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The redox-associated adaptive response of brain to physical exercise

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Abstract
Reactive oxygen species (ROS) are continuously generated during metabolism. ROS are involved in redox signaling, but in significant concentrations they can greatly elevate oxidative damage leading to neurodegeneration. Because of the enhanced sensitivity of brain to ROS, it is especially important to maintain a normal redox state in brain and spinal cord cell types. The complex effects of exercise benefit brain function, including functional enhancement as well as its preventive and therapeutic roles. Exercise can induce neurogenesis via neurotrophic factors, increase capillarization, decrease oxidative damage, and enhance repair of oxidative damage. Exercise is also effective in attenuating age-associated loss in brain function, which suggests that physical activity-related complex metabolic and redox changes are important for a healthy neural system.

Keywords: exercise, oxidative stress, oxidative damage, neurotrophins brain function

Introduction
Brain is an organ which is sensitive to oxidative stress due to its high metabolic rate and iron content. Iron can readily interact with diffusible hydrogen peroxide, resulting in the generation of the extremely reactive hydroxyl radical that mediates oxidative damage to proteins, lipids, and DNA [1–3]. Hydrogen peroxide can be generated by a number of systems, including reactions catalyzed by monoamine oxidase A and B, with a described location of neuronal and glial mitochondrial membranes [4]. Besides the possible iron–hydrogen peroxide interactions, high levels of intracellular Ca²⁺ could be associated with the generation of reactive oxygen species (ROS) in the brain by α-glycerophosphate dehydrogenase [5]. Both inhibition and activation of neurons activate Ca²⁺-traffic, and excess glutamate could result in large increases in ROS production [6,7]. Neuronal membranes are packed with phospholipids containing polyunsaturated fatty acid esters, which are very sensitive to attack by ROS, causing a chain reaction, which generates lipid radicals and extensive membrane damage [8]. NADPH oxidases are potent cellular generators of superoxide including neurons and glias [9]. Increased NADPH oxidase ROS generation can be influenced by free fatty acids, especially mono and polyunsaturated long-chain fatty acids, which could increase ROS production [10]. In an experimental model using mice, it has been shown that stress upregulated NADPH, which was associated with an increased expression of the subunits of p47phox and p67phox, resulting in an elevated production of superoxide [11].

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 [12]. This observation suggests that ROS-mediated events distant from brain can cause oxidative stress to the brain via circulation [13].

It is well established that oxidative stress is closely linked to the pathology of a variety of neurodegenerative diseases, including age-associated disorders [14–16]. Due to its high reactivity, short lifespan, and the problems related to the direct detection of ROS, the amount of ROS 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 [3,17].

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, are suggested to be causative factors in the progress of specific diseases [18–20]. However, besides ROS-associated neurodegeneration, which could be a result of significant ROS load, moderate amounts of these reactive species could have beneficial effects on signaling, neurogenesis, and in epigenetic regulation [21].
For instance, during physical exercise, there is an increased generation of ROS [21], 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, type II diabetes, etc. [22]. The systemic effects of exercise include the nervous system as well, and it is clear that regular exercise beneficially affects brain function, and could play an important preventive and therapeutic role in stroke, Alzheimer’s (AD), and Parkinson diseases (PD) [16,23,24]. 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 proteasomes and nephrilysin [25–31]. The present review focuses on oxidative challenges related to the effects of exercise, and attempts to summarize the available knowledge in this area.

