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Review

The complex role of physical exercise and reactive oxygen species on brain

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Abstract

Reactive oxygen species (ROS) are continuously generated during aerobic metabolism and at moderate level. They play a role in redox signaling, but in significant concentration they cause oxidative damage and neurodegeneration. Because of the enhanced sensitivity of brain to ROS, it is especially important to maintain the normal redox state in different types of neuron cells. In last decade it became clear that regular exercise beneficially affects brain function, and can play an important preventive and therapeutic role in stroke, Alzheimer, and Parkinson diseases. The effects of exercise appear to be very complex and could include neurogenesis via neurotrophic factors, increased capillarization, decreased oxidative damage, and increased proteolytic degradation by proteasome and neprilysin. Data from our and other laboratories indicate that exercise-induced modulation of ROS levels plays a role in the protein content and expression of brain-derived neurotrophic factor, tyrosine-related kinase B (TrkB), and cAMP response element binding protein, resulting in better function and increased neurogenesis. Therefore, it appears that exercise-induced modulation of the redox state is an important means, by which exercise benefits brain function, increases the resistance against oxidative stress, facilitates recovery from oxidative stress, and attenuates age-associated decline in cognition.

Copyright © 2013, Shanghai University of Sport. Production and hosting by Elsevier B.V. Open access under [CC BY-NC-ND license](http://creativecommons.org/licenses/by-nc-nd/3.0/).**Keywords:** Exercise; Neurotrophins brain function; Oxidative damage; Oxidative stress

1. Introduction

Brain is an organ very sensitive to oxidative stress and this is partly due to the high metabolic rate and the large amount of iron and copper found in the organ. These interact with the diffusible hydrogen peroxide and result in the generation of the extremely reactive hydroxyl radical that yields damage to proteins, lipids and DNA.^{1,2} Hydrogen peroxide is generated by a number of systems, including reactions catalyzed by monoamine oxidases A and B with a described location of

neuronal and glial mitochondrial membranes.³ Besides the possible iron-hydrogen peroxide interactions, Ca²⁺-associated reactive oxygen species (ROS) generation is also a potent source of ROS in the brain. Both inhibition and activation of neurons activates Ca²⁺-traffic and the excess of glutamate could result in large increases in ROS production.^{4,5} Neuronal membranes are packed with phospholipids containing polyunsaturated fatty acid esters, which are very sensitive to attack of ROS, causing a chain reaction which generates lipid radicals and extensive membrane damage. Nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidases are potent cellular generators of superoxide including neurons and glia.⁶ NAD(P)H oxidase ROS generation can be influenced by free fatty acids especially mono and polyunsaturated long-chain fatty acids, which could increase ROS production.⁷ Despite the fact that brain is well protected by the blood brain barrier, it is important to note that it cannot provide full protection against circulating inflammatory agents that can generate radicals in the brain.⁸

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It is well established that oxidative stress is closely linked to the pathology of a variety of neurodegenerative diseases, including age-associated disorders.^{9–11} Due to its high reactivity and short lifespan, the direct detection of ROS is difficult, and hence, the amount is often judged from the alteration of antioxidant status or the accumulation of relatively stable products of lipid, protein and DNA interactions. However, the levels of oxidative damage, besides the concentration and reactivity of ROS, are also influenced by the activity of the repair systems.

The levels of oxidative modification of lipids, proteins, and DNA are generally used as markers of oxidative damage, which are increased with the neuropathology of aging, and in some cases suggested to be a causative factor of the progress of specific diseases.^{12–14} However, besides ROS-associated neurodegeneration which could be a result of significant load of ROS, moderate amount of these reactive species could have beneficial effects on signaling, neurogenesis, and in epigenetic regulation as well.

