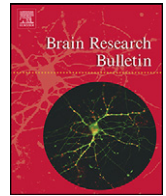




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Research report

## Physical exercise improves motor and short-term social memory deficits in reserpinized rats

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### ABSTRACT

Previous studies have shown that cognitive deficits precede the classical motor symptoms seen in Parkinson's disease (PD) and that physical exercise may exert beneficial effects on PD. We have recently verified that the monoamine-depleting drug reserpine – at doses that do not modify motor function – impairs memory processes in rats. Here, we evaluated the potential of physical exercise to improve cognitive and motor deficits induced by reserpine. Adult Wistar rats were assigned to six groups: (1) untrained-vehicle; (2) untrained-reserpine; (3) running wheel (RW)-vehicle; (4) RW-reserpine; (5) treadmill-vehicle; and (6) treadmill-reserpine. Exercise groups were given free nocturnal access to RW or continuous treadmill exercise (20–25 min/day) for 5 days/week over 4 weeks. The animals were injected subcutaneously with reserpine (1.0 or 5.0 mg/kg) or vehicle 48 h after the end of physical program, and 24 h later they were tested in a battery of behavioral paradigms. RW and treadmill improved the motor deficits induced by a high reserpine dose (5.0 mg/kg), as evaluated in the rotarod and open-field tests. Moreover, untrained rats treated with a low reserpine dose (1.0 mg/kg) presented short-term social memory deficits (without motor or olfactory disturbance) that were selectively improved by the exercise training. Our results reinforce the potential of low to moderate physical exercise as a useful tool in the prevention of motor and cognitive impairments associated to CNS monoaminergic depletion.

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### 1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that affects approximately 1% of the population older than 50 years [10]. Classically, PD is considered a motor system disease, and its diagnosis is based on the presence of a set of cardinal motoric signs (e.g. rigidity, bradykinesia, tremor and postural reflex disturbance). In addition to the characteristic motor symptoms, subtle cognitive impairments are often present even during the earlier phases of PD that includes attentional and working memory deficits [9,19]. In about 20–40% of patients, these problems may eventually proceed to dementia, which constitutes an important risk factor for caregiver distress, decreased quality of life, and nursing home placement [1]. The beneficial effects of the drugs currently avail-

able for the treatment of PD (such as levodopa) on improving the cognitive function affected in PD is controversial [14,25]. Thus, the management of non-motor symptoms of PD remains a challenge.

Several lines of evidence suggest that preventive strategies such as a physically active lifestyle may help to delay the onset of cognitive decline and reduce the risk for age-related neurological diseases (for review see Ref. [16]). Regular exercise attenuated the age-associated decline in memory and reduced the accumulation of proteins affected by oxidative damage in the brain [29]. Moreover, regular physical exercise has been related to an increased brain plasticity [7], neurogenesis [33,34], and production of neurotrophic factors [3,7].

Results from previous clinical studies on the efficacy of physical exercise to counteract or reverse PD symptoms have been inconsistent, which can be largely attributed to methodological issues (for review see Ref. [17]). On the other hand, recent findings from different laboratories have shown that exercise programs with running wheel (RW), voluntary and low-intensity exercise, or treadmill, forced and moderate-intensity exercise, can present beneficial effects in neurotoxic rodent models of PD such as 6-hydroxydopamine (6-OHDA) [20,32] and 1-methyl-4-phenyl-

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1,2,3,6-tetrahydropyridine (MPTP) [11,24]. In such studies, exercise initiated either before or during neurotoxicant exposure, have been shown to be neuroprotective, as demonstrated by the attenuation of striatal dopamine loss [24,32], decrease in the dopamine transporter (DAT) activity [11] and improvement of motor coordination [11,24]. However, no consistent evidence for the potential of exercise to prevent cognitive impairments in animal models of PD has to date been documented.

The systemic administration of reserpine to rodents has been suggested as a pharmacological model of PD based on the effects of this monoamine-depleting agent on motor activity [6,12]. More recently, it has been shown that reserpine – at doses (0.1–1.0 mg/kg) that do not modify motor function – impairs rodent memory in different behavioral paradigms such as passive avoidance [4] and social recognition [28] tasks. Therefore, here we evaluated the potential of physical exercise to prevent cognitive and motor deficits induced by subcutaneous (s.c.) injection of reserpine (1.0 or 5.0 mg/kg) in rats.

