Effects of physical exercise over the redox brain state

Aderbal S. Aguiar Jr.[1] and Ricardo A. Pinho[1]

ABSTRACT

Physical activity is known for promoting health and well-being. Exercise is also responsible for increasing the production of Oxygen Reactive Species (ORS) by increasing mitochondrial oxygen consumption causing tissue oxidative stress. The imbalance between ORS production and tissue antioxidant defenses can cause oxidative damage to proteins, lipids and DNA. Brain oxidative damage is a common etiopathology mechanism of apoptosis and neurodegeneration. The brain-derived neurotrophic factor plays an important role in this context. In this review, we showed the results of different models and configurations of physical exercise in oxidative and neurotrophic metabolism of the Central Nervous System (CNS). We also reviewed studies that utilized antioxidant supplementation to prevent exercise-induced oxidative damage to CNS. The commonest physical exercise models were running wheels, swimming and treadmill with very different configurations of physical training such as duration and intensity. The results of physical training on brain tissues are very controversial, but generally show improvement in synaptic plasticity and cognition function with low and moderate intensity exercises.

Keywords: Physical activity. Oxidative stress. Antioxidants. Neurotrophins. Brain.

INTRODUCTION

Neurosciences have introduced a variety of new neurological concepts as well as scientific methods of investigation of the nervous system associating the discussion of factors of physical and environmental stress, such as physical exercise[1]. Despite the evidence of general health benefits caused by regular physical exercise to healthy individuals and to the ones with diabetes mellitus, asthma, obesity, hypertension, arthrosis and arthritis[2-4]; the effects of the exercise on the brain still present controversial results.

It is believed that moderate exercises increase cognition; moreover, it has been demonstrated that the brain is responsive to physical activity[5-8]. It means that physical activity presents potential in the prevention and treatment of cerebral traumatic damage[9] as well as in neurodegenerative diseases such as Parkinson disease[10-11] and Alzheimer's disease[12-13]. Studies support that many of these alterations occur in specific areas of important brain functions such as long-run memory[14-15] and prevention of cognitive decline during the aging process[16]. Some studies also demonstrate evidence on neurogenesis and brain plasticity[17-19] specifically induced by families of neurotrophic molecules[20-21]; however, the mechanisms of these alterations are still unknown.

The majority of the research with the aim to study the neurological adaptation mechanisms to exercise develops research with animal models due to the possibility to evaluate the nervous tissue in vivo[22-25]. Studies involving humans indirectly evaluate the brain function mainly by nuclear magnetic resonance[26-27], electrophysiology[28], neuroendocrinology[29] and brain function scales[30]. The aim of this investigation is to review and discuss some of the brain mechanisms under physical exercise influence, as well as the adaptations of the brain tissue and the consequences in the neurological functions.

PHYSICAL EXERCISE MODEL FOR STUDY OF THE CNS

Rodents are the main study animal models for the physical exercise paradigms in the brain functions and their mechanisms, where the two main physical activity models are: (1) voluntary activities such as activities in running wheels[31-34] and enriched environments[35-38], and (2) forced exercises such as swimming[39-42] and treadmill[43-47]. These models usually aim to stimulate the responses to training with predominance of aerobic metabolism, once this kind of exercise is associated with general health benefits.

Enriched environment is a reference to the standardized kind of cage, where a set of different stimuli are given to the animals, namely: access to running wheels, group interaction, and complex environments containing toys, tunnels and frequent changes in the food placement, which is usually followed by gains in the brain function, especially the ones associated with learning and memory[48]. The running wheel is a circadian intermittent[5], voluntary and of free access physical activity[1] which allows running at a self-determined velocity. The velocity spontaneously chosen corresponds to the level of optimum bioenergetic efficiency leveling the oxidative metabolism level[49].

Forced activities make the animals perform physical exercise at higher intensities, that is, higher energetic demands. Forced swimming allows selecting exercise overloads through the variation from 3% to 6% of body mass of the animal's body and imposes lower mechanical stress due to the water thrust, recruiting different muscle groups and reducing the gravity effects[50].