**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 10⁶ to 10⁷ in a base/cell as a result of the antioxidant scavenging system [32]. The findings of an early study suggested that exercise (voluntary running) results in oxidative damage to low vitamin E-fed animals [33]. Swimming–exposed rats suffered significant increases in lipid peroxidation, and glutathione peroxidase (GPX) activity was also increased [34], while 6-hydroxymelatonin supplementation prevented oxidative lipid damage. On the other hand [35], 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 results in increased activities of superoxide dismutase (SOD) and GPX [35]. We have previously reported that a single bout of exercise, which caused oxidative damage to skeletal muscle [36], liver, and kidney [37], did not cause damage to the brain [36]. Further, the activities of antioxidant enzymes (Cu, Zn-SOD, Mn-SOD, catalase [CAT], and 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 [38]. In a model of stroke-prone spontaneously hypertensive rats, it has been shown that exercise training can inhibit sympathetic nerve activity by decreasing oxidative stress through blocked angiotensin II type I receptor A [39]. In our recent study on middle-aged rats, it was found that regular exercise increases the content of Cu, Zn-SOD, GPX, and peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) and the latter transcription co-activator is important since it is involved in mitochondrial biogenesis [40]. PGC-1α activation could result in a decreased oxidative challenge, either by upregulation of antioxidant enzymes including GPX and Mn-SOD, and/or by an increased number of mitochondria that allow lower levels of respiratory activity for the same degree of ATP generation. Indeed, PGC-1α knock-out mice are much more sensitive to the neurodegenerative effects of oxidative stressors, affecting the substantia nigra and hippocampus, respectively, than wild mice [41]. A nearly linear relationship exists between the levels of PGC-1α and the rate of protection of neural cells, in culture, from oxidative-stressor-mediated death [41]. Studies suggest that treadmill running induces the expression of PGC-1α which is heavily involved in the exercise-induced mitochondrial biogenesis in the brain of rats after ischemia, which has been used to mimic stroke [42,43]. Weekly administration of human mitochondrial transcription factor A (TFAM) was used to cope with the age-associated decline in mitochondrial function and the results revealed increased expression of PGC-1α in the brain and decreased oxidative stress [44].

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

**Oxidative damage and functional changes**

The first study to describe a relationship between the accumulation of oxidative damage to proteins, reactive carboxylative (RCD), and certain brain functions was age related [45]. A spin-trapping agent of N-t-butyl-phenylnitromine (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 in the brain [45]. 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 [46,47], the results were later confirmed by other laboratories [48]. Liu et al. [49] immobilized rats overnight and this resulted in increased oxidative damage to lipids, proteins, and DNA in the brains of the 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 [50]. 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 concurrence with Liu et al., and we found that exercise after immobilization appeared to decrease damage.

Chronic exercise training in rats did not cause significant alteration of lipid peroxidation levels in the brain [51]. On the other hand, the supplementation of vitamin
C elevated the oxidative damage of lipids [52]. Ogonovszky et al. [53] 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 rat brains were treated with N-methyl-D-aspartate (NMDA) to induce lesion, a method used to mimic AD, it was found that exercise alone and with supplementation of nettle reduced ROS formation and levels of carbonyl groups [54]. It was also shown in that study that lower levels of oxidative damage were associated with better function, as assessed by the passive avoidance test.

Oxidative damage has been associated with poor physiological function of the brain. We have 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 [51]. The activation of proteasome in the brain could be an important benefit of exercise training, since it has been recently found that inhibition of proteasome results in accumulation of beta-amyloids [55]. Using 3xTg-AD mice as a model of AD, it has been shown that exercise alone and with a combination of melatonin was neuroprotective [56].

Accumulation of hyperphosphorylated tau proteins is also hallmark of AD. Lysine residues of tau, especially Lys311, have ubiquitination sites, indicating interaction of tau aggregation by oligomerization and ubiquitination-mediated degradation by the proteasome system [57]. In addition, proteasome could be important for learning, since inhibition of proteasome by the injection of the inhibitor lactacystin into the CA1 region of the hippocampus blocks long-term memory in an avoidance task [58]. Another proteasome inhibitor, MG132, impaired long-term potentiation, suggesting proteasome could play a role in shaping and strengthening synapses [59]. Besides AD, the progress of PD could be also related to proteasome. The results of a recent study on zebrafish suggest that inhibition of proteasome results in the appearance of cardinal features of PD including locomotor dysfunction, selective dopaminergic cell loss, and inclusive body formation [60]. Although, these data are not from mammals, the findings suggest that elevated activity of proteasome might be important in counterbalancing increased levels of PD. Overall, these data suggest that exercise-mediated regulation of proteasome in the brain could be related to a wide range of neuroprotective mechanisms.

Oxidative modification of DNA could lead to increased apoptosis. Impaired function and accumulation of DNA damage in neurons have been suggested as major factors related to brain aging and neurodegenerative diseases [61,62]. Koltsi et al. observed that aging increases the levels of 8-oxoguanine (8-oxoG) in hippocampus of rats [3], which potentially could jeopardize brain function [63,64]. 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 is increased in aging rats, which could be a cellular attempt to combat the enhanced levels of 8-oxoG, although in this case, without significant success [3].

