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Physical exercise prevents short and long-term deficits on aversive and recognition memory and attenuates brain oxidative damage induced by maternal deprivation

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HIGHLIGHTS

- Maternal deprivation causes deficits in short- and long-term memory.
- Physical exercise avoids memory deficits related to maternal deprivation.
- Maternal deprivation promotes oxidative damage in hippocampus.
- Maternal deprivation promotes oxidative damage in prefrontal cortex.
- Physical exercise avoids brain oxidative damage caused by maternal deprivation.

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ABSTRACT

It is known from previous research that physical exercise prevents long-term memory deficits induced by maternal deprivation in rats. But we could not assume similar effects of physical exercise on short-term memory, as short- and long-term memories are known to result from some different memory consolidation processes. Here we demonstrated that, in addition to long-term memory deficit, the short-term memory deficit resultant from maternal deprivation in object recognition and aversive memory tasks is also prevented by physical exercise. Additionally, one of the mechanisms by which the physical exercise influences the memory processes involves its effects attenuating the oxidative damage in the maternal deprived rats' hippocampus and prefrontal cortex.

1. Introduction

Maternal deprivation (MD) is one of the most potent natural stressors during neonatal development and can results in permanent deficits during adulthood [1,2]. At the same time, in humans, a significant trauma experienced during childhood is the primary cause of increased stress and the subsequent emergence of mental disorders in adulthood [3]. Animal studies have demonstrated that MD results in behavioral changes that persist into adulthood [4–6], including increased anxiety [7], personality disorders [8], schizophrenia, depression [9], anhedonia [10], and memory deficits [6].

The impact of MD during the neonatal period is certainly related to the neural changes that occur during this period. For example, most granular neurons of the hippocampus develop and extend their axons between the 1st and 21st day of life [11]. During this period, the pups undergo an anatomical consolidation of their nervous system along with the continued proliferation and maturation of synapses [12]. The behavioral alterations observed in adult rats that were submitted to early-life stress could be related to alterations in gene expression [4,8,13], a reduction in brain-derived neurotrophic factor expression [14,15], an increase of corticosterone levels [16] and/or alterations in oxidative balance [17].

Considering the changes that have been observed in the adult brains of MD rats, several studies have attempted to identify strategies to avoid or decrease the behavioral deficits related to MD. Physical exercise can prevent the long-term memory deficits caused by MD, but little is known about the mechanisms involved in these this effect [18,19]. Because physical exercise has shown beneficial effects in improving oxidative balance [20], which is disrupted in the brains of MD rats [17], we investigated whether the effects of aerobic exercise on memory

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deficits are related to its effect on oxidative balance. Our results show that physical exercise prevents memory deficits on object recognition and inhibitory avoidance task, including short-term memory deficits for which the beneficial effects of physical exercise have not previously been studied. Additionally, physical exercise attenuates the oxidative damage induced by maternal deprivation in neural tissues.

2. Materials and methods

2.1. Animals

Pregnant female Wistar rats were obtained from Central Vivarium of Federal University of Santa Maria (RS/Brazil). All animals were maintained on a constant 12 h light/12 h dark cycle (lights on at 7:00 h) at controlled room temperature (23 ± 2 °C) and air humidity (60 ± 5%). Pregnant females were individually housed with sawdust bedding and with food and water available *ad libitum*. The day of delivery was considered to be day zero. At postnatal day 1 (PND-1), the MD protocol was initiated with half of the pups, which lasted until PND-10. Animals were weaned at 21 days of age (PND-21) and were housed 5 per cage in regular cages. Only the males were used in the following experiments. All experiments were conducted in accordance with the principles of laboratory animal care (NIH publication no. 80-23, revised 1996) and were approved by the Institutional Animal Care and Use Committee of the Local Institution (#001/2014).

The male rats were divided in four groups: (i) control, in which rats were not submitted to any intervention; (ii) deprived, which includes those rats submitted to MD as described below, without any additional intervention; (iii) physical exercise, which includes rats that were submitted to physical exercise as described below after PND-45; and (iv) deprived with physical exercise, which includes those rats submitted to MD from PND-1 until PND-10 and then submitted to physical exercise from PND-45 onward (Fig. 1). Rats in all four groups were submitted to the following behavioral tests starting at PND-100: open field; object recognition; inhibitory avoidance; tail flick; and elevated plus maze. After behavioral testing, the brains were isolated, and the hippocampus and prefrontal cortex dissected for use in the biochemical tests.

