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Research report

Treadmill running prevents age-related memory deficit and alters neurotrophic factors and oxidative damage in the hippocampus of Wistar rats

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ABSTRACT

Clinical and pre-clinical studies indicate that exercise is beneficial to many aspects of brain function especially during aging. The present study investigated the effects of a treadmill running protocol in young (3 month-old) and aged (22 month-old) male Wistar rats, on: I) cognitive function, as assessed by spatial reference memory in the Morris water maze; II) oxidative stress parameters and the expression of neurotrophic factors BDNF, NT-3, IGF-1 and VEGF in the hippocampus. Animals of both ages were assigned to sedentary (non-exercised) and exercised (20 min of daily running sessions, 3 times per week for 4 weeks) groups. Cognition was assessed by a reference memory task run in the Morris water maze; twenty four hours after last session of behavioral testing hippocampi were collected for biochemical analysis. Results demonstrate that the moderate treadmill running exercise: I) prevented age-related deficits in reference memory in the Morris water maze; II) prevented the age-related increase of reactive oxygen species levels and lipid peroxidation in the hippocampus; III) caused an increase of BDNF, NT-3 and IGF-1 expression in the hippocampus of aged rats. Taken together, results suggest that both exercise molecular effects, namely the reduction of oxidative stress and the increase of neurotrophic factors expression in the hippocampus, might be related to its positive effect on memory performance in aged rats.

1. Introduction

Aging is a time-dependent process leading to anatomical and physical changes that reduce physiological activity of many organs [1,2]. It is well known that aging is frequently associated with age-mediated structural and functional alterations in the hippocampus [3], i.e., decrease in cognitive performance that is associated to impairment of synaptic transmission, changes in neurotransmitter levels [4], as well as to the attenuation of hippocampal neurogenesis [5]. Aging is also associated with oxidative stress, impairment of mitochondrial function and DNA repair, and with decreased tissue regeneration activity [6]. The increase in reactive oxygen species may be a decisive contributor to brain senescence and neurodegeneration in aged rodents and humans [7,8], and has been tentatively related to cognitive impairment. Free radicals cause oxidative damage to critical biological molecules and, in order to handle that, organisms utilize endogenous defenses, including antioxidant enzymes as superoxide dismutase, catalase and glutathione peroxidase, as well as non-enzymatic antioxidants (as, for example, glutathione, ascorbate and tocopherol) [9]. These molecules provide support for aerobic cells to maintain a reducing state despite the oxidizing environment [10].

A number of trophic factors, important proteins for survival and functioning of neurons, have also shown neuroprotective/neurotrophic properties [11]. The levels of factors such as the vascular endothelial growth factor (VEGF), the brain-derived neurotrophic factor (BDNF), the insulin-like growth factor-1 (IGF-1) and the neurotrophin-3 (NT-3)

Abbreviations: BDNF, brain-derived neurotrophic factor; CAT, catalase; DCF, dichlorofluorescein; EXE, exercised; FGF-2, fibroblast growth factor 2; H_2DCF, 2′7′-dichlorofluorescein; IGF-1, insulin-like growth factor-1; NT-3, neurotrophin-3; MDA, malondialdehyde; VO_2, peak oxygen uptake; ROS, reactive oxygen species; SED, sedentary; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; VEGF, vascular endothelial growth factor

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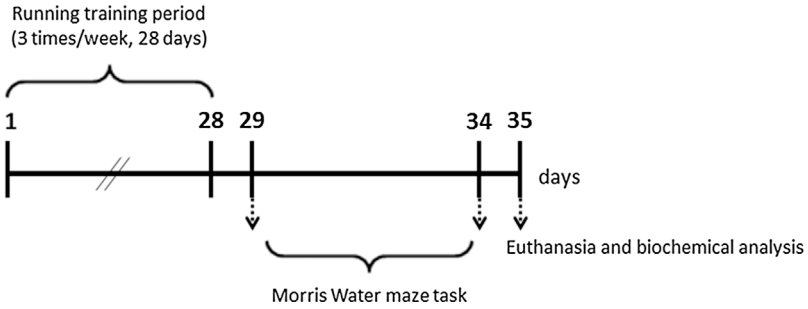

Fig. 1. Diagram showing the timeline of experimental design. The treadmill running exercise protocol (20 min/day, 3 times per week during 28 days) was used. Morris water maze training started 24 h after the last session of treadmill exercise and was performed during 5 days, followed by the probe trial. Rats were euthanized twenty four after behavioral assessment and the hippocampus was dissected out for biochemical analysis.

are dynamically regulated in the brain [12,13], as well as are positively related to the enhancement of cognitive function [14]. In addition, there is evidence on the importance of NT-3 expression for cognition during aging, particularly in the hippocampus [15].