**2. Materials and methods**

**2.1. Animals**

A total of 96 adult male Wistar rats (3 months old, 250–370 g) and 20 juvenile male Wistar rats (25–30 days old, 100–150 g) from our own colony were used in two experiments. Juvenile rats were kept in groups of 10 per cage and served as social stimuli for the adult rats. The animals were maintained in a room under controlled temperature (23 ± 1 °C) and were subjected to a 12-h light/dark cycle (lights on 7:00 a.m.) with free access to food and water. All behavioral tests were carried out between 9:00 and 14:00 h. All efforts were made to minimize the number of animals used and their suffering and the experiments were carried out following the guidelines of the European Communities Council (86/609/EEC).

**2.2. Drugs**

Reserpine (methyl reserpate 3,4,5-trimethoxybenzoic acid ester, Sigma Chemical Co., St. Louis, MO, USA) was dissolved in 50 µl of glacial acetic acid plus 0.9% NaCl (saline). The control solution consisted of saline plus 50 µl of glacial acetic acid. Reserpine doses (1.0 and 5.0 mg/kg) were administered subcutaneously (s.c.) in a volume of 1.0 ml/kg of body weight. Reserpine or control solution was given 48 h after the end of the exercise program and all behavioral tests were performed 24 h after the reserpine injection (Figs. 1A and 2A). The present treatment schedule was selected according to the previous literature [4,23,28] and was designed to investigate the chronic consequences of physical exercise in the cognitive and motor deficits induced by reserpine.

**2.3. Exercise paradigm**

The animals in the running wheel (RW) exercise groups were transferred during the nights into individual cages, where they had nocturnal (19:00–07:00 h) free access to the running wheel (diameter 31.8 cm, width 10 cm), thus characterizing voluntary and low-intensity exercise.

One week before the start of the treadmill exercise paradigm, 32 rats that could maintain a forward position on the 45 cm treadmill belt for 5 min at 5 m/min were randomly assigned to the four groups (vehicle vs. reserpine 1.0 mg/kg; vehicle vs. reserpine 5.0 mg/kg) to ensure that all animals performed similarly on the treadmill task before reserpine administration. The treadmill used in these studies was an EXER-6M model manufactured by Columbus Instruments (Columbus, OH). A non-noxious stimulus (metal-beaded curtain) was used as a tactile incentive to prevent animals from drifting back on the treadmill. As a result, shock-plate incentive was not used and stress related to the activity was minimized.

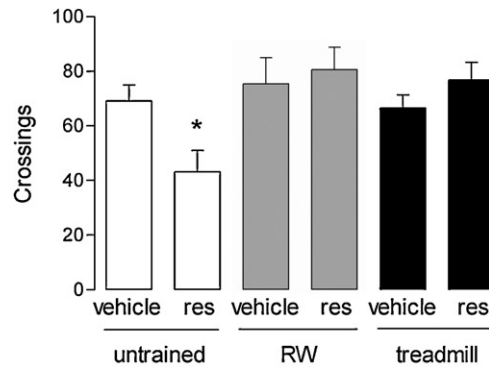
As summarized in Table 1, the treadmill-training groups initially were habituated to a six-channel motor-driven treadmill at a speed of 8.3 m/min for 10 min/day during 1 week. Exercise duration and treadmill speed were progressively increased,

**Table 1**  
Parameters of the physical training performed by the rats of the treadmill group.

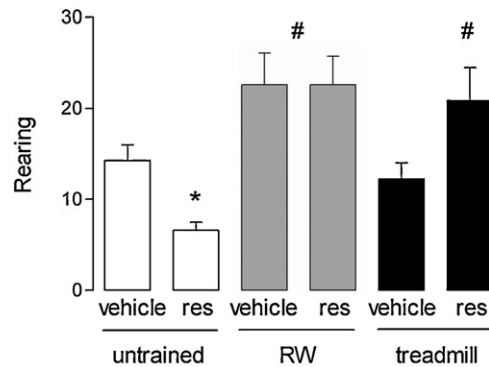
Week	Belt speed (m/min)	Daily duration (min)	Distance traveled (m/day)
Adaptation	8.5	10	85
1	16.5	20	330
2	20.0	20	400
3	25.0	20	500
4	25.0	25	625



