REVIEW / SYNTHÈSE

Effects of exercise on brain function: role of free radicals

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Abstract: Reactive oxygen species (ROS) are continuously generated during aerobic metabolism. Certain levels of ROS, which could be dependent on the type of cell, cell age, history of ROS exposure, etc., could facilitate specific cell functions. Indeed, ROS stimulate a number of stress responses and activate gene expression for a wide range of proteins. It is well known that increased levels of ROS are involved in the aging process and the pathogenesis of a number of neurodegenerative diseases. Because of the enhanced sensitivity of the central nervous system to ROS, it is especially important to maintain the normal redox state in different types of neuro cells. In the last decade it became clear that regular exercise beneficially affects brain function as well, and can play an important preventive and therapeutic role in stroke and in Alzheimer's and Parkinson's 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 recepetor kinase B, and cAMP response element binding protein, resulting in better function and increased neurogenesis. The enhanced activities of proteasome and neprilysin result in decreased accumulation of carbonyls and amyloid beta-proteins, as well as improved memory. 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, and facilitates recovery from oxidative stress.

Key words: exercise, oxidative stress, oxidative damage, neurotrophins brain function.

Résumé : Au cours du métabolisme aérobie, il y a une production continue d'espèces oxygénées radicalaires (ROS). Un certain niveau de ROS, selon la nature et l'âge des cellules, les antécédents d'exposition aux ROS, etc., pourrait favoriser des fonctions cellulaires spécifiques. Effectivement, les ROS stimulent un certain nombre de réponses au stress et activent chez les gènes l'expression d'un large éventail de protéines. Dans le processus du vieillissement et de la pathogenèse de plusieurs maladies dégénératives, on observe la présence de plus hautes concentrations de ROS. Comme le système nerveux central (CNS) affiche une plus grande sensibilité aux ROS, il importe de maintenir l'activité d'oxydo-réduction dans les diverses variétés de cellules nerveuses. Au cours de la dernière décennie, les études ont démontré le rôle positif de l'activité physique sur les fonctions cérébrales ainsi qu'un rôle préventif et thérapeutique chez des patients ayant eu un accident vasculaire cérébral ou souffrant de la maladie d'Alzheimer ou de Parkinson. Les effets de l'activité physique, quoique complexes, pourraient inclure la neurogenèse au moyen de facteurs neurotrophiques, une augmentation de la capillarisation, une diminution des lésions dues aux oxydations et une plus grande dégradation protéolytique par le protéasome et la néprilysine. Des observations faites dans nos laboratoires et ailleurs indiquent que la modulation par l'activité physique des niveaux de ROS joue un rôle dans le contenu protéique et l'expression des facteurs neurotrophiques dérivés du cerveau (BDNF), de la kinase B du récepteur de la tyrosine (TrkB) et de la protéine CREB (« cAMP response element binding protein »), ce qui améliore les fonctions et favorise la neurogenèse. L'augmentation de l'activité du protéasome et de la néprilysine minimise l'accumulation de carbonyles et de protéines bêta-amyloïdes et améliore la mémoire. La modulation de l'activité d'oxydo-réduction apportée par l'activité physique constituerait un bon moyen de stimuler les fonctions cérébrales, d'augmenter la résistance au stress oxydatif et de faciliter la récupération consécutive au stress oxydatif.

Mots-clés : activité physique, stress oxydatif, lésion oxydative, neurotrophines, fonctions cérébrales.

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Introduction

Reactive oxygen species (ROS) are normal products of aerobic metabolism. ROS in a certain concentration, which could be dependent on the kind of cell, cell age, history of ROS exposure, etc., could mediate certain cell functions. Indeed, ROS are necessary activators of stress responses, and activate gene expression for a wide range of proteins. Naturally, ROS induce the antioxidant enzyme activity—content, heat-shock proteins, repair proteins, and inflammation-related proteins, and affect other housekeeping proteins as well. It seems to be indisputable that ROS above the cell-dependent tolerance level can induce significant oxidative damage to macromolecules, jeopardize the vitality of cells, and lead to apoptosis and necrosis. Cells are very well accustomed to ROS, which actually can result in an adaptive response and increased resistance towards the damaging effect of ROS.

