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Physical exercise, reactive oxygen species and neuroprotection

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ABSTRACT

Regular exercise has systemic beneficial effects, including the promotion of brain function. The adaptive response to regular exercise involves the up-regulation of the enzymatic antioxidant system and modulation of oxidative damage. Reactive oxygen species (ROS) are important regulators of cell signaling. Exercise, via intensity-dependent modulation of metabolism and/or directly activated ROS generating enzymes, regulates the cellular redox state of the brain. ROS are also involved in the self-renewal and differentiation of neuronal stem cells and the exercise-mediated neurogenesis could be partly associated with ROS production. Exercise has strong effects on the immune system and readily alters the production of cytokines. Certain cytokines, especially IL-6, IL-1, TNF-α, IL-18 and IFN gamma, are actively involved in the modulation of synaptic plasticity and neurogenesis. Cytokines can also contribute to ROS production. ROS-mediated alteration of lipids, protein, and DNA could directly affect brain function, while exercise modulates the accumulation of oxidative damage. Oxidative alteration of macromolecules can activate signaling processes, membrane remodeling, and gene transcription. The well known neuroprotective effects of exercise are partly due to redox-associated adaptation.

1. Introduction

During the evolution of *Homo sapiens*, daily physical activity was an important part of life, because of the need for traveling, hunting, gathering, fighting and escaping. Therefore, for survival, a high level of physical fitness could be essential [1]. From the second half of the 20th century the contribution of physical fitness to survival success started to decline in an exponential manner. As a result, physical inactivity became a part of everyday life [2]. Moreover, physical inactivity emerged as a risk factor for a wide range of diseases, resulting in a huge burden on the health care system. These diseases include cardiovascular diseases [3], metabolism related diseases [4], certain types of cancer [5] and neurodegenerative diseases [6].

Physical exercise can significantly increase the metabolic rate, and in extreme situations, the energy expenditure can be as high as 6–7000 kcal/day, the arterio-venous oxygen difference can increase 3-fold, blood flow to tissues can increase 30 fold, and the oxygen flux in working skeletal muscle can increase by 100-fold [7]. Metabolic changes of this magnitude would affect all organs. However, it has been shown that exercise, even of moderate intensity, has systemic effects on the body including the central nervous system. Therefore, it cannot be excluded that, besides the metabolic effects of exercise, other exercise-associated factors play a role in the adaptive effects of exercise. Although the generation of reactive oxygen species (ROS) is related to metabolism, this is not always the case. Some of the ROS, for example, nitric oxide and hydrogen peroxide, with moderate reactivity, are important for

Abbreviations: (AP-1), activator protein 1; (KGDHC), α-ketoglutarate dehydrogenase; (AD), Alzheimer's disease; (APE1), apurinic/apyrimidinic endonuclease 1; (BER), base excision repair; (iPLA), Ca(2+)-independent phospholipase A(2); (CREB), cyclic AMP response element-binding protein; (EPR), electron paramagnetic resonance; (ERK), extracellular-signal-regulated kinases; (FOXO), forkhead box O; (IGF-1), insulin like growth-factor-1; (IL-1), interleukin-1; (IL-6), interleukin-6; (IL-8), interleukin-8; (IFN gamma), interferon-gamma; (LPS), lipopolysaccharide; (mTOR), mammalian target of rapamycin complex 1; (SOD2), manganese-dependent superoxide dismutase; (MAPK), mitogen-activated protein kinases; (NGF), nerve growth factor; (NSCs), neuronal stem cells; (BDNF), neurotrophic factor; (NF-kB), nuclear factor kappa-light-chain-enhancer of activated B cells; (PGC-1α), proliferator-activated receptor gamma coactivator 1-alpha; ROS, reactive oxygen species; (SIRT1), silent mating-type information regulation 2 homolog-1; SWI/SNF, (SWItch/sucrose nonfermentable); (TNF-α), tumor necrosis factor alpha; (TrkB), tyrosine receptor kinase B; (OGG1), 8-oxoguanineDNA glycosylase

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cell signaling [1]. Those with high reactivity, such as superoxide, hydroxyl radical or peroxynitrite, are considered to be more dangerous to the cells, causing structural and functional alteration of macro-molecules leading to neurodegeneration [8].

The resistance of brain to oxidative stress is moderate, due to its high metabolic rate and the significant levels of iron and copper found in this organ. It appears that physical exercise can readily alter the level of ROS and thus influence a wide range of signaling processes, and therefore, the function of this organ. The present review aims to summarize the ROS-dependent effects of physical exercise on brain function and point out that moderate levels of oxidative damage might be a necessary part of the adaptive response to exercise and even important to survival.

1.1. Exercise, ROS production, and endogenous antioxidant defense

In all likelihood, during evolution, humans have evolved via a mechanism by which muscle contraction-induced ROS stimulates the level of glucose transport to meet the need for increased metabolism, as well as other metabolic adaptations to exercise [9]. However, it is still unclear whether moderate levels of ROS play a role in glucose uptake in the brain. It is well known that the metabolic demand with intensive exercise is different in skeletal muscle and brain, even though there is an increase in cerebral blood flow to and cerebral metabolism in the brain [10–12]. With high intensity exercise, skeletal muscle produces increased lactate, which is taken up by the brain and used as an energy source [12]. Lactate can impact redox signaling since it could be oxidized to pyruvate or exchanged to pyruvate, which could alter the cellular redox milieu at micromolar levels [13]. Changes in the redox state at micro- or nano-molar levels could be sufficient to result in activation of redox sensitive pathways.

