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Review Article

Systemic adaptation to oxidative challenge induced by regular exercise

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Abstract

Exercise is associated with increased ATP need and an enhanced aerobic and/or anaerobic metabolism, which results in an increased formation of reactive oxygen species (ROS). Regular exercise seems to decrease the incidence of a wide range of ROS-associated diseases, including heart disease, type II diabetes, rheumatic arthritis, Alzheimer and Parkinson diseases, and certain cancers. The preventive effect of regular exercise, at least in part, is due to oxidative stress-induced adaptation. The oxidative challenge-related adaptive process of exercise is probably not just dependent upon the generated level of ROS but primarily on the increase in antioxidant and housekeeping enzyme activities, which involves the oxidative damage repair enzymes. Therefore, the effects of exercise resemble the characteristics of hormesis. In addition, it seems that the oxidative challenge-related effects of exercise are systemic. Skeletal muscle, liver, and brain have very different metabolic rates and functions during exercise, but the adaptive response is very similar: increased antioxidant/damage repair enzyme activity, lower oxidative damage, and increased resistance to oxidative stress, due to the changes in redox homeostasis. Hence, it is highly possible that the well-known beneficial effects of exercise are due to the capability of exercise to produce increased levels of ROS. Or in other words, it seems that the vulnerability of the body to oxidative stress and diseases is significantly enhanced in a sedentary compared to a physically active lifestyle.

Keyword: Exercise; Oxidative stress; Hormesis; Oxidative damage/repair; DNA repair; Free radicals

Contents

Reactive oxygen species (ROS) are physiological products of aerobic metabolism and are used by organisms for a variety of tasks such as signaling, metabolizing of xenobiotics, initiating apoptosis, and stimulation of antioxidant and repair processes [1]. On the other hand, ROS are also believed to be involved in a number of pathological processes such as cachexia, atherosclerosis, cancer, ischemia/reperfusion, inflammation, rheumatic arthritis, and neurodegenerative diseases such as Alzheimer and Parkinson diseases. The most accepted theory of aging also incorporates the damaging effects of ROS that are considered to be unavoidable by-products of aerobic metabolism [2,3]. Interestingly, certain conditions that result in low levels of exposure to free radicals or free radical-generating systems,

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such as radiation, could lead to extension of the life span [4,5]. Caloric restriction, which is the only known method to extend both mean and maximal life span, can be regarded as a mild stressor [6].

Regular physical exercise, which has been proven to increase mean life span, could also serve as a stimulating stressor. Indeed, there is little doubt that the generation of ROS is increased during exercise [7–10]. However, mounting epidemiological data have proven that exercise decreases the incidence of oxidative stress-associated diseases [11]. This phenomenon is not a paradox; it is a result of exercise-induced adaptation. The adaptation process involves activation of the antioxidant system, interferes with the oxidative damage repair/eliminating systems, and influences redox-sensitive transcription, hence the gene expression and protein assembly. Therefore, low levels of this ROS-induced adaptation process, evoked by exercise, create a system that resembles hormesis. The hormesis theory claims that biological systems respond in a bell-shaped curve fashion to exposure to chemicals, toxins, and radiation. In toxicology, hormesis is a dose –response phenomenon characterized by a low-dose stimulation and high-dose inhibition, resulting in either a J-shaped or an inverted U-shaped dose response: a nonmonotonic curve [12]. The stimulating "toxin" during exercise is ROS formation, which evokes specific adaptation, such as increased antioxidant/oxidative damage-repairing enzyme activity, increased resistance to oxidative stress, and lower levels of oxidative damage. This specific adaptation seems to be systemic. Skeletal muscle, liver, and brain react very differently to changes in oxygen supply during exercise. However, the oxidative challenge-related adaptive processes are very similar. The present review attempts to provide a view of the exercise-induced systemic oxidative challenge-related adaptation of skeletal muscle, liver, and brain.

Skeletal muscle

The resting energy expenditure for skeletal muscle is very moderate and it is around 13 kcal/kg organ mass/day [13], which, during heavy exercise, results in a large increase in energy turnover (>100-fold) and introduces a major energetic challenge with a massive oxygen flow to mitochondria [14]. Therefore, it is not surprising that mitochondrial generation of ROS is significantly enhanced during exercise [7]. In addition to mitochondria, NADPH oxidase is a potential generator of ROS during exercise [15]. The increase in activation of glutathione level, the activation of redox-sensitive transcription factors and antioxidant enzymes, as well as the extent of oxidative damage, clearly indicate the enhanced presence of oxidizing agents [15–17]. Moreover, not only mitochondria, but other factors such as xanthine oxidase (XO) could significantly contribute to the oxidative stress, which targets skeletal muscle [18]. Exhaustive exercise on the treadmill has been shown to result in significant increases in lipid peroxidation of rats, and this was prevented by superoxide dismutase derivatives, which protected the endothelium [18]. A significant linear relationship was found between the concentrations of lactic acid and XO in the blood, indicating that anaerobic exercise-induced oxidative challenge could be due to XO. The potential of a single bout of exercise to induce ROS might be important because the inhibition of XO by allopurinol negatively affected the exercise-induced adaptation to oxidative stress [16]. Moreover, it has been shown that contraction-produced ROS, up to a certain level, stimulate, and above this level reduce, force production [19]. In addition, muscle soreness-associated increases in nitric oxide levels could be involved in a drop in maximal force production and contractile protein damage induced by peroxynitrite, which has been observed with muscle soreness [10]. Therefore, it seems that the levels of ROS and NO modulate muscle function in a "bell-shaped" manner, with low and high concentrations of ROS and RNS causing decreases in function.