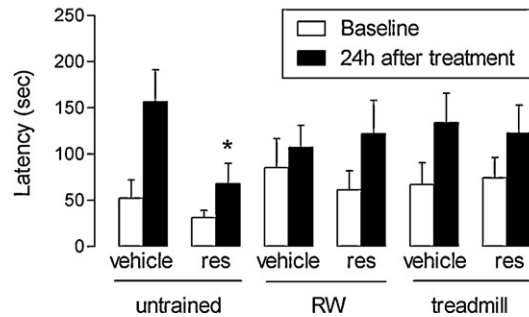
**(B) Open field**



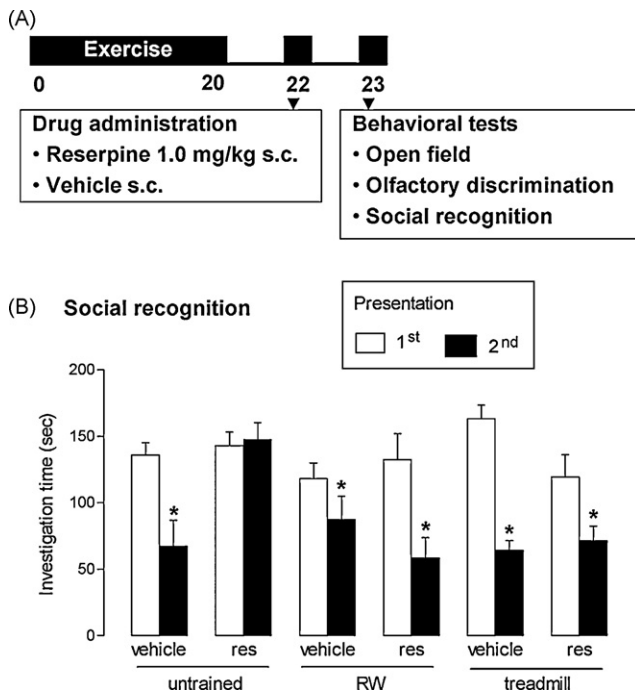
**(C) Open field**



**(D) Rota rod**



**Fig. 1.** Effects of the administration of reserpine (5.0 mg/kg, s.c.) or vehicle (s.c.), 24 h before the experiments, on motor performance of sedentary (untrained) rats and rats submitted to exercise training in running wheel (RW) or treadmill during 20 days. Data are expressed as means ± S.E.M. (n = 8 animals in each group) of the total number of (B) squares crossed and (C) rearing in the open field task, and (D) the latency to fall from the accelerating rotarod. \*P ≤ 0.05 compared to untrained-vehicle group. #P ≤ 0.05 compared to the respective treatment of untrained group (Student–Newman–Keuls test).



**Fig. 2.** Effects of the administration of reserpine (1.0 mg/kg, s.c.) or vehicle (s.c.), 24 h before the experiments, on (B) short-term social recognition memory of sedentary (untrained) rats and rats submitted to exercise training in running wheel (RW) or treadmill during 20 days. Data are expressed as means  $\pm$  S.E.M. of 8 animals in each group. (B) The bars represent the investigation time (s), during the first (white) and second (black) presentations of the same juvenile with an inter-trial interval of 30 min. \* $P \leq 0.05$  compared to the first presentation of the same group (Student–Newman–Keuls test).

starting with 20 min and 16.5 m/min in the first week to reach the goal of 25 min of duration and 25 m/min on the fourth week to achieve moderate-intensity of exercise. To control for any non-exercise effects of treadmill running (handling, novel environment, noise, and vibration), untrained control rats (sedentary) were placed on top of the treadmill apparatus for a time period equivalent to exercise training [24].

Rats from both exercise types (RW and treadmill) performed physical training during 4 weeks, 5 days/week, performing a total of 20 days of exercise (Figs. 1A and 2A). The animals were randomly assigned to six groups ( $n=8$  animals per group): (1) untrained-vehicle, (2) untrained-reserpine, (3) RW-vehicle, (4) RW-reserpine, (5) treadmill-vehicle, and (6) treadmill-reserpine.

#### 2.4. Behavioral tests

##### 2.4.1. Open field

We evaluated the effects of exercise and reserpine treatment in locomotor activity according to open field arena. The apparatus, made of wood covered with impermeable Formica, had a white floor of 100 cm  $\times$  100 cm (divided by black lines into 25 squares of 20 cm  $\times$  20 cm) and white walls, 40 cm high. Each rat was placed in the center of the open field, and the total number of squares crossed (crossings) and rearing were registered in 5 min.