Acetylation of OGG1 is a posttranslational activation of incision activity of this enzyme [65,66]. Thus, the age-associated increase in 8-oxoG levels could be due to the large decrease in acetylation of OGG1 [3]. On the other hand, exercise with IGF-1 supplementation increases the levels of OGG1 acetylation. It has also been shown that acetylation of OGG1 takes place in vivo and exercise increases the rate of acetylation. Acetylation of OGG1 is carried out by p300 [65], and our data suggest that sirtuins could be potential deacetylases of OGG1. It has been repeatedly shown that exercise mediates the acetylation level of OGG1 and the activity of this enzyme [67–69]. The findings of several studies indicate that regular exercise acts as a preconditioner against oxidative stress [70–72]. Hence, trained rats suffer less damage during stroke or other oxidative stress-associated challenges [73]. 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 (Figure 1).

**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 seminal role in the learning process, memory, locomotion, behavior, and in a wide range of stress responses [74]. It has been suggested that BDNF regulates brain development, neuroplasticity, neurogenesis, neurite outgrowth, synaptic plasticity, and cell survival [75]. BDNF can activate the protein kinase B (PKB, Akt)/cAMP response element binding protein (CREB) and mitogen-activated protein kinase (MAPK)/CREB pathways [76], the signaling of which are involved in synaptogenesis [77] and long-term memory formation [78]. It was recently reported that treadmill training increases the level of BDNF and the signaling of PKA/Akt/CREB and MAPK/CREB pathways in the hippocampus of middle-aged and old rats [79]. Indeed, the expression and protein content of BDNF have been shown to be upregulated by exercise and oxidative stress [80]. Exercise does not simply upregulate the content and expression of BDNF in different brain regions, but also impacts downstream effectors of BDNF, such as CREB.

DNA binding of CREB does not directly translate to gene transcription but activates inducible transcription factors such as NF-kB, cFos, and Jun and this transactivation causes persistent expression of genes [81]. CREB DNA binding sites contribute to the activation of mRNA of BDNF transcription and this process can be regulated by ROS [82,83]. It has been reported that glutamate neurotoxicity and treatment with hydrogen peroxide decreases the DNA binding of CREB and increases the DNA binding of NF-kB [84]. Moreover, it appears that BDNF acts through tyrosine-related kinase B (TrkB) receptors that activate CREB, thus creating a positive loop for the cascades [84]. Exercise 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 [17]. However, when
BDNF is blocked, the exercise-induced increase in CREB mRNA levels, as well as the phosphorylation of CREB, are curtailed [85,86]. ROS stimulate the expression of BDNF, at least in cell culture, and antioxidants prevent this increase [87]. Relatively short exposure (6 h) of neurons to ROS results in activation of CREB, while a longer exposure (24 h) suppresses the protein content and mRNA levels of ROS [88]. In some brain regions, exercise training increases the levels of ROS, although the level of oxidative damage does not increase [53,89,90].

In addition to ROS, nitric oxide might act as a modulator of exercise-induced changes in BDNF levels. Administration of L-NAME, a nonselective nitric oxide synthase inhibitor, has been shown to decrease the activation of CREB [91], and the exercise-induced BDNF mRNA expression seems to be related to nitric oxide production [92]. Thus, the exact regulation pathway by which exercise increases the content and expression of BDNF, CREB is vague, but it appears that the redox homeostasis could play a significant 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). Recent reports indicate that exercisemediated induction of VEGF levels is regulated by the activation of mammalian Target of Rapamycin (mTOR) [93].

It is also well established that exercise increases neurogenesis, one of the processes by which exercise benefits brain function [75]. However, in our recent study, increased levels of neurogenesis were observed in IGF-1 treated rats, but differences in spatial memory, as assessed by the Morris maze test, were not detected [3]. This intriguing observation 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. VEGF is also heavily involved in neurogenesis [73,94] and exercise effects seem to be dependent on the dose of exercise relative to VEGF content and mRNA expression [73]. Recent reports suggest that ROS play an important role in angiogenesis; however, its underlying molecular mechanisms remain unknown [93,95]. But it is known that VEGF induces angiogenesis by stimulating endothelial cell proliferation and migration [96]. Therefore, it seems that exercise training could result in greater oxygen and fuel supply to the brain.