2.2. Maternal deprivation (MD) protocol

Female Wistar rats were maintained in individual boxes until their delivery day (considered to be day 0). Rats from groups (ii) and (iv) were submitted to maternal deprivation (MD) for 3 h per day during the light part of the cycle from PND-1 to PND-10. The MD protocol consisted of removing the mother from the residence box to other room. Pups were maintained in their home cage, and while the mothers were absent, the room temperature was increased to 32 °C to compensate for the absence of the mother's body heat [1]. At the conclusion of each daily deprivation session, the mothers were returned to their home boxes.

The rats in groups (i) and (iii) remained in their resident boxes together with their mothers during the first ten days of life. Only on PND-11 the boxes were cleaned normally again, according to the standard laboratory routine [21]. On PND-21, the animals were weaned, and the males were maintained in groups of 5 in plastic boxes with food and water available *ad libitum*, as with all the other animals in our animal housing facility.

2.3. Physical exercise protocol

Rats from groups (iii) and (iv) were submitted to chronic aerobic treadmill exercise during 8 weeks beginning on PND-45. One week prior to starting the training, all animals were placed in the treadmill for 10 min for habituation. On the first day of the second and fifth week, an indirect VO_2 maximum (peak oxygen uptake) test was conducted on a motorized rodent treadmill. The indirect VO_2 was used to determine and adjust the exercise intensity during the training period. An indirect measurement of VO_2 was determined as recommended by Brooks and White [22]: each rat ran on the treadmill at a low initial speed followed by speed increase of 5 m/min every 3 min, until they reached their exhaustion point. The intensity of physical exercise training (50 min/day; 5 day per week) was maintained between 50% and 70% of their respective VO_2 maximum for 8 weeks. Each training session started with a 10-min gradual acceleration followed by 30 min at the target intensity; the last 10 min of each session consisted of a gradual deceleration [23]. The treadmill used had individual 10 cm wide, 50 cm long lanes separated by plastic walls. No electric shock

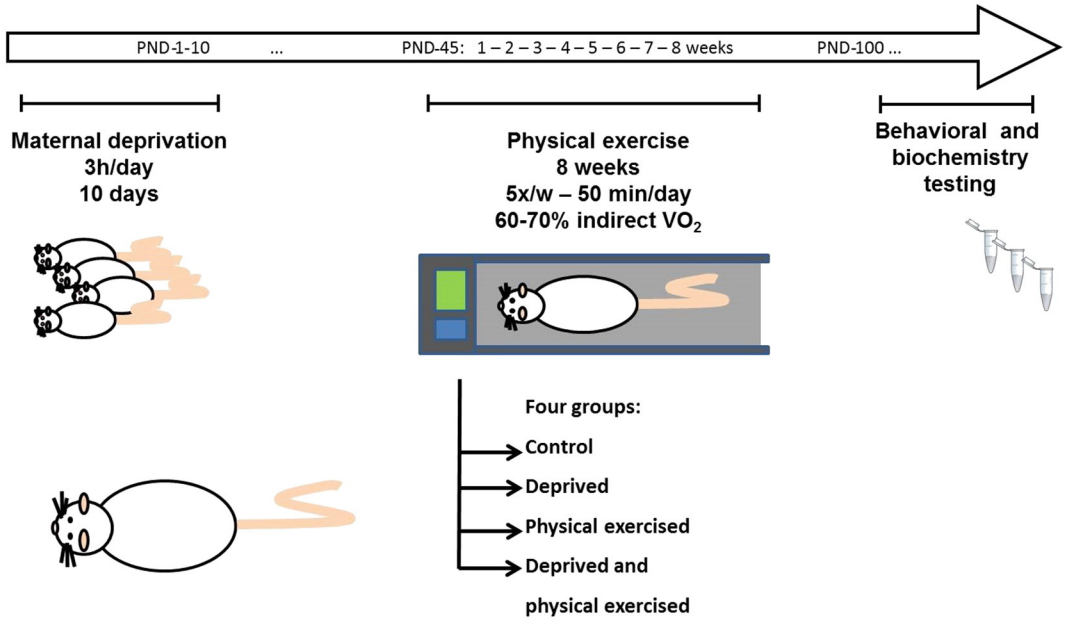

Fig. 1. Experimental design. Animals were submitted to maternal deprivation from PND-1 until PND-10 for 3 h per day (groups (ii) and (iv)). After, rats of the groups (iii) and (iv) were submitted to physical exercise lasting 8 weeks, from PND-45 on. In PND-100 the behavioral testing were started, followed by biochemical tests.