Running on treadmill activates the stress neuroendocrin responses and makes the animal run at a steady velocity, according to the experiment's configurations of the physical training: time, duration, velocity[5] and inclination[51-52]. Running on treadmill is usually selected due to aerobic metabolism responses higher than swimming[53], since it is characterized by relative inactivity of the hinder legs[54]. Treadmill training with controlled intensity induces to some of the highest and most consistent effects of physical training[55-56].

PHYSICAL EXERCISE AND NEUROTHROPHINS

Neurothrophins are a family of essential cytokines for the differentiation, growth and survival of the CNS dopaminergic, cholinergic and noradrenergic hormones and of sympathetic and sensory hormones of the Peripheral Nervous System (PNS) during adulthood[57-59]. Up to the present time, they are represented by five proteins of related structure which constitute the neurothrophins family, including the nerve growth factor (NGF), and the Brain Derived Neurothrophic Factor (BDNF), and the neurothrophins 3, 4/5 and 6 (NT 3, NT 4/5 and NT 6 – Neurothrophic Factor)[60-61].

1. Laboratório de Fisiologia e Bioquímica do Exercício, Programa de Pós-Graduação em Ciências da Saúde, Universidade do Extremo Sul Catarinense, Criciúma, SC, Brasil.

Approved in 31/1/07.

Correspondence to: Prof. Ricardo A. Pinho, Laboratório de Fisiologia do Exercício, PPGCS, Universidade do Extremo Sul Catarinense – 88806-000 – Criciúma, SC, Brazil. Fax: (55 48) 3431-2644. E-mail: pinho @unesc.net

Evidence has shown the BDNF role as critical modulator in the synaptic plasticity in the hypofield[62]. The deletion or inhibition of the BDNF gene[63] produces a deficiency in the long-run memory (LTP). This deficiency in the synaptic function may be corrected by exogenous applications[64] or over-expression[65] of the BDNF. Many genes associated to the BDNF action in the synapses increase their expression as an exercise result and may support the synaptic function or neuroplasticity[66].

The exercise increases the expression of many genes associated with the synaptic function[66]. Additionally to the synapsin I, exercise increases the mRNA levels for syntaxin and synaptogamin. Synapsin I is predominantly increased at short periods of exercise (3 and 7 days), being hence consistent to its role in the release of synaptic vesicles[67]. Synaptogamin progressively increases after long periods of exercise, being consistent to its role of synaptic vesicles[68]. The deletion of the BDNF gene in mice results in reduction of the synaptic proteins as well as their vesicles resulting in damage in the neurotransmissors release[69]. The BDNF promotes the phosphorylation of the synapsin I via activation of the TrκB receptors in the pre-synaptic terminal, resulting in release of neurotransmissors[70]. The exercise increases the mRNA levels and TrκB protein and synapsin I in the synapses via BDNF[71-74]. It is possible that high levels of induced-exercise BDNF facilitate the formation and mobilization of synaptic vesicles, and the extension of these events may be translated in long alterations in the synaptic plasticity[66].

These increases in the gene concentration and expression of the neurothrophins as well as their receptors present a distinct behavior to the different physical training studied. After two weeks of free access to the running wheel, the rats developed higher concentrations of BDNF in the hypofield, persisting up to a week after the exercise interruption[71]. The hypofield BDNF, TrκB, NT-3 mRNA levels returned to the normal concentrations with the total interruption of the exercise, meaning that these increases are dependent on the continuity of the exercise and reversible[74]. The higher the exercise volume, both swimming and running, the higher the BDNF levels were in the brains of the mice[75-77]. There is strong evidence that the exercise develops neurological alterations via BDNF, since the increase in the neurothrophins levels and their gene expression in running wheels was cancelled in the CA3 area and dented spin in the hypofield of rats, when blockers of the neuronal receptors of neurothrophins such as the K252a are administered, which inhibits the Trκ receptor of the BDNF[78]. Similar effects have been found with the use of the KN-62 antagonists, an inhibitor of the nicotinodiamide (NMDA) or PD98059 channels which inhibits the MAPK[78].