Numerous experimental approaches have been used with the aim of reducing age-related brain changes, and physical exercise has revealed many beneficial effects. Both voluntary and forced exercise have been used to investigate the effects of physical activity on brain function; however, it has been argued that forced exercise gives more consistent results since all subjects are submitted to the same experimental conditions [16]. Regular physical activity improves performance in different memory and learning tasks in aged and young rodents [17–20]. Moreover, previous studies show that exercise increases brain antioxidant capacity and reduces oxidative stress [18,21,22]. It was also reported that exercise increases the expression and levels of several neurotrophic and growth factors, including IGF-1 [23], fibroblast growth factor 2 (FGF-2) [24] and BDNF [25]. Indeed, it is well known that the beneficial effects of physical exercise on brain function are mediated by both BDNF and IGF-1 [14,23]; however, little is known about exercise effects on brain NT-3 expression.

The present study investigated the effect of a moderate treadmill running exercise protocol in young and aged Wistar rats on: I) cognitive function, as assessed by spatial reference memory in the Morris water maze; II) oxidative stress parameters, namely the reactive oxygen species, lipid peroxidation, superoxide dismutase and catalase activities and the expression of neurotrophic factors BDNF, NT-3, IGF-1 and VEGF in the hippocampus. The working hypothesis is that treadmill running exercise will prevent aged-related memory deficits, and that such effect is possibly associated to a reduction of oxidative stress and to increased expression of neurotrophic factors in the hippocampus of aged rats.

2. Materials and methods

2.1. Animals

Young (3 months-old) and aged (22 months-old) male Wistar rats were obtained from the Central Animal House of the Department of Biochemistry of the Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil. They were maintained in a temperature controlled room (22 ± 1 °C), on a 12/12 h light/dark cycle, with food and water available ad libitum. The NIH "Guide for the Care and Use of Laboratory Animals" (NIH publication No. 80-23, revised 1996) and the official governmental guidelines, in compliance with the Federação das Sociedades Brasileiras de Biologia Experimental, were followed in all experiments. The young animals were housed five per cage, while the aged rats were housed three per cage. The study was approved by the Ethics Committee of the University under protocol number 24199.

2.2. Exercise training

Rats were habituated to the treadmill apparatus to minimize novelty stress and randomly divided into sedentary (SED, non-exercised) and exercised (EXE, 20 min of daily running sessions, 3 times per week for 4 weeks) groups. The exercise training consisted of running sessions in an adapted motorized rodent treadmill (INBRAMED TK 01, Porto Alegre, Brazil) at 60% of the animals' maximal oxygen uptake [26]. Peak oxygen uptake (VO_2) was measured indirectly in all animals before training, as follows. Each rat ran at a low initial speed on the treadmill; the speed was increased by 5m/min every 3 min until the point of exhaustion (i.e., failure of the rats to continue running). The time to fatigue (in min) and the workload (in m/min) were taken as indexes of exercise capacity, which was in turn taken as VO_2 max [26,27].

The protocol of exercise was of daily 20 min running sessions, three times per week for 4 weeks [28,29]. Any animal that refused to run was encouraged by gently tapping on the back. Sedentary rats were handled exactly as the experimental animals and were left on the treadmill for 5 min without any stimulus to run. All procedures occurred between 7 and 12 a.m. The experimental design is shown in Fig. 1. The number of animals per group was: SED young = 11, EXE young = 11, SED aged = 10 and EXE aged = 10.

2.3. Reference memory assessment

Hippocampus-dependent spatial learning and memory were assessed using the Morris water maze. The maze consisted of a black circular pool with 200 cm in diameter filled with water (temperature around 23 °C, depth 40 cm) situated in a room with visual cues on the walls. A transparent platform with 10 cm in diameter was submerged in the water (2 cm below the water surface) and the pool was conceptually divided into four quadrants and had four points designated as starting positions (N, S, W or E) [30,31].

Twenty four hours after the last exercise session rats were submitted to the reference memory task. They were trained on 5 consecutive days, receiving 4 trials per day, and 24 h after the last training session a probe trial was performed. Each daily session consisted of four trials with a 10 min intertrial interval. A trial began when the rat was placed in the water at one of the four starting positions, chosen at random, facing the wall. The order of starting position varied in every trial and any given sequence was not repeated on acquisition phase days. The rat was given 60 s to locate the platform; if the animal did not succeed it was gently guided to the platform and left on it for 10 s. Rats were dried and returned to their home cages after each trial. The latency to find the platform was measured in each trial and the mean latency for every training day was calculated. The probe consisted of a single trial with the platform removed. Here, the latency to find the original platform position, the time spent in the target and in the opposite quadrants and the path length were analyzed [31–33].

2.4. Tissue preparation

Animals were euthanized by decapitation without anesthesia, twenty four hours after the last session of behavioral assessment. The brain was rapidly removed and the hippocampus was quickly dissected out on a glass dish over ice. The hippocampus was homogenized in 10 vols (1:10, w/v) of 20 mM sodium phosphate buffer, pH 7.4 containing

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