We and others have shown that the accumulation of reactive carbonyl derivatives (RCD) occurs in a protein-selective manner and actin, carbonic anhydrase III, and aconitase are potentially sensitive to accumulating carbonyl moieties [19–25]. Oxidative modification can serve as a tag, which marks the degradation of proteins [26–29] by changing the hydrophobicity of the proteins [30,31]. Exercise can induce the activity of the proteasome complex, which is significantly involved in the degradation of oxidatively modified proteins [26–34]. Increased activity of proteasome could be an important factor that affects the rate of protein turnover and the remodeling of skeletal muscle after injury [35]. An increased rate of protein turnover with exercise training [36–39] decreases the accumulation of oxidative damage, hence beneficially affecting the physiological function of proteins [40].The proteasome complex plays a critical role in this process.

It seems that the activity of the proteasome complex can be induced by hydrogen peroxide treatment in cell culture [41] and in whole animal models as well [42]. Moreover, the combined effects of exercise and hydrogen peroxide treatment result in enhanced activity of the proteasome complex in myocardium of rats [42].

Exercise training increases the resistance against oxidative stress, providing enhanced protection [8,42,43].

The effects of exercise on the proteasome complex could manipulate the regulation of the DNA repair process [44,45], although the interaction of the proteasome system and DNA repair has not been investigated in exercise studies. The data from our laboratory indicate that exercise modulates the activity of DNA repair enzymes in skeletal muscle [43,46].

It has been estimated that about 180 guanines are oxidized to 8-oxoguanosine by ROS daily in mammalian cells [47] and these oxidized guanines are primarily recognized and removed by oxoguanine DNA glycosylase (OGG1), while paired with cytosine. We have shown that marathon running results in an increased activity of OGG1, when measured from the crude cell extracts of muscle biopsy samples of runners [46]. Aging was found to be associated with increased accumulation of nuclear 8-hydroxydeoxyguanosine (8-OHdG) in quadriceps muscle of rats and this was attenuated by exercise training, probably by the induction of OGG1, as measured from crude cell extracts [43]. Because the rates of oxidative damage in the nuclei and mitochondria differ significantly [48], different levels of activation of OGG1 are suggested in these organelles. Our

recent data indicate that the regulation of OGG1 might be different in nuclei and mitochondria, because exercise training increases the activity of OGG1 in nuclei and decreases it in the mitochondria [49]. We investigated whether these effects are reversible, and we found that, indeed, exercise training increases the OGG1 in nuclei and decreases the OGG1 in mitochondria, and detraining reverses these changes (Z. Radak et al., submitted for publication). Our limited knowledge and data on the activity and regulation of OGG1 so far indicate that exercise training regulates the activity of this enzyme in nuclei and mitochondria of skeletal muscle differently, which could have an impact on physiological function. On the other hand, the activity of uracil DNA glycosylase (UDG), which removes uracil in DNA created by deamination of cytosine, resulting in mutagenic U:G mispairs and misincorporation of dUMP, seems to be induced by exercise training in the nucleus and in the mitochondria [49].

Increased activity of OGG1 and UDG in the nucleus could provide enhanced protection and a decreased level of mutation, which can be associated with the decreased incidence of cancer observed in physically fit individuals [50].

Because the oxidative challenge-associated adaptive response after exercise training is most significant in skeletal muscle, it is not surprising that redox-sensitive transcription factors are heavily involved in the adaptive response. The DNA binding of NF-κB, AP-1, MAPK, and CREB is increased by a single bout of exercise, whereas the training process-induced adaptation might attenuate this binding [16,17,51,52]. The regulation of these redox-sensitive transcription factors by exercise is curricular for adaptive response and cell survival.

Liver

Liver has a very high metabolic rate (200 kcal/kg organ mass/day [21]), which is naturally associated with high oxygen flux, but this is significantly decreased during exercise.