For instance, during physical exercise there is an increased generation of ROS,¹⁵ but regular exercise is known to improve the physiological performance of skeletal and cardiac muscle and decrease the incidence of a wide range of diseases, including heart and vascular diseases, certain kind of cancer, diabetes II, *etc.*¹⁶ In last decade it became clear that regular exercise beneficially affects brain function as well, and could play an important preventive and therapeutic role in stroke, Alzheimer, and Parkinson diseases.^{11,17} The effects of exercise appear to be very complex and could include neurogenesis via neurotrophic factors, increased capillarization, decreased oxidative damage, and increased proteolytic degradation by proteasome and neprilysin.^{18–24} The present review focuses on oxidative challenges related to the effects of exercise, and attempts to summarize the available knowledge in this area.

2. Exercise and antioxidants in the brain

There are conflicting data on the effect of exercise on the activities of antioxidant enzymes. It has been suggested that, for instance, in the case of DNA, the damage can be reduced from 10^9 to 10^6 in a daily base/cell as a result of the antioxidant scavenging system.²⁵

The findings of an early study suggested that exercise, voluntary running, results in oxidative damage to low vitamin E fed animals.²⁶ Swimming-exposed rats suffered significant increases in lipid peroxidation, and glutathione peroxidase (GPx) activity was also increased,²⁷ while 6-hydroxymelatonin supplementation prevented oxidative lipid damage. On the other hand,²⁸ it was noted that the activities of antioxidant enzymes were dependent on brain region, and the effects of exercise were also dependent on the brain portion. In certain brain parts such as the stem and corpus striatum, exercise training resulted in increased activities of superoxide dismutase (SOD) and GPx.²⁸ We have reported that a single bout of exercise, which caused oxidative damage to skeletal muscle,²⁹ liver and kidney,³⁰ did not cause damage to the brain.²⁹ 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.³¹ In our recent study we found that regular exercise increases the content of Cu, Zn-SOD, GPx, and peroxisome proliferator-activated receptor- γ co-activator 1 α (PGC-1 α) and the later transcription co-activator is important since it is involved in mitochondrial biogenesis.³² Indeed, PGC-1 α activation could result in decreased oxidative challenge, either by up-regulation of antioxidant enzymes and/or by an increased number of mitochondria that allow lower levels of respiratory activity for the same degree of ATP generation.

The available information on brain antioxidant status for exercise suggests that exercise training selectively regulates the activity of antioxidant enzymes in different brain regions. The activity response of antioxidant enzymes in the brain, with exercise, is probably dependent on the type of physical activity, the intensity and duration of exercise training, and the age, sex, and strain of rats.

3. Oxidative damage and functional changes

The first study, which described a relationship between the accumulation of oxidative damage to proteins, reactive carbonyl derivative (RCD), and certain brain functions, was an age related study.³³ A spin trapping agent of α Phenyl t-Butyl Nitron (PBN) was administered for 2 weeks to aged and young gerbils, and after this period the activities of glutamine synthase and proteasome increased, while the level of RCD decreased significantly, and these changes were accompanied by improved brain function, as measured by the Morris Maze test. Although, the findings of this study were questioned at the time by Cao and Cuttler,^{34,35} the results of the original study were later confirmed by other laboratories.³⁶

Liu et al.³⁷ immobilized rats overnight and this resulted in increased oxidative damage of lipids, proteins, and DNA in the brain of animals. We applied the same immobilizing method and measured brain function 2 h after immobilization using the passive avoidance test and found performance to be impaired.³⁸ We then added groups, which were exposed to a single bout of exhaustive swimming or swimming after immobilization. The oxidative damage of macromolecules increased as a result of immobilization, in accordance with Liu and co-workers, and we found that exercise after immobilization appeared to decrease damage.