It is well known that increased levels of ROS are involved in the aging process and the pathogenesis of a number of neurodegenerative diseases (Halliwell and Gutteridge 1985). The central nervous system contains a significant amount of iron, and the interaction of hydrogen peroxide with iron could be quite dangerous because of the generation of highly reactive hydroxyl radicals that can yield serious damage to DNA and proteins (Halliwell and Gutteridge 1985). Therefore, because of the enhanced sensitivity of the central nervous system to ROS, it is especially important to maintain the normal redox state in different types of neuro cells.

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 kinds of cancers, type 2 diabetes, etc. (Radak et al. 2005). In the 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 and in Alzheimer's and Parkinson's diseases (Mattson 2005; Mattson and Wan 2005; Mattson and Magnus 2006; Stummer et al. 1995). 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 (Adlard and Cotman 2004; Adlard et al. 2005; Cotman and Berchtold 2002; Cotman and Engesser-Cesar 2002; Johnson and Mitchell 2003; Molteni et al. 2004; Neeper et al. 1995; Oliff et al. 1998; Lazarov et al. 2005). The present review focuses on the 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 (Devi and Kiran 2004; Radak et al. 2001*c*). 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 (Beckman and Ames 1998).

The findings of an early study suggested that exercise, in the form of voluntary running, results in oxidative damage to low vitamin E fed animals (Suzuki et al. 1983). Swimming-exposed rats suffered significant increase in lipid peroxidation, and glutathione peroxidase (GPX) activity was also increased (Hara et al. 1997), whereas 6-hydroxymelatonin supplementation prevented oxidative lipid damage. On the other hand, Somani et al. (1995) noted that the activities of antioxidant enzymes were dependent on the 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 (Somani et al. 1995). Meanwhile, we have reported that a single bout of exercise, which caused oxidative damage to skeletal muscle, liver, and kidney (Radak et al. 1996), did not cause damage to the brain. Furthermore, the activities of antioxidant enzymes (Cu, Zn-superoxide dismutase (SOD), Mn-SOD, catalase, 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, catalase, or GPX in the brain of rats. However, rats with steptozotocin-induced diabetes have shown decreased Cu, Zn-SOD, and GPX activities in the brain of exercise-trained animals (Özkaya et al. 2002).

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.

Oxidative damage and functional changes

The first study to describe a relationship between the accumulation of oxidative damage to proteins, reactive carbonyl derivative (RCD), and certain brain functions was an age-related study (Carney et al. 1991). A spin trapping agent, *N*-t-butyl-phenylnitrone, 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 Moris maze test. Although the findings of this study were questioned at the time by Cao and Cutler (1995*a*, 1995*b*), the results of the original study were later confirmed by other laboratories (Foster 2006).

Liu et al. (1996) immobilized rats overnight, and this resulted in increased oxidative damage of lipids, proteins, and DNA in the brain 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 (Radak et al. 2001*a*). We then added groups that 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 et al. (1996), and 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 the protea-

some complex, and improved brain function (Radak et al. 2001*b*). Chronic exercise training, using a rat model, did not cause significant alteration of lipid peroxidation levels in the brain of the rats. On the other hand, the supplementation of vitamin C elevated the oxidative damage of lipids (Coskun et al. 2005). Ogonovszky et al. (2005*a*) subjected rats to moderate training, very hard training, and overtraining, and found, even with very hard training and overtraining, beneficial effects on brain function and lowered accumulation of RCD. The finding of a recent investigation, in which transgenic mice to accumulate beta-amyloid proteins were used, revealed that voluntary exercise decreases the accumulation of beta-amyloid in the brain (Lazarov et al. 2005). Moreover, it was also observed that exercise increased the activity of neprilysin, which is responsible for the degradation of beta-amyloids (Lazarov et al. 2005).

The content of 8-oxoguanine was not significantly altered by the overtraining protocol, and the activity of 8-oxoguanine DNA glycosylase 1 (this enzyme specifically targets the 8-oxoguanine modification on the DNA) was also not changed in the crude cell extract (Ogonovszky et al. 2005*b*). We recently evaluated the activity of the DNA damage–repair enzyme of 8-oxoguanine DNA glycosylase 1 in the nucleus and mitochondria of trained and detrained rats and did not detect any significant alterations (Radak et al. 2006).