##### 2.4.2. Rotarod

The rotarod was used to evaluate the effects of exercise and reserpine treatment on the motor coordination of the animals. The accelerating rotarod apparatus (Insight Scientific Equipments, Ribeirão Preto, SP, Brazil) consists of a grooved metal roller (6 cm in diameter) and separated 9-cm wide compartments elevated 16 cm. The spindle speed was increased from 6 to 20 rpm over a maximal period of 300 s, and the time spent on the accelerating rotarod and the corresponding rpm were determined. The animals that were able to perform for 30–120 s during the baseline (performed 1 h before treatments) were chosen for the experiment. After the selection, vehicle and reserpine groups were matched according to body weight and mean performance. With this procedure, the animals presented similar baseline values for all groups. Then, all animals were tested on the rotarod 24 h after s.c. administration of vehicle or reserpine (5 mg/kg).

##### 2.4.3. Olfactory discrimination

The olfactory discrimination ability of adult rats was assessed with an olfactory discrimination test similar to one described in a previous study [27]. This test consisted of placing each rat for 5 min in a cage divided into two identical com-

partments (30 cm  $\times$  30 cm  $\times$  20 cm) separated by an open door. In this cage, it could choose between a compartment with fresh sawdust (non-familiar) and another with unchanged sawdust (familiar) that the same rat had occupied for 48 h before the test. The time (s) spent by the rat in both compartments (familiar vs. non-familiar) was recorded. Usually, mature male rats are able to discriminate between the familiar and the non-familiar compartments, spending much more time in the familiar compartment, since they significantly prefer their own odor to no odor at all [27].

##### 2.4.4. Social recognition

Short-term social memory was assessed using the social recognition test [8] previously evaluated in our laboratory [27,28]. Adult rats were housed individually in plastic cages (42 cm  $\times$  34 cm  $\times$  17 cm) and they were used only after at least 7 days of habituation to their new environment. The test was scored by the same rater in an observation room, where the rats had been habituated for at least 1 h before the beginning of the test. All juveniles were isolated in individual cages for 20 min prior to the beginning of the experiment.

The social recognition test consisted of two successive presentations (5 min each) separated by a short period of time where a juvenile rat was placed in the home cage of the adult rat and the time spent by the adult in investigating the juvenile (nosing, sniffing, grooming or pawing) was recorded. At the end of the first presentation, the juvenile was removed and kept in an individual cage during the delay period and re-exposed to the adult rat after 30 min. What usually takes place in this kind of test is that if the delay period is less than 40 min, adult male rats display recognition of this juvenile, as indicated by a significant reduction in the social investigation time during the second presentation. Therefore, a 30 min interval between two presentations of the same conspecific juvenile was used to demonstrate possible deficit in social recognition memory consecutive to reserpine administration.

##### 2.5. Statistical analysis

All values are expressed as means  $\pm$  S.E.M. ( $n$  equals the number of rats included in each analysis). Group differences were examined with one-way analysis of variance (ANOVA), repeated-measures ANOVA, or multivariate ANOVA (MANOVA [General Linear Model procedure]) using the Wilks  $\lambda$  result. When necessary, post hoc analyses were performed using the Student–Newman–Keuls (SNK) test. The accepted level of significance for the tests was  $P \leq 0.05$ . All tests were performed using the Statistical Package for the Social Sciences® software package (SPSS Inc., Chicago, IL, USA).

### 3. Results

#### 3.1. Experiment 1 – effects of physical exercise on the motor deficits induced by reserpine (5 mg/kg) in rats

Fig. 1B and C summarizes the results for the effects of physical exercise (RW and treadmill) on the behavioral parameters of reserpine-treated (5.0 mg/kg, s.c.) rats evaluated in the open-field test. Two-way ANOVA (condition vs. treatment) revealed a significant effect for the condition factor and for the interaction factor between condition and treatment on total squares crossed [condition:  $F_{2,46} = 4.79$ ,  $P \leq 0.05$ ; interaction:  $F_{5,43} = 3.66$ ,  $P \leq 0.05$ ] and rearings [condition:  $F_{2,46} = 10.60$ ,  $P \leq 0.0001$ ; interaction:  $F_{5,43} = 4.72$ ,  $P \leq 0.05$ ]. However, it indicated a non-significant effect for the treatment factor on total squares crossed [ $F_{1,47} = 0.87$ ,  $P = 0.33$ ] and rearings [ $F_{1,47} = 0.76$ ,  $P = 0.52$ ]. Subsequent SNK post hoc comparisons indicated that RW trained groups, regardless of the treatment, control or reserpine, presented an increased number of rearings when compared to sedentary groups (Fig. 1C). Moreover, untrained-reserpine-treated rats presented significant motor impairments in the open field, as indicated by reduction in total squares crossed (Fig. 1B) and rearings (Fig. 1C). More importantly, SNK post hoc comparisons indicated that both exercises programs (RW or treadmill) improved significantly these behavioral deficits in reserpinized rats evaluated in the open field arena (Fig. 1B and C).