Oxidative damage has been associated with poor physiological function of the brain. We have also shown that regular exercise training attenuated the age-related accumulation of RCD in the brain, increased the activity of proteasome complex, and improved brain function.³⁹ Chronic exercise training in rats 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.⁴⁰ Ogonovszky et al.⁴¹ subjected rats to moderate-, very hard- and

over-training, and found beneficial effects on brain function and lowered accumulation of RCD even with very hard training and over-training. On the other hand, when rats brain were treated by N-methyl-D-aspartate (NMDA) to induce lesion, a method used to mimic Alzheimer diseases (AD), it was found that exercise alone and with supplementation of nettle reduced ROS formation and levels of carbonyl groups.⁴² We could also show in this study, that lower level of oxidative damage was associated with better function, assessed by passive avoidance test.

Oxidative modification of DNA could lead to increased apoptosis. Impaired function and accumulation of DNA damage in neurons have been suggested to be major factors related to brain aging and neurodegenerative diseases.^{43,44} Koltai et al.⁴⁵ observed that aging increases the levels of 8-oxoguanine (8-oxoG) in hippocampus of rats, which potentially could jeopardize brain function.^{46,47} Indeed, the repair of 8-oxoG, by the enzyme 8-oxoguanine glycosylase (OGG1), is a high priority of cells for survival. The total protein content of OGG1 was increased in aged rats, which could be a cellular attempt to combat the enhanced levels of 8-oxoG, although in this case, without significant success.⁴⁵

Acetylation of OGG1 is a posttranslational activation of incision activity of this enzyme.^{48,49} Thus, the age-associated increase in 8-oxoG levels, which we recently reported could be due to the large decrease in acetylation of OGG1.⁴⁵ On the other hand, exercise with IGF-1 supplementation increased the levels of OGG1 acetylation. It was also shown that acetylation of OGG1 takes place *in vivo* and exercise increases the rate of acetylation. This finding could suggest that pharmacological manipulations, which induce OGG1 acetylation, might be beneficial in the aging process and affect specific diseases where 8-oxoG-mediated apoptosis and mutations are markedly enhanced. Exercise, therefore could decrease the age-associated DNA damage in rats brain, and we have shown earlier that exercise with a huge load did not increase 8-oxoG level in brain of rats.⁵⁰

The findings of several studies indicate that regular exercise acts as a pre-conditioner against oxidative stress. Hence, trained rats suffer less damage during stroke or other oxidative stress-associated challenges.⁵¹

Thus, available data indicate that accumulation of oxidative damage impairs brain function, and exercise, under certain conditions, can attenuate the accumulation of damage causing a decline in function.

4. Neurotrophins, trophic factors, and physiological function

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, memory, locomotion, behaviors, and a wide range of stress responses.⁵² It has been suggested that BDNF regulates brain development, neuroplasticity, neurogenesis, neurite outgrowth, synaptic plasticity, and cell survival.⁵³ The expression and protein content of BDNF have been shown to be up-regulated by

exercise, and oxidative stress.⁵⁴ Exercise does not simply up-regulate the content and expression of *BDNF* in different brain regions, but also impacts downstream effectors of BDNF, namely the transcription factor cAMP response element binding protein (CREB). DNA binding of CREB does not directly translate to gene transcription but activates inducible transcription factors, such as *NF-κB*, *cFos*, and *Jun*, and this trans-activation causes persistent expression of genes. CREB DNA binding sites contribute to the activation of mRNA of *BDNF* transcription and this process can be regulated by ROS. It has been reported that glutamate neurotoxicity and treatment with hydrogen peroxide decreased the DNA binding of CREB and increased the DNA binding of *NF-κB*.⁵⁵ Moreover, it appears that BDNF acts through tyrosine-related kinase B (TrkB) receptors that activate CREB, thus creating a positive loop for the cascades.⁵⁵ Exercise, which enhances the content of BDNF and TrkB, activates CREB and increases the expression of *BDNF* to make the neurons more resistant to oxidative stress, probably by the alteration of redox state in the neurons. On the other hand, when *BDNF* was blocked, the exercise-induced increase in *CREB* mRNA levels, as well as the phosphorylation of CREB, were prevented.^{56,57} It has been shown, that ROS stimulate the expression of *BDNF*, at least in cell culture, and antioxidants prevent this increase.⁵⁸ Relatively short exposure (6 h) of neurons to ROS resulted in activation of *CREB*, while a longer exposure (24 h) suppressed the protein content and mRNA levels of ROS.⁵⁹ In some brain regions, exercise training increases the level of ROS, although the level of oxidative damage does not increase.^{41,60,61} We have recently shown that regular exercise decreased the level of RCD in hippocampus of aging rats.³²