The findings of several studies indicate that regular exercise acts as a preconditioner against oxidative stress. Hence, trained rats suffer less damage during stroke or other oxidative stress-associated challenges (Ding et al. 2006; Engesser-Cesar et al. 2005). We attempted to mimic some characteristics of Alzheimer's disease; that is, causing lesions by the injection of *N*-methyl-D-aspartate into the brain (Toldy et al. 2005). Exercise and nettle supplementation significantly reduced the ROS content, decreased oxidative protein damage, and modulated the activity of redox sensitive transcription factors (Toldy et al. 2005; A. Toldy et al. unpublished).

Data indicate that accumulation of oxidative damage impairs brain function and that exercise under certain conditions can attenuate the accumulation of oxidative damage.

Neurotrophins, trophic factors, and physiological function

Brain-derived neurotrophic factor (BDNF) is one of the most versatile and important neurotrophic factors in the brain. It plays a critical role in the learning process, memory, locomotion, behaviors, and a wide range of stress responses (Barde 1989). It has been suggested that BDNF regulates brain development, neuroplasticity, neurogenesis, neurite outgrowth, synaptic plasticity, and cell survival (van Praag et al. 1999; Berchtold et al. 2005). The expression and protein content of BDNF have been shown to be upregulated by exercise and oxidative stress (Mattson et al. 2004). Exercise does not simply upregulate 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-kB, cFos, and Jun, and this transactivation 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 was recently reported that glutamate neurotoxicity and treatment with hydrogen peroxide decreased the DNA binding of CREB and increased the DNA binding of NF-kB (Zou and Crews 2006). Moreover, it appears that BDNF acts through TrkB receptors that activate CREB, thus creating a positive loop for the cascades (Zou and Crews 2006). Exercise, which enhances the content of BDNF and tyrosine receptor kinase B, 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 phophorylation of CREB, were prevented (Vaynman et al. 2003, 2004). It has been shown that ROS stimulate the expression of BDNF, at least in cell culture, and antioxidants prevent this increase (Wang et al. 2006). 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 (Pugazhenthi et al. 2003). In some brain regions, exercise training increases the level of ROS, although the level of oxidative damage does not increase (Ogonovszky et al. 2005*a*; Toldy et al. 2005; Szabo unpublished; Siamilis unpublished).

In addition to ROS, nitric oxide might also act as a modulator of exercise-induced changes in BDNF levels. Administration of N(G)-nitro-L-arginine methyl ester, a nonselective nitric oxide sythase inhibitor, has been shown to decrease the activation of CREB (Park et al. 2004), and the exercise-induced BDNF mRNA expression seems to be related to nitric oxide production (Chen et al. 2006). On the other hand, we could not detect an increased neuronal nitric oxide synthase protein content in the brain of exercise-trained and caloric-restricted animals (Szabo et al. unpublished). Thus, the exact regulation pathways by which exercise increases the content and expression of BDNF and CREB are vague, but it appears that the redox homeostasis could play a critical role in the regulation 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 (van Praag et al. 1999). 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 (Fabel et al. 2003; Ding et al. 2006). The exercise effects on VEGF content and mRNA expression seem to be dependent on the dose of exercise (Ding et al. 2006). Recent reports suggest that ROS play an important role in angiogenesis; however, its underlying molecular mechanisms remain unknown. Nonetheless, it is known that VEGF induces angiogenesis by stimulating endothelial cell proliferation and migration (Ushio-Fukai and Alexander 2004). Therefore, it seems that exercise training could result in better oxygen and fuel supply to the brain.

IGF-1 is essential for nerve growth, as well as neurotransmitter synthesis and release (Anlar et al. 1999), and it is be-

lieved to be functionally associated with the action of BDNF (Ding et al. 2006). IGF-1 may protect from hyperglycemia-induced oxidative stress and neuronal injuries, by regulating mitochondrial inner membrane potential, possibly by the involvement of uncoupling protein 3 (Gustafsson et al. 2004). 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.

Conclusions

There is a mounting body of evidence that suggests regular exercise improves brain function and causes structural, biochemical, and physiological adaptations via different pathways. However, this phenomenon might be also interpreted in a different way: exercise attenuates the inactivity-caused deteriorative effects on the central nervous system. 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-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, 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 2 critical checkpoints (too little and too much), resulting in increased resistance and tolerance against oxidative challenge. Exercise can influence the ROS generation in the brain via Ca^{2+}-dependent pathways, which might be linked to the activity of neurons. In addition, oxidizing enzymes, cytokines, and mitochondria are potent generators of ROS in the brain during exercise.

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