Effects of physical exercise over the redox brain state

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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 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. 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.

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 exercise¹¹. 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 arthritis²⁻⁴; 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 activity⁶⁻⁸. It means that physical activity presents potential in the prevention and treatment of cerebral traumatic damage⁵⁸ as well as in neurodegenerative diseases such as Parkinson disease¹⁰⁻¹¹ and Alzheimer’s disease¹²⁻¹₃. Studies support that many of these alterations occur in specific areas of important brain functions such as long-run memory¹⁴⁻¹⁵ and prevention of cognitive decline during the aging process¹⁶. Some studies also demonstrate evidence on neurogenesis and brain plasticity¹⁷⁻¹₈ specifically induced by families of neurotrophic molecules²⁰⁻²¹; 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 vivo²²⁻²⁵. Studies involving humans indirectly evaluate the brain function mainly by nuclear magnetic resonance²⁶⁻²⁷, electrophysiology²⁸ and neuroendocrinology²⁹ and brain function scales³⁰. 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 wheels³¹⁻³⁴ and enriched environments³⁵⁻³⁸, and (2) forced exercises such as swimming³⁹⁻⁴² and treadmill³⁴⁻⁴⁷. 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 memory⁴⁸. The running wheel is a circadian intermittent³⁶, voluntary and of free access physical activity¹⁷ which allows running at a self-determined velocity. The velocity spontaneously chosen corresponds to the level of optimum bioenergetic efficiency leveling the oxidative metabolism level⁴⁹.

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 effects⁵⁰. 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, velocity⁵¹ and inclination⁵₁⁻⁵₂. Running on treadmill is usually selected due to aerobic metabolism responses higher than swimming⁵₃, since it is characterized by relative inactivity of the hinder legs⁵₄. Treadmill training with controlled intensity induces to some of the highest and most consistent effects of physical training⁵₅⁻⁵₈.

PHYSICAL EXERCISE AND NEUROTROPHINS

Neurotrophins 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 adulthood⁵⁷⁻⁵⁹. Up to the present time, they are represented by five proteins of related structure which constitute the neurotrophins family, including the nerve growth factor (NGF), and the Brain Derived Neurotrophic Factor (BDNF), and the neurotrophins 3, 4/5 and 6 (NT 3, NT 4/5 and NT 6 – Neurotrophic Factor)⁶₀⁻⁶₁.

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 produces a deficiency in the long-run memory (LTP). This deficiency in the synaptic function may be corrected by exogenous applications or over-expression 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.

The exercise increases the expression of many genes associated with the synaptic function.85 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.87 Synaptogamin progressively increases after long periods of exercise, being consistent to its role of synaptic vesicles.86 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 neurotransmitters release.88 The BDNF promotes the phosphorylation of the synapsin I via activation of the TrkB receptors in the pre-synaptic terminal, resulting in release of neurotransmitters.70 The exercise increases the mRNA levels and TrkB 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.86

These increases in the gene concentration and expression of the neurotrophins 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, TrkB, 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 neurotrophins levels and their gene expression in running wheels was cancelled in the CA3 area and dentated spin in the hypofield of rats, when blockers of the neuronal receptors of neurotrophins such as the K252a are administered, which inhibits the Trk receptor of the BDNF.78 Similar effects have been found with the use of the KN-62 antagonists, an inhibitor of the nictinodiamide (NMDA) or PD98059 channels which inhibits the MAPK78.

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 Trk 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 systems82. The CaM-KII affects the Ca2+ post-synaptic important for the synaptic function,83 and is involved in the formation of hippocud-dependent memory84. The PK-c d expression increased after 7 days of exercise85. PK-c d is necessary for the activation of the MAP-K cascade and for nerves growth85. 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 days86.

Exercising increases the expression of the CREB transcription factor86. 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 transcription88. CREB is necessary for many kinds of memory,189-201, and seem to play an important role in the neuronal resistance to insults201. The hypofield of mice with CREB low levels presented harm in the maintenance of LTP202. The highest increases in the mRNA levels of the CREB were observed after 7 days of consistent exercise, with induction of the MAP-K members86.