The exercise increases the gene expression of many complements of the MAP-K cascade such as the MAP-KI and MAP-KII. The MAP-K way is the largest signaling cascade of the Trκ receptors[79]. The MAP-K is involved in the synaptic plasticity, memory formation and integration of multiple extra cellular signals[80-81]. It seems that the MAP-K ways coordinate many synaptic events in conjunction with the CaM-K ways. For instance, the synapsin I is phosphorylated by the MAP-K and CaM-KII systems[82]. The CaM-KII affects the Ca^{+2} post-synaptic important for the synaptic function[83], and is involved in the formation of hypofield-dependent memory[84]. The PKC-d expression increased after 7 days of exercise[66]. PKC-d is necessary for the activation of the MAP-K cascade and for nerves growth[85]. Members of the CaM-K family increased their activity after short periods of exercise while members of the MAP-K way increased their activity according to the exercise tie, especially after 7 days[66].

Exercising increases the expression of the CREB transcription factor[66]. The CREB may regulate the BDNF gene transcription in the calcium-dependent mechanism[86-87]. Thus, through the MAP-K cascade, the BDNF causes the CREB phosphorylation resulting in its activation and gene transcription[88]. CREB is necessary for many kinds of memory[89-90], and seem to play an important role in the neuronal resistance to insults[91]. The hypofield of mice with CREB low levels presented harm in the maintenance of LTP[90]. The highest increases in the mRNA levels of the CREB were observed after 7 days of consistent exercise, with induction of the MAP-K members[66].

Plenty of evidence has shown increase of the neurothrophic proteins concentrations and their transcription associated with regular physical activity practice[92-93]. Treadmill running and running wheels increased the protein levels and mRNA of BDNF[14,93] as well as NT-3[77] in the hypofield of rats, in cortex and cerebellum[59]. The same fact was observed in swimming as well[94]. Additionally, exercising protects the neurons from many kinds of insults[95], since the BDNF promotes neurogenesis in adults[96] and increases the synaptic efficiency[62]. Twelve weeks of running on treadmill decreased the brain ischemic volume induced by occlusion of the medium brain artery of rats, being followed by increase of the mRNA concentration of NGF and its p75 GAPDH receptor, that is, the induced exercise increased the gene expression of neurothrophins causing neuroprotection to neuronal ischemia[97].

There are studies showing that exercising increases memory and spatial learning. Increase of the LTP occurs with increase of the neurothrophic factors endogenous to exercise[19]. The LTP can also be moderated by alterations in endogenous cytokines such as TNF-α (necrosis α transcription factor) and the IL-1β (Interleukin 1β)[98-99] as a straight consequence from exercise[100].

EXERCISE AND OXIDATIVE STRESS

The molecular oxygen in its diatomic state ($^3\Sigma g\text{-}O_2$) is a highly oxidant species essential to the energy production during the oxidative mitochondrial phosphorylation[101]. The extra reactive oxygen has a strong oxidative potential: according to the exclusion principle by Pauli, the O_2 oxidizes the other molecule by accepting an electronic pair, only if both electrons from the pair have a pair of spins anti parallel to their own non-paired electrons[101]. Due to this criterion rarely found, the O_2 slowly reacts in the lack of catalyzers and tends to accept a single electron during its redox chemistry[102-103].

In vivo, enzymes usually use an electron in the period in which they perform O_2 multi electronic reductions. If a single electron is accepted, it must enter an orbital and produce $O_2^{\bullet-}$[104].

$$O_2 + e \rightarrow O2^{\bullet-} \qquad \text{(Equation 1)}$$

The reduction of the two electrons of the O_2 plus the addition of 2 protons (H^+) generates H_2O_2.

$$O_2 + 2e + 2H^+ \rightarrow H_2O_2 \qquad \text{(Equation 2)}$$

Many oxidases use this mechanism to reduce O_2 directly to H_2O_2. The $O2^{\bullet-}$ spontaneous or catalyzed dismutation by the peroxide dismutase also produces H_2O_2[104].

$$O_2 + O_2^{\bullet-} + 2H^+ \rightarrow H_2O_2 + O_2 \qquad \text{(Equation 3)}$$

Peroxide is a non-radical intermediary which oxidizes a wide range of biological media, despite being a non-reactive species.