In addition to ROS, nitric oxide might also act as a modulator of exercise-induced changes in BDNF levels. Administration of *L-NAME*, a non-selective nitric oxide synthase inhibitor, has been shown to decrease the activation of CREB,⁶² and the exercise-induced *BDNF* mRNA expression seems to be related to nitric oxide production.⁶³ On the other hand, we could not detect increased nNOS protein content in the brain of exercise-trained and caloric restricted animals (Szabo et al., unpublished data). Thus, the exact regulation pathways by which exercise increase the content and expression of *BDNF*, *CREB* are vague, but it appears that the redox homeostasis could play a curricular role in the regulatory process.

Among the other trophic factors, elevated by exercise, are insulin-like growth factor (IGF-1), and vascular endothelial growth factor (VEGF). It is well established that exercise increases neurogenesis and this is one of the processes by which exercise benefits brain function.⁵³ However, in our recent study the increased level of neurogenesis was observed in IGF-1 treated rats compared to untreated group, but we could not detect differences in spatial memory, assessed by Morris Maze test.⁴⁵ This was an intriguing observation, which questions the dogma that IGF-1 is always neuroprotective and beneficial.

It has been suggested that BDNF is one of the major regulators of neurogenesis. However, the findings of a recent paper indicate that VEGF is also heavily involved in

neurogenesis.^{51,64} The exercise effects seem to be dependent on the dose of exercise on VEGF content and mRNA expression.⁵¹ Recent reports suggest that ROS play an important role in angiogenesis; however, its underlying molecular mechanisms remain unknown. But it is known that VEGF induces angiogenesis by stimulating endothelial cell proliferation and migration.⁶⁵ Therefore, it seems that exercise training could result in better oxygen and fuel supply to the brain.

IGF-1 is essential for nerve growth, neurotransmitter synthesis and release,⁶⁶ and it is believed to be functionally associated with the action of BDNF.⁵¹ IGF-1 may protect from hyperglycemia-induced oxidative stress and neuronal injuries by regulating MMP, possibly by the involvement of uncoupling protein (UCP)-3.⁶⁷ The main functional effects of IGF-1 are not dependent on redox homeostasis, but observations indicate that IGF-1 could act as a regulator of oxidative challenge.

Exercise is a very potent modulator of certain neurotrophins and these agents could be significantly involved in the beneficial effects of exercise on the function of the nervous system. Moreover, exercise-induced alteration of redox balance might be delicately engaged in some of the regulatory pathways.

5. Neurogenesis

Neurons are non-dividing cells, however, it is well established that neuronal precursor cells in the dentate gyrus are able to proliferate throughout the life and differentiate and their progeny can lead to neurogenesis.⁶⁸ Observations suggest that progenitor cells readily respond to changes in energy homeostasis, therefore ischemia/reperfusion, aging and metabolic pathology or even physical exercise can change the rate of neurogenesis. Indeed, precursor cells exhibit high mitotic and potential and ROS are one of the important signals that control their ability to divide and differentiate.⁶⁹ One of the reasons is precursor cells are very sensitive to oxygen level which is suggested to be around 2% in the brain.⁷⁰ Lowering the level of oxygen concentration by transient middle cerebral artery occlusion on rat brain leads to increases in neurogenesis.⁷¹ It has been shown that neuronal precursor cells exhibit about four times higher ROS levels than other cell types, and the concentration of ROS which is dependent on the density of precursor cells is associated with the rate of proliferation.⁶⁹ The fine redox tuning is a necessary modulator of the proliferation of neuronal progenitor cells, and of course the bell-shape dose–response is true to the relation of ROS and neurogenesis.⁷²