Fig. 1D shows the results for the effects of physical exercise (RW and treadmill) on the mean latency of reserpine-treated (5 mg/kg, s.c.) rats to fall from the accelerating rotarod. Three-way ANOVA (condition vs. treatment vs. repetition) revealed a significant effect for the repetition factor [ $F_{5,89} = 29.50$ ,  $P \leq 0.05$ ] and for the interaction factor between condition and treatment [ $F_{5,89} = 3.50$ ,  $P \leq 0.05$ ] in the latency to fall 24 h after treatment. According to SNK post hoc

**Table 2**  
The effects of 20 days of running wheel (RW) or treadmill training on behavioral parameters of reserpine-treated (1.0 mg/kg, s.c.) rats tested (for 5 min) in the open field and olfactory discrimination tests.

Condition	Treatment (1.0 mg/kg, s.c.)	n	Locomotor activity		Olfactory discrimination	
			Squares crossed	Rearing	% TFC	% TNFC
Untrained	Vehicle	8	103.2 ± 7.4	17.3 ± 2.4	58.0 ± 3.6	42.0 ± 3.6 <sup>a</sup>
	Reserpine	8	108.9 ± 7.8	15.9 ± 1.6	58.7 ± 2.0	41.3 ± 2.0 <sup>a</sup>
RW	Vehicle	8	105.6 ± 12.9	31.0 ± 3.8 <sup>b</sup>	64.5 ± 4.9	35.5 ± 4.9 <sup>a</sup>
	Reserpine	8	112.0 ± 13.7	32.9 ± 3.5	65.6 ± 2.4	34.4 ± 2.4 <sup>a</sup>
Treadmill	Vehicle	8	106.9 ± 12.5	24.7 ± 2.0	70.1 ± 2.9	29.9 ± 2.9 <sup>a</sup>
	Reserpine	8	108.3 ± 11.7	22.4 ± 3.2	61.0 ± 6.2	39.0 ± 6.2 <sup>a</sup>

Data are expressed as means ± S.E.M. % TFC, mean percentage of time spent in the familiar compartment. % TNFC, mean percentage of time spent in the non-familiar compartment.

<sup>a</sup>  $P \leq 0.05$  compared to the percentage of time spent in the familiar compartment (Student–Newman–Keuls test).

<sup>b</sup>  $P \leq 0.05$  compared to the number of rearings of untrained-vehicle group (Student–Newman–Keuls test).

comparisons, rats from all groups did not differ in their baseline performance (1 h before drug injection). Confirming the preceding experiment, SNK post hoc comparisons indicated that untrained reserpinized rats presented a poor performance in the rotarod in comparison to control group. Moreover, SNK comparisons indicated that both exercises programs (RW or treadmill) increased significantly the latency of reserpinized rats to fall from the accelerating rotarod (Fig. 1D).

Collectively, these results indicate no major differences in motor performance of untreated controls after the two physical exercise regimes. Therefore, the present exercise programs (RW or treadmill) were able to improve selectively the motor impairments in reserpinized rats, but failed to modify behavior of control-treated rats.

### 3.2. Experiment 2 – effects of physical exercise on the cognitive deficits induced by reserpine (1 mg/kg) in rats

A first set of experiments was conducted to investigate possible deficits in the locomotor activity and/or olfactory discrimination ability of rats injected with a low reserpine dose (1.0 mg/kg, s.c.). As summarized in Table 2, MANOVA revealed no significant effect for the treatment factor in the behavioral parameter evaluated in the open field [squares crossed: Wilks  $\lambda$   $F_{5,43} = 0.17$ ,  $P = 0.68$ ; rearing: Wilks  $\lambda$   $F_{5,43} = 0.06$ ,  $P = 0.79$ ]. However, it revealed a significant effect for the condition factor in the number of rearings [Wilks  $\lambda$   $F_{5,43} = 15.24$ ,  $P \leq 0.05$ ]. Confirming the previous results, SNK post hoc comparisons indicated an increased number of rearings in the RW trained rats when compared to untrained controls in the open field (Table 2). More importantly, SNK post hoc comparisons indicated that this low reserpine dose (1.0 mg/kg, s.c.) did not cause motor impairments in the animals, since no alterations in total squares crossed and rearing were