In the Haber-Weiss reaction (also known as Fenton superoxide-guided chemistry), chelatings of transition free or of low molecular weight metals, such as the Fe^{3+} are reduced by the $O_2^{\bullet-}$ to Fe^{2+}. The metallic reduced ion which reacts with the H_2O_2 generates the extremely reactive $HO^{\bullet}$[101].

$$Fe^{2+} + H_2O_2 \rightarrow HO^{\bullet} + HO^- + Fe^{3+} \qquad \text{(Equation 4)}$$

This species has been widely postulated as being the most important cause of damage to proteins, lipids, carbohydrates and DNA; however, there is slight straight evidence that the $HO^{\bullet}$ is generated in biological systems[104]. The biggest unsolved issue concerning the biological relevance of the Haber-Weiss reaction is the need

of free Fe^{3+} or Cu^{2+} due to the great variety of metal-transporter and metal-ligant proteins keeping the concentration of free active-redox metallic ions at low levels in the normal tissues. Nevertheless, this destruction may release active-redox metallic ions[101,105].

Massive attention has been directed to the production of oxidative species by the $O_2^{\bullet-}$. However, it is important highlighting that $O_2^{\bullet-}$ is a strong reducing agent. Its properties are added to its easy ability to rapidly react with the metallic ions (Mn^+)[104].

$$O_2^{\bullet-} + Mn^+ \rightarrow O_2 + M^{(n-1)} \qquad \text{(Equation 5)}$$

This reaction has been proposed to generate the reduced metals needed for the $HO^{\bullet}$ production by the Haber-Weiss reaction (equation 4)[104]. Recent studies suggest that proteins containing transition metals, such as the aconitase, an enzyme of the tricarboxilic acid cycle, are vulnerable to reduction by $O_2^{\bullet-}$ damage, which can be a contributing factor to muscular fatigue during exercise[101,105].

The oxidative phosphorylation generates the greatest part of the cellular ATP, and mitochondrial dysfunctions do harm to the energetic metabolism, where 1% of the mitochondrial electronic flow generates superoxide anions ($O_2^{\bullet}$), the first mitochondrial oxygen reactive species (ORS), demonstrating the importance of an efficient antioxidant system for preservation of the transporter chain of mitochondrial electrons[106]. Thus, there is a critical balance between the blood continuous supply of nutrients and oxidative energetic metabolism of the cerebral mitochondria[107], also regulated by additional mechanisms such as the mitochondrial calcium, membrane potential, and coupling-membrane proteins[106]. A dysfunction in the mitochondrial chain of electrons transport may be the highest source of toxic oxidants, including mitochondrial DNA, proteins and lipids oxidation, and opening of mitochondrial permeability pores, an event associated with neurodegeneration and death[101,107].

The brain represents approximately 2% of the body mass, but its O_2 ($CMRO_2$: 5 ml/min/100g) and glucose (CMRglu: 31 µMol/min/100g) consumption represents respectively 20 and 25% of the total consumption of the body at rest. The cerebral blood debt is consequently high: 14-20% of the rest blood debt. This energetic metabolism is well-evidenced by the continuous activity of neuronal intercellular communication[108], kept by the high glycemic metabolism through small supplies of high energy carbohydrates and phosphates, with no oxygen supplies[107].

The CNS is more susceptible to oxidative damage, since it represents great oxygen-dependant mitochondrial activity, associated with high free iron and polyunsaturated lipids and low levels of antioxidant enzymes[108]. The brain has 3% of the peroxides glutathione and 1% of the liver catalase. The glutathione is precursor of the antioxidant enzyme glutathione peroxidase[109]. The basis glands have high iron concentration and altered iron metabolism has high oxidant potential by the Haber-Weiss reaction.