IGF-1 is essential for nerve growth, neurotransmitter synthesis and release [97], and believed to be functionally associated with the action of BDNF [73]. IGF-1 may protect from hyperglycemia-induced oxidative stress and neuronal injuries by regulating MMP, possibly by the involvement of uncoupling proteins (UCP)-3 [98]. 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 in redox balance might be delicately engaged in some of the regulatory pathways.

**Neurogenesis**

Neurons are nondividing cells. However, it is well established that neuronal precursor cells in the dentate gyrus are able to proliferate throughout life and differentiate, and
their progeny can lead to neurogenesis [99]. Observations suggest that progenitor cells readily respond to changes in energy homeostasis [100]. Therefore, ischemia/reperfusion, aging and metabolic pathology or even physical exercise can change the rate of neurogenesis [67,101].

Indeed, progenitor cells exhibit high mitotic potential and ROS are one of the important signals that control their ability to divide and differentiate [102]. One of the reasons for this is that precursor cells are very sensitive to oxygen levels, which are suggested to be around 2% in the brain [103]. Lowering the level of oxygen concentration by transient middle cerebral artery occlusion in rat brain leads to increases in neurogenesis [104]. It has been shown that neuronal precursor cells exhibit about four times higher ROS levels than that of other cell types, and the concentration of ROS, which is dependent on the density of precursor cells is associated with the rate of proliferation [102]. The fine redox tuning is a necessary modulator of the proliferation of neuronal progenitor cells, and, of course, the bell-shaped dose response is true to the relationship between ROS and neurogenesis [105].

The landmark paper of van Praag et al. [75], showing that exercise not only improves spatial memory but also results in neurogenesis, has been confirmed by others [106], van Praag et al. [107] 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. [108]). 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 [109].

Most studies on neurogenesis have used voluntary running [110,111], but studies using enforced running [112,113] have shown similar results. The data from these studies further suggest that voluntary and treadmill running have different effects on brain plasticity in different regions of the brain [114]. Furthermore, the nature of exercise-induced neurogenesis has been shown to be different in mice and rats [115]. 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 Kempermann [116]). Few data exist on the effects of treadmill running on neurogenesis in healthy rats, and only one study has reported unchanged neurogenesis after high intensity, enforced exercise [117]. This paucity of available data makes comparisons of treadmill-trained rats and aging difficult. Exercise-induced neurogenesis can take place after middle cerebral artery occlusion along with enhanced neurological function [118]. In this study the exercise program increased the content of IGF-1 positive cells. IGF-1 is considered to be neuroprotective [119]. Indeed exercise training increases the levels of IGF-1 and p-Akt [120], indicating that activation of this system could be involved in neuroprotection, since supplementation of IGF-1 improved spatial learning [3]. 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

Figure 2. Exercise can lead to neurogenesis, increased degradation of oxidized proteins, and beta amyloids. Exercise-induced BDNF levels can modulate a wide range of neuroprotective effects.
find a hidden platform in the Morris maze test [121]. IGF-1 affects exercise-mediated neurogenesis, but brain plasticity could be an IGF-1-dependent and/or-independent process [121]. Indeed, it has been suggested that the beneficial effects of exercise on brain function are partly dependent upon IGF-1 [122]. IGF-1 and insulin act through insulin/insulin resistance (IR) signaling pathway, the activation of which supports neuronal survival and brain plasticity [123]. The neuroprotective effects of the IR pathway are well-documented [80,124], but it has also been shown that insulin injection could impair brain function [125,126]. It is known 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 [127] (Figure 2). Therefore, the available data suggest that activation of IGF-1/insulin signaling could be both beneficial and harmful, thus emphasizing 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.

Conclusion

Accumulating evidence suggests that regular exercise improves brain function and causes structural, biochemical, and physiological adaptations via a wide range of different pathways (Figure 1). It appears that ROS and changes in redox homeostasis could play a role in the very complex mechanism by which exercise training benefits brain. The relationship between ROS concentration and brain function can be characterized by a bell-shaped 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 result in 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 probably increases the window between the two critical checkpoints (too little and too much), resulting in increased resistance and tolerance to oxidative challenge.

References


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Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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Exercise and brain function

between oxidative stress and ROS-dependent adaptive signaling.


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