PMID: 15292740. Epub 2004/08/05. eng.

[161] Bryant RJ, Ryder J, Martino P, Kim J, Craig BW. Effects of vitamin E and C supplementation either alone or in combination on exercise-induced lipid peroxidation in trained cyclists. Journal of strength and conditioning research / National Strength & Conditioning Association. 2003 Nov;17(4):792-800. PubMed PMID: 14666945. Epub 2003/12/12. eng.

[162] Childs A, Jacobs C, Kaminski T, Halliwell B, Leeuwenburgh C. Supplementation with vitamin C and N-acetyl-cysteine increases oxidative stress in humans after an acute muscle injury induced by eccentric exercise. Free radical biology & medicine. 2001 Sep 15;31(6):745-53. PubMed PMID: 11557312. Epub 2001/09/15. eng.

[163] Balakrishnan SD, Anuradha CV. Exercise, depletion of antioxidants and antioxidant manipulation. Cell biochemistry and function. 1998 Dec;16(4):269-75. PubMed PMID: 9857489. Epub 1998/12/19. eng.

[164] Venditti P, Di Meo S. Effect of training on antioxidant capacity, tissue damage, and endurance of adult male rats. International journal of sports medicine. 1997 Oct;18(7): 497-502. PubMed PMID: 9414071. Epub 1997/12/31. eng.

[165] Venditti P, Di Meo S. Antioxidants, tissue damage, and endurance in trained and untrained young male rats. Archives of biochemistry and biophysics. 1996 Jul 1;331(1): 63-8. PubMed PMID: 8660684. Epub 1996/07/01. eng.

[166] Kingsley MI, Wadsworth D, Kilduff LP, McEneny J, Benton D. Effects of phosphatidylserine on oxidative stress following intermittent running. Medicine and science in sports and exercise. 2005 Aug;37(8):1300-6. PubMed PMID: 16118575. Epub 2005/08/25. eng.

[167] Leelarungrayub D, Khansuwan R, Pothongsunun P, Klaphajone J. N-acetylcysteine supplementation controls total antioxidant capacity, creatine kinase, lactate, and tumor necrotic factor-alpha against oxidative stress induced by graded exercise in sedentary men. Oxidative medicine and cellular longevity. 2011;2011:329643. PubMed PMID: 21904641. Pubmed Central PMCID: 3163015. Epub 2011/09/10. eng.

[168] Medved I, Brown MJ, Bjorksten AR, Leppik JA, Sostaric S, McKenna MJ. N-acetylcysteine infusion alters blood redox status but not time to fatigue during intense exercise in humans. Journal of applied physiology (Bethesda, Md : 1985). 2003 Apr;94(4): 1572-82. PubMed PMID: 12496140. Epub 2002/12/24. eng.

[169] Medved I, Brown MJ, Bjorksten AR, McKenna MJ. Effects of intravenous N-acetylcysteine infusion on time to fatigue and potassium regulation during prolonged cycling exercise. Journal of applied physiology (Bethesda, Md : 1985). 2004 Jan;96(1): 211-7. PubMed PMID: 12959960. Epub 2003/09/10. eng.

[170] Close GL, Ashton T, McArdle A, Maclaren DP. The emerging role of free radicals in delayed onset muscle soreness and contraction-induced muscle injury. Comparative biochemistry and physiology Part A, Molecular & integrative physiology. 2005 Nov; 142(3):257-66. PubMed PMID: 16153865. Epub 2005/09/13. eng.

[171] Urso ML, Clarkson PM. Oxidative stress, exercise, and antioxidant supplementation. Toxicology. 2003 Jul 15;189(1-2):41-54. PubMed PMID: 12821281. Epub 2003/06/25. eng.

[172] McGinley C, Shafat A, Donnelly AE. Does antioxidant vitamin supplementation protect against muscle damage? Sports Med. 2009;39(12):1011-32. PubMed PMID: 19902983. Epub 2009/11/12. eng.

[173] Kingsley MI, Kilduff LP, McEneny J, Dietzig RE, Benton D. Phosphatidylserine supplementation and recovery following downhill running. Medicine and science in sports and exercise. 2006 Sep;38(9):1617-25. PubMed PMID: 16960523. Epub 2006/09/09. eng.

[174] Kaikkonen J, Kosonen L, Nyyssonen K, Porkkala-Sarataho E, Salonen R, Korpela H, et al. Effect of combined coenzyme Q10 and d-alpha-tocopheryl acetate supplementation on exercise-induced lipid peroxidation and muscular damage: a placebo-controlled double-blind study in marathon runners. Free radical research. 1998 Jul;29(1): 85-92. PubMed PMID: 9733025. Epub 1998/09/11. eng.

[175] Calabrese EJ, Bachmann KA, Bailer AJ, Bolger PM, Borak J, Cai L, et al. Biological stress response terminology: Integrating the concepts of adaptive response and preconditioning stress within a hormetic dose-response framework. ToxicolApplPharmacol. 2007;222(1):122-8.

[176] Le Bourg E, Rattan SIS. Mild Stress and Healthy Aging: Applying hormesis in aging research and interventions. Dordrecht: Springer; 2008.

[177] Mattson MP. Hormesis defined. Ageing Res Rev. 2008;7(1):1-7.

[178] Goldfarb AH, McIntosh MK, Boyer BT. Vitamin E attenuates myocardial oxidative stress induced by DHEA in rested and exercised rats. Journal of applied physiology (Bethesda, Md : 1985). 1996 Feb;80(2):486-90. PubMed PMID: 8929588. Epub 1996/02/01. eng.

[179] Sterling P, Eyer J, Fisher S, Reason J. Allostasis: a new paradigm to explain arousal pathology. Handbook of life stress, cognition and health. New York: John Wiley & Sons; 1988. p. 629-49.

[180] Irrcher I, Adhihetty PJ, Joseph AM, Ljubicic V, Hood DA. Regulation of mitochondrial biogenesis in muscle by endurance exercise. Sports Med. 2003;33(11):783-93.

[181] Menshikova EV, Ritov VB, Ferrell RE, Azuma K, Goodpaster BH, Kelley DE. Characteristics of skeletal muscle mitochondrial biogenesis induced by moderate-intensity exercise and weight loss in obesity. Journal of Applied Physiology. 2007;103(1):21-7.

[182] Starnes JW, Barnes BD, Olsen ME. Exercise training decreases rat heart mitochondria free radical generation but does not prevent Ca2+-induced dysfunction. JApplPhysiol. 2007;102(5):1793-8.

[183] Guarente L. Mitochondria-a nexus for aging, calorie restriction, and sirtuins? Cell. 2008;132(2):171-6.

[184] Wallace DC. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. AnnuRev Genet. 2005;39:359-407.

[185] Ji LL. Modulation of skeletal muscle antioxidant defense by exercise: Role of redox signaling. Free RadicBiolMed. 2008;44(2):142-52.

[186] Wakshlag JJ, Kallfelz FA, Barr SC, Ordway G, Haley NJ, Flaherty CE, et al. Effects of exercise on canine skeletal muscle proteolysis: an investigation of the ubiquitin-proteasome pathway and other metabolic markers. VetTher. 2002;3(3):215-25.