When polynsaturated fatty acids in the biomembranes are attacked by free radicals in the presence of molecular oxygen, a chain of peroxidation reactions occurs, occasionally leading to formation of hydrocarbon gases (e.g. methane, ethane and pentane) and aldeids (e.g. malonaldehyde, MDA). Bioproducts of the lipid peroxidation are the most studies markers of oxidative tissue injury during exercise, as well as the oxidative alterations caused to the proteins (including enzymes) and nucleic acids[101,105].

Young and old rats have improved learning and memory after swimming training[110] as well as decreased proteins carbonilyzation[50,111-112] and lypoperoxidation in the cerebellum[94], hypofield and cerebral cortex[50]. These adaptations have persisted even after the same period of lack of exercise[94]. These swimming outcomes were well-evidenced with a high intensity exercise[111].

After 8 weeks of treadmill running, diabetic rats presented higher concentrations of cerebral lypoperoxidation[113]. In normal rats, the lypoperoxidation in the brain occurred with vitamin C supplementation[114]. The lipids oxidation in the CNS usually demonstrates different concentrations at different regions of the brain, and it can be attributed to regional differences in the O_2 consumption[115-116].

An acute exercise bout may increase the activity of some antioxidant enzymes with no new protein synthesis. This protection activity is limited to individual enzymatic characteristics and the involved tissue. As long-run strategy, the cells may increase the protein synthesis of antioxidant proteins in order to control the oxidative stress.

It has been demonstrated that intense exercise does not alter the SOD and GPx enzymes activities in the hypofield, striated and pre-frontal cortex 24 hours after the exercise[3].

The acute effects of the exercise over the brain antioxidant enzymes did not show differences in the SOD activity in the spinal cord and hypothalamus[117], cerebellum[118], cerebral cortex and hypofield either[50]. The increase in antioxidant enzymes activity in the brain as response to regular physical exercise is more probable linked to excess of free radicals formation[118-120].

The oxygen reactive species and associated damage are some of the possible associated factors in the cerebral function regulation[118-121]. The activity of the superoxide dismutase enzyme increased in the cerebral and striated trunk of rats after treadmill running training, followed by increase in the glutathione concentration in the cerebral cortex and trunk[111].

The general health benefits as well as diseases prevention by the exercise are widely known. However, chronic exercise also represents a kind of oxidative stress for the organism and may alter the balance between oxidants and anti-oxidants. The biological antioxidants play an important role in the cellular protection of the oxidative stress induced by exercising. Both a great production of free radicals and the deficiency or depletion of many antioxidant systems may reveal exacerbation of the oxidative cellular injury, while the supplementation of many antioxidants generates diverse outcomes[101,105].

Vitamin E (α-tocopherol) is an important soluble lipid, screening open-chain free radicals. Its unique location in the cellular membrane decreases its efficiency in acting in the free radicals originated from the internal mitochondrial membrane and other biomembranes[101,105]. Moderate physical exercise increased the mitochondrial oxidative damage in the brain of old rats[122]. Integration between physical training and vitamin E supplementation has been demonstrated, which caused neuroprotection against the decrease concerning age in the antioxidant enzymes and in the increase of the lipid peroxidation in the brain[50,123].

The antioxidant role of the vitamin C is well established; however, its importance in the protection against exercise-induced stress is not clear. It is suggested that vitamin C plays its function recycling vitamin E radical again to vitamin E[105]. Vitamin C isolated supplementation was not beneficial to the nervous tissue, once it increased the oxidation of lipids of the brain of trained rats[114].

CONCLUSION

We presented massive evidence of the exercise effects in the cognitive function and synaptic plasticity in the neurothrophic and cerebral oxidative mechanisms. The brain responses follow the model and configuration of the exercise, and may be influenced by the administration of antioxidants. Another factor is the differentiated responsitivity of the brain regions to acute and chronic exercise. Since studies concerning exercise and brain are scant, they widely vary from the model and exercise configuration, to the variables and adopted methodologies, a fact which decreases the capacity of results comparison. Thus, the effects and action mechanisms of physical exercise in the central nervous system still need further understanding.

All the authors declared there is not any potential conflict of interests regarding this article.

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