Unlike skeletal muscle, liver contains high levels of xanthine dehydrogenase (XD) and during exercise XD is converted to XO, generating ROS and, therefore, oxidative damage [53]. The exercise and recovery period after exercise in liver might be similar to the ischemia/reperfusion phenomenon, but this is unknown at this time. As a result of an exercise-induced adaptation, ROS production is significantly reduced in the liver of rats [54]. Moreover, the age-associated increase in the activity of the redox-sensitive transcription factor NF-κB can be significantly attenuated by regular exercise [54]. NF-κB is involved in the regulation of various cellular processes and one of the most well studied is the transcription of inflammation-related proteins. It is well accepted that aging increases the incidence of diseases associated with inflammation [55,56], and the protecting mechanism of exercise could be mediated partly through the altered DNA binding of NF-κB.

The protection of DNA from oxidative damage is very important for survival and although it has been shown that NF-κB could be involved in DNA repair by affecting p53 [57], the major role in oxidative DNA repair is that of base excision enzymes. We have measured the 8-OHdG content in the liver of middle-aged and old sedentary and old exercise-trained animals. The 8-OHdG was increased significantly in mitochondria and nuclei of aged animals compared to middle-aged animals; moreover the mitochondrial 8-OHdG level was about 10 times higher than that of nuclei [58]. Regular exercise, on the other hand, significantly reduced the age-associated increase in 8-OHdG content in both organelles and, possibly by this mechanism, ultimately reduced the occurrence of mutation in cellular DNA of both types of organelle. The decline in 8-OHdG was possibly due to the induction of OGG1 at the nucleus. However, similar to skeletal muscle mitochondrial OGG1, exercise training reduced the activity of mitochondrial OGG1 in the liver [58]. This observation could mean that nuclear and mitochondrial OGG1 are regulated differently as a result of exercise training. Moreover, this thought would be in accordance with our data, obtained from skeletal muscle, which suggests that the regulation of the OGG1 in these organelles is similar.

It is often stated, but poorly demonstrated, that exercise training could have adverse effects related to ROS production and accumulation of oxidative damage. Therefore, we designed a study in which we trained animals with different exercise loads, including overtraining [59]. The nuclear 8-OHdG content increased in liver but not in skeletal muscle and brain, suggesting that liver is one of the most sensitive targets of exercise-induced oxidative stress among organs, although the lipid peroxidation and RCD content remained significantly unchanged [59]. The activity of OGG1, measured from crude cell extract, increased in the liver in moderately and strenuously trained animals, but not in the overtrained group.

Our observations suggest that the overall oxidative challenge-related adaptation in the liver of exercise-trained animals might lead to a reduced rate of mutation in both nuclear and mitochondrial DNA and attenuate the age-associated inflammation process, hence increasing resistance to oxidative stress.

Brain

The resting energy expenditure for the brain is 240 kcal/kg organ mass/day [21] and the oxygen flow is relatively constant during exercise, and despite this relative stability of energy metabolism and oxygen supply it seems that oxidative challenge-associated adaptation occurs in the brain. In the past decade it has become clear that regular exercise beneficially affects brain function and could play an important preventive and therapeutic role in oxidative stress-associated diseases [60,61]. The effects of exercise seem to be very complex and could include neurogenesis via neurotrophic factors, increased capillarization, decreased oxidative damage, and increased proteolytic degradation by proteasome and neprilysin [62–67].

Somani et al. [67] reported that the effects of exercise on the activities of antioxidant enzymes were dependent on brain region. In certain brain regions such as the stem and corpus striatum, exercise training resulted in increased activities of superoxide dismutase (SOD) and glutathione peroxidase (GPX)

[68,69]. We have reported that a single bout of exercise, which caused oxidative damage to skeletal muscle [18], liver, and kidney [53], did not cause damage to the brain [70]. Further, the activities of antioxidant enzymes (Cu,Zn-SOD, Mn-SOD, catalase (CAT), GPX) were not significantly altered by an exercise session. A similar phenomenon has been reported after exercise training. Treadmill running did not alter the activities of SOD, CAT, or GPX in the brain of rats. However, exercised rats with diabetes have shown decreased Cu,Zn-SOD and GPX activities [71].

The first study, which described a causative relationship between the accumulation of oxidative damage to brain proteins, RCD, and certain cognitive functions, was an age-related study [72], and their results have been confirmed by other laboratories [73]. Oxidative damage has been associated with poor physiological function of the brain [72–74]. We have also shown that regular exercise training attenuated the age-related accumulation of RCD in the brain, increased the activity of the proteasome complex, and improved brain function [75]. Chronic exercise training, using the rat model, did not cause significant alteration of lipid peroxidation levels in the brain. On the other hand, the supplementation of vitamin C elevated the oxidative damage of lipids [76]. We have subjected rats to moderate, very hard, and overtraining and found, even with very hard training and overtraining, beneficial effects on brain function and lowered accumulation of RCD [77]. The content of 8-OHdG was not significantly altered by the overtraining protocol, and activity of OGG1 was also not changed in the crude cell extract [77]. We recently evaluated the activity of the DNA damage/repair enzyme of OGG1, in the nucleus and mitochondria of trained and detrained rats, and did not detect any significant alterations [78].