There are a number of sources of ROS production in neuronal cells, the most important being the mitochondrial electron transport chain. The highest rate of ROS production in brain mitochondria has been found in complex I and complex III [14]. Based on the results of studies which used inhibitors of different electron chain complexes of brain mitochondria, complex III appears to be the most powerful ROS generator [15]. As a result of aging, significant increase has been found in ROS production in brain mitochondria of dogs [16]. The ROS generation of mitochondria is closely related to the nature of substrates that feed the respiratory chain: the availability of oxygen, pH, mitochondrial membrane potential or the Ca^{++} content of surrounding cellular environment [17] and these factors are all influenced by neurodegenerative diseases [18,19] or by physical exercise [20–22]. It has been shown that repeated stress causes depressive behavior with the up-regulation of the subunits of NADPH-oxidase, which is a powerful ROS generator [23]. Regular exercise has an anti-depressive role [24] and one of the acting points could be the down-regulation of NADPH oxidase in the brain [25].

Monoamine oxidases A and B, are located in neuronal and glial mitochondrial membranes. Monoamine oxidases, especially A, interact with dopamine, serotonin, or noradrenaline, among other monoamids, and the deamination of these monoamids generates hydrogen peroxide [26], the molecule that in a dose-dependent manner is important to redox signaling but which, with interaction with iron, could be deleterious to cells. Regular exercise-mediated down-regulation of monoamine oxidase A in heart and brain is believed to be cardio and neuro-protective [27–29].

Besides the possible iron–hydrogen peroxide interactions, Ca^{++}-mediated ROS generation is also a potent source of ROS in the brain. Both inhibition and activation of neurons activates Ca^{++}-traffic, and the excess of glutamate could result in large increases in ROS production [30,31]. It has been demonstrated that a massive Ca^{++} load can stimulate ROS production through the activation of calpain and xanthine oxidase (Fig. 1) [32].

The enzyme complex of α-ketoglutarate dehydrogenase (KGDHC) is involved in the Krebs cycle, glutamate removal, and hence metabolism and detoxification. KGDHC is very sensitive to oxidative modification and is inhibited by a wide range of oxidants such as NO, H_2O_2, and hypochlorite. Moreover, it has been shown that peroxynitrite also inhibits KGDHC [33]. Down regulation of KGDHC is associated with increased ROS production, oxidative damage and a wide range of diseases including Alzheimer's and Parkinson's [34]. The activity of KGDHC has been shown to be very closely related to maximal oxidative metabolism. The relationship is actually closer than citrate synthase, or succinate dehydrogenase [35], and KGDHC can be readily induced by exercise training [36]. Needless to say, acute and regular physical exercise influence the redox milieu of cells in the central nervous system, and partially regulate important neuronal processes.

As mentioned above, mitochondria are a dominant source of ROS, and it is well known that regular exercise has measurable effects on the mitochondrial network and ROS production. Regular, high intensity treadmill running has been shown to result in increased mitochondrial biogenesis in 21-month-old C57BL mice [37]. An increased number of mitochondria, at the same level of energy production, would work at a lower respiration rate, and thus generate lower levels of ROS [1]. Mitochondrial biogenesis is a consequence of the activation of proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and regular exercise has been shown to activate PGC-1α [38], which, besides its crucial role in mitochondrial biogenesis, is also involved in the activation of manganese-dependent superoxide dismutase (SOD2) [39]. Indeed, it is well established that regular exercise results in increased activity of antioxidant enzymes in different organs, including brain [38,40–42].

The activities of oxidative damage repairing/degrading enzymes, which can be considered as a second line of antioxidant defense, are also up-regulated with exercise training. We have shown that regular exercise decreases the amount of carbonyl bonds in the amino acid residues of proteins of rat brain, which could be the consequence of increased activity of the proteasome complex [43–45]. Degradation of oxidatively-damaged proteins is important in the prevention of a significant accumulation of these "junk" proteins, which impair cellular function. Interestingly, it has been shown that systemic inhibition of proteasome leads to the appearance of Parkinson-related diseases, including clinical symptoms of locomotor dysfunction, selective dopaminergic cell loss, and inclusion body formation [46]. Similar phenomena have been reported for Alzheimer's disease (AD), where proteasome inhibition results in increased tau phosphorylation and AD pathology [47]. In addition, it has been shown that Abeta oligomers inhibit proteasome, which can cause the accumulation of Abeta and tau proteins and the pathogenesis of AD [48]. These results indicate that exercise-associated increases in proteasome might be an important means by which exercise decreases the incidence of AD.

We and others have shown that exercise could increase the activity of base excision repair (BER) enzymes in skeletal muscle [49–54], and hence, alter DNA purity. There are few studies which have investigated DNA repair in the brain as a consequence of exercise training. We have investigated the effects of moderate to severe exercise training and overtraining on oxidative damage and repair in the brain. Interestingly, our results revealed that even severe training or overtraining did not increase DNA damage in the brain nor alter the activity of 8-oxoguanineDNA glycosylase (OGG1), the enzyme which repairs 8-oxo-7,8-dihydroguanine [45]. Acetylation of OGG1 increases the activity of this repair enzyme, and we observed that exercise with IGF-1 supplementation increased the activity of OGG1 in the hippocampus of young, but not