Plenty of evidence has shown increase of the neurotrophic proteins concentrations and their transcription associated with regular physical activity practice.203-209 Treadmill running and running wheels increased the protein levels and mRNA of BDNF 14,203 as well as NT-3 77 in the hypofield of rats, in cortex and cerebellum.89 The same fact was observed in swimming as well.94 Additionally, exercising protects the neurons from many kinds of insults95, since the BDNF promotes neurogenesis in adults96 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 GPDH receptor, that is, the induced exercise increased the gene expression of neurotrophins 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 neurotrophic factors endogenous to exercise.189 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 exercise100.

EXERCISE AND OXIDATIVE STRESS

The molecular oxygen in its diatomic state (\( \Sigma_2 \text{O}_2 \)) is a highly oxidant species essential to the energy production during the oxidative mitochondrial phosphorylation101. The extra reactive oxygen has a strong oxidative potential: according to the exclusion principle by Pauli, the \( \text{O}_2 \) 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 electrons101. Due to this criterion rarely found, the \( \text{O}_2 \) slowly reacts in the lack of catalysts 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 \( \text{O}_2 \) multiple electronic reductions. If a single electron is accepted, it must enter an orbital and produce \( \text{O}_2^- \).\(^{104}\)

\[
\text{O}_2 + e^{-} \rightarrow \text{O}_2^- \quad (\text{Equation 1})
\]

The reduction of the two electrons of the \( \text{O}_2 \) plus the addition of 2 protons (H+) generates \( \text{H}_2\text{O}_2 \).\(^{105}\)

\[
\text{O}_2 + 2e^- + 2\text{H}^+ \rightarrow \text{H}_2\text{O}_2 \quad (\text{Equation 2})
\]

Many oxidases use this mechanism to reduce \( \text{O}_2 \) directly to \( \text{H}_2\text{O}_2 \). The \( \text{O}_2^- \) spontaneous or catalyzed dismutation by the peroxide dismutase also produces \( \text{H}_2\text{O}_2 \).\(^{106}\)

\[
\text{O}_2 + \text{O}_2^- + 2\text{H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2 \quad (\text{Equation 3})
\]

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), gredations of transition free or of low molecular weight metals, such as the Fe2 to Fe3.\(^{107}\)

The metallic reduced ion which reacts with the \( \text{H}_2\text{O}_2 \) generates the extremely reactive \( \text{HO}^- \).\(^{108}\)

\[
\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{HO}^- + \text{H}_2\text{O} + \text{Fe}^{3+} \quad (\text{Equation 4})
\]

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 \( \text{HO}^- \) is generated in biological systems.\(^{109}\) The biggest unsolved issue concerning the biological relevance of the Haber-Weiss reaction is the need for 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-ligand 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$^{101,125}$. Massive attention has been directed to the production of oxidative species by the O$_2^*$. However, it is important highlighting that O$_2^*$ is a strong reducing agent. Its properties are added to its easy ability to rapidly react with the metallic ions (Mn$^{2+}$)$^{104}$. 

$$O_2^* + Mn^{2+} \rightarrow O_2 + Mn^{2+}$$  

(Equation 5)

This reaction has been proposed to generate the reduced metals needed for the HO$^*$ 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 tricarboxylic acid cycle, are vulnerable to reduction by O$_2^*$ 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 electron flow generates superoxide anions (O$_2^*$), 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 mechanism$^{107}$, 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 glycolytic 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 polyunsaturated 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 aldehydes (e.g. malonaldehyde, MDA). Bioproductions 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 improved proteins carboxylation$^{110,111,112}$ and lypoperoxidation in the cerebellum$^{113}$, hypofield and cerebral cortex$^{114}$. These adaptations have persisted even after the same period of lack of exercise$^{110,113}$. 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 supple-mentation$^{114}$. 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 protein 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$^{31}$. 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$^{106}$. 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$^{118,123}$.

The oxygen reactive species and associated damage are some of the possible associated factors in the cerebral function regulation$^{118,124}$. 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$^{101,109}$.

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$^{121,122}$.

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$^{109}$. 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 responsivity 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.

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