Brain-derived neurotrophic factor (BDNF) is one of the most versatile, important neurotrophic factors in the brain. It plays a curricular role in the learning process, including memory, locomotion, behaviors, and a wide range of stress responses [79,80]. It has been suggested that BDNF regulates brain development, neuroplasticity, neurogenesis, neurite outgrowth, synaptic plasticity, and cell survival [81,82]. The expression and protein content of BDNF have been shown to be up-regulated by exercise and oxidative stress [60]. We have measured ROS levels by electron spin resonance and found that in some brain regions, exercise training increases the levels of ROS, although the level of oxidative damage does not increase ([78,83]; Z. Szabo, unpublished; S. Siamilis, unpublished), and a correlation was found between ROS level and BDNF concentration in the spinal cord (S. Siamilis et al., unpublished). In addition, exercise results in angiogenesis in the brain by increasing the level of vascular endothelial growth factor (VEGF) in the hippocampus [84] and it seems that ROS are the mediators of VEGF expression [85].

The activity of some redox-sensitive transcription factors was investigated in exercise studies and the findings revealed that CREB, synapsin, and MAPK activity increased in the brain with exercise, and oxidative challenge alone also regulated these [79,80], suggesting that exercise-induced changes in redox homeostasis could be, at least in some part, mediated by ROS. The observation that exercise training attenuates the oxidative stress-related damage in brain is in accordance with this statement [62,66,74,86].

Data relating to the effects of exercise on brain indicate that accumulation of oxidative damage impairs brain function, and exercise, under certain conditions, can attenuate the accumulation of damage, causing improved brain function. Moreover, ROS could play a role in the induction of neurotrophins, which might be important for neurotrophin-caused neurogenesis.

Conclusion

The available data strongly indicate that regular exercise plays a preventive role against lifestyle-dependent diseases and the molecular mechanism behind this favorable effect could be linked to redox homeostasis, a free radical-related adaptive mechanism. The adaptive mechanism is initiated by transcription factors, resulting in increased activities of the antioxidant enzymes, and more effective repair and housekeeping by the DNA repair enzymes and proteasome complex. The molecular adaptation then leads to an improved physiological function and enhanced resistance to oxidative stress. Most importantly, the exercise-induced oxidative challenge-associated adaptation is systemic. These beneficial consequences of regular exercise are in sharp contrast to the effects of exhaustive exercise on unprepared tissues that results in, apparently, harmful outcomes (Fig. 1). These consequences of exercise fit well with the concept of hormesis [87].

On the other hand, physical inactivity leads to impairment in physiological functions and reduces the whole body resistance to oxidative stress. Moreover, it seems that physical inactivity through molecular pathways could facilitate the incidence of

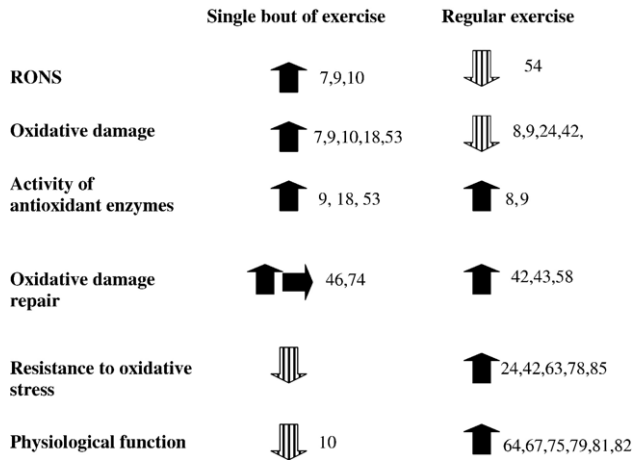

Fig. 1. The redox homeostasis-associated changes as a result of single bout of exercise and regular exercise compared to physical inactivity. Sedentary lifestyle, of human beings or experimental animals, is often regarded as a control, but this most probably should be considered as a nonphysiological, physically inactive condition. One can consider that regular exercise is a normal part of everyday life and it is phylogenetically conserved in evolution; hence inactivity has very serious consequences, which are reflected in redox homeostasis. The numbers represent selected references that support the hypothesis. RONS, reactive oxygen and nitrogen species.

oxidative stress-related diseases, such as cardiovascular diseases, cachexia, atherosclerosis, cancer, ischemia/reperfusion, inflammation, rheumatic arthritis, and neurodegenerative diseases such as Alzheimer and Parkinson diseases. Therefore it seems that the human being is not designed to be inactive for survival.

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