The landmark paper of van Praag et al.⁵³ showed that exercise not only improves spatial memory, but also results in neurogenesis. This finding has been confirmed by others.⁷³ Moreover, van Praag et al.⁷⁴ also showed that the newly formed neurons were functional. Hence, a link was established between newly formed neurons and the functional benefits of exercise (see the recent review of Lazarov et al.⁷⁵). However, a recent report has challenged this finding, as the data from this

study showed that exercise was able to improve results on the Morris Maze test, even with inhibition of neurogenesis.⁷⁶

Most studies on neurogenesis have used voluntary running,^{77,78} but studies using enforced running^{79,80} have shown similar results. However, the data from these studies further suggest that voluntary and treadmill running have different effects on brain plasticity in different regions of the brain.⁸¹ Furthermore, the nature of exercise-induced neurogenesis has been shown to be different in mice and rats.⁸² In that study, treadmill running failed to increase the number of BrdU/NeuN positive cells in young and old exercise groups, a finding which differs from most earlier observations (see review by Fabel and Kempermann⁸³). Few data exist on the effects of treadmill running on neurogenesis in healthy rats, and only one study reported unchanged neurogenesis after high intensity enforced exercise,⁸⁴ as observed in the mentioned study. This paucity of available data makes comparisons of treadmill trained rats and aging difficult.

Supplementation of IGF-1 increased the levels of new neuron formation in aged groups, but unexpectedly, eliminated the beneficial effects of exercise on spatial learning.⁴⁵ A recent finding suggests that the administration of anti-IGF-1 antibody to block the function of IGF-1 is not influenced by the time it takes mice to find a hidden platform in the Morris Maze test.⁸⁵ IGF-1 affects exercise-mediated neurogenesis, but brain plasticity could be an IGF-1-dependent and/or IGF-1-independent process.⁸⁵ Indeed, it has been suggested that the beneficial effects of exercise on brain function are partly dependent upon IGF-1.⁸⁶ IGF-1 and insulin act through insulin/insulin resistance (IR) signaling pathway, the activation of which supports neuronal surviving and brain plasticity.⁸⁷ The neuroprotective effects of the IR pathway are well documented,^{54,88} but it has also been shown that insulin injection could impair brain function.^{89,90} Also, a recent paper reports findings similar to ours, namely, that insulin injection eliminates the beneficial effects of exercise as shown on the Morris Maze test and it was suggested that this could be a result of the IR signaling on NMDA receptors.^{89,91} Therefore, the available data suggest that activation of IGF-1/insulin signaling could be both beneficial and harmful, thus, stressing the importance of the very delicate IR signaling in the brain. This finding could also suggest that, while certain IGF-1/insulin signaling has been shown to benefit brain function, insulin resistance is closely related to the etiology of neurodegenerative diseases.

6. Conclusion

There is mounting body of evidence, which suggests that regular exercise improves brain function and causes structural, biochemical and physiological adaptation via different pathways. However, this phenomenon might be also interpreted in a different way: exercise attenuates the inactivity-caused deteriorative effects on the CNS. Either interpretation could be correct, as it appears that ROS, and the changes in redox homeostasis could play a role in the very complex mechanism by which exercise training benefits the brain. The relationship between ROS concentration and brain function can be

characterized by a bell-shape curve, which is the typical curve of hormesis. We suggest, here, that both low and high levels of ROS could impair cell function. Low levels of ROS might cause insufficient gene expression for redox homeostasis and, therefore, impaired response to oxidative challenge, eventually leading to increased vulnerability. On the other hand, high levels of ROS exceed the adaptive tolerance of cells, resulting in significant oxidative damage, apoptosis, and necrosis. Exercise training likely increases the window between the two critical checkpoints (too little and too much) resulting in increased resistance and tolerance against oxidative challenge.

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