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Cortical and hippocampal expression of inflammatory and intracellular signaling proteins in aged rats submitted to aerobic and resistance physical training

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ABSTRACT

Aging is often accompanied by an increase in pro-inflammatory markers. This inflammatory process is directly related to cellular dysfunctions that induce events such as the exacerbated activation of cell death signaling pathways. In the aged brain, dysregulation of the normal activities of neuronal cells compromises brain functions, thereby favoring the onset of neurodegenerative diseases and cognitive deficits. Interactions between various stimuli, such as stress, are responsible for the modulation of cellular processes and activities. Physical exercise is a controllable model of stress, largely used as a strategy for studying the physiological mechanisms of inflammatory responses and their consequences. However, different types of physical exercise promote different responses in the organism. The present study was designed to investigate the expression of inflammatory cytokines and chemokines, and expression and activation of intracellular signaling proteins (CREB, ERK, Akt, p70S6k, STAT5, JNK, NFkB e p38) in the cerebral cortex and hippocampal formation of aged rats submitted to aerobic and resistance exercise. Inflammatory analysis showed that aged rats that underwent resistance training had decreased cortical levels of RANTES and a reduction in the hippocampal levels of MIP-2 when compared with control animals (sedentary). No significant difference was detected in the cortical and hippocampal inflammatory response between aerobic and sedentary groups. However, when comparing the two training models (aerobic *vs* resistance), it was observed that aerobic training increased the cortical levels of IL-13, IL-6, IL-17α compared with resistance training. Regarding the signaling proteins, a significant increase in cortical expression of the proteins JNK, ERK and p70S6k was found in the aerobic group in relation to the sedentary group. No significant change in the cortical and hippocampal expression of signaling proteins was detected between resistance training and sedentary groups. Nevertheless, when training models were compared, it was observed that aerobic training increased cortical expression of the total proteins p38, ERK, Akt and p70S6k in relation to resistance training. Taken together, these results show that changes in the brain expression of inflammatory and cell survival proteins in aged rats depend on the type of physical training.

1. Introduction

In biological terms, aging is associated with a progressive combination of cellular and molecular damage, which over time increases the risk of developing chronic diseases and decreases the individual's physical and mental capacity (Vasto et al., 2010; Steve et al., 2012). The impairment of brain function is related to dysregulations of normal neuronal cell activity in brain regions such as cerebral cortex and hippocampal formation. In fact, several macroscopic and microscopic changes in weight and volume and a decrease in cortical volume are found in the aged brain, which leads to sensory and cognitive deficits (Mattson, 2007). Furthermore, the hippocampus, a structure located in

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the temporal lobe of the brain, which plays an essential role in the processes of memory and learning, has its function compromised in the aged brain (Mattson, 2007). Chronic inflammation is also present in the aging process negatively impacts brain functions. In fact, the balance between pro-inflammatory and anti-inflammatory cytokines is compromised in the aging brain with a shift towards a pro-inflammatory state (Godbout & Johnson, 2009). This inflammatory process is directly related to cellular dysfunctions that induce events such as the exacerbated activation of cell death signaling pathways.

Cellular activities can be modulated by several stimuli. In this sense, physical exercise has been extensively used for studying the physiological mechanisms of cellular processes and its outcomes. However, different types of physical exercise promote different responses in the organism. A growing number of animal studies have demonstrated that aerobic exercise can modulate the expression of cytokines in the brain (Chennaoui et al., 2008; Nichol et al., 2008; Packer et al., 2010; Leem et al., 2011; Pervaiz & Hoffman-Goetz, 2011; Gomes da Silva et al., 2013). For instance, physical exercise inhibits the production of the pro-inflammatory cytokine TNF-α, which in low levels decreases the process of apoptosis *via* the extrinsic pathway (Packer et al., 2010). Furthermore, in a study with aged rats, 10 days of treadmill exercise increased anti-inflammatory cytokine levels of IL10 and reduced IL1β/IL10, IL6/IL10 and TNFα/IL10 ratios in the hippocampal formation (Gomes da Silva et al., 2013). Although results from aerobic exercise studies are well elucidated, little is known about the effects of resistance training on the brain. A study showed that strength training results in the increased formation of new neurons, thus enhancing cognitive performance in the aged brain (Portugal et al., 2015). Controversially, an increase in apoptotic biomarkers such as p73, caspase-3 and caspase-9 has been observed in young subjects undergoing an acute resistance training program (Sarafi & Rahimi, 2012). In hypothesis, this effect was attributed to the intracellular oxidative stress generated by the resistance exercise. This stress could cause damage to the mitochondrial membrane, thus generating a signaling cascade for cell death (Sarafi & Rahimi, 2012). However, it is not clear whether resistance training would result in similar effects on the aged brain. We therefore conducted a study to investigate the effects of two types of physical exercise (aerobic and resistance) on the inflammatory and intracellular proteins in the brain of aged rats. For this, cortical and hippocampal levels of pro- and anti-inflammatory cytokines and chemokines, and the expression and activation of intracellular signaling proteins were analyzed in 21-month-old rats submitted to seven weeks of treadmill aerobic exercise and resistance training on a vertical ladder.

2. Methods

2.1. Animals

Twenty-one-month-old male Wistar rats (n = 17) were used in this study. The colony room was maintained at 21 ± 2 °C with a 12 h light/dark schedule (light: 7 am until 7 pm), and food and water were provided *ad libitum* throughout the experimental period. The aged rats were randomly distributed into three groups: resistance exercise (RES; n = 6), aerobic exercise (AERO; n = 6) and control (CTL; n = 5). All experimental protocols were approved by the ethics committee of the Universidade Federal de São Paulo (UNIFESP) (#7592250716) and all efforts were made to minimize animal suffering in accordance with the proposals of the International Ethical Guideline for Biomedical Research (CIOMS 1985) (CIOMS, Council for International Organizations of Medical Sciences, 1985).

2.2. Resistance exercise protocol

Before determining the experimental groups, all animals were subjected to a familiarization period using an 80° inclined vertical ladder (110 cm high × 18 cm wide, with 2 cm grid steps) constructed for rat training as conducted in previous studies (Cassilhas et al., 2012a; Peixinho-Pena et al., 2012). A housing chamber (L × W × H = 20 × 20 × 20 cm) located at the top of the ladder served as a shelter during the resting period. The familiarization protocol consisted of three trials per day for three days. In the first trial, the rats were kept in the housing chamber for 60 s and then placed on the ladder, 35 cm from the top. In the second trial, the rats were placed in the middle of the ladder. In the third trial, the rats were placed at the bottom of the ladder. Following the familiarization protocol, the rats were randomly assigned to the RES, AERO and CTL groups. We use this familiarization protocol for the ladder climbing exercise in order to ensure that all rats perform the proposed task satisfactorily and also to reduce possible motor and functional differences between the studied groups. It is important to note that all the aged rats in our study performed well during the familiarization protocol and none of them needed to be excluded from the study.

The aged rats from the RES group underwent a resistance exercise protocol with increasing intensity over seven weeks. Each week consisted of one day to determine the maximum supported load, four days of resistance training, and two days to rest. To determine and equalize the training intensity of aged rats from the RES group, the supported maximum load test was performed in a series of climbs. The maximal load test started with an initial climb with a load corresponding to 50% of the animal's body weight attached to the proximal part of the rat's tail with a coastlock snap swivel and Scotch 23 rubber tape (Scotch 3 M). An additional 20 g weight (added in each 60 s rest interval) was then added to the previous load until the rat was unable to climb the entire length of the ladder. Failure was determined when the animal could not progress up the ladder after three successive gentle stimuli to the tail. The highest load successfully carried along the entire length of the ladder was considered the rat's maximal loading capacity (Hornberger Jr & Farrar, 2004). The resistance exercise protocol consisted of a series of eight climbs with a progressively heavier load. Each series contained an average of eight to 12 climbing movements (repetitions). In the first two weeks, the overload was set at 50% of the rat's maximal loading capacity (evaluated every Monday). In subsequent weeks, the load was progressively increased up to a final load of 75% (Supplementary Table 1). The resting interval between the series was set at 60 s in the shelter at the top of the ladder. In our study (for both familiarization and training periods), no aversive stimulus was used in aged rats to motivate the resistance exercise by climbing a vertical ladder with a load.

2.3. Aerobic exercise protocol

As with the resistance exercise protocol, all the animals in the study were also subjected to a familiarization period on a treadmill before determining the experimental groups. Animals were familiarized with the apparatus for three days by placing them on a treadmill (Columbus instruments) for 5 min/day at a speed of 8 m/min at a 0% degree incline. Electric shocks were used sparingly to motivate the rats to run. A measure of each animal's treadmill performance was placed on a scale between 1 and 5 [1, refused to run, 2, below average runner (sporadic, stop and go, wrong direction), 3, average runner, 4, above average runner (consistent runner, occasionally fell back on the treadmill), 5, good runner (consistently stayed at the front of the treadmill)] (Dishman et al., 1988; Arida et al., 2011). Only animals with a mean rating of 3 or higher were included in the RES, AERO and CTL groups. This procedure was used to exclude possible differences in stress levels between aged rats. We use this familiarization protocol for the treadmill exercise in order to ensure that all rats perform the proposed task satisfactorily and also to reduce possible motor and functional differences between the studied groups. In our study, none of the animals had to be excluded (all animals submitted to the familiarization protocol were good runners).

Following this, aged rats from the AERO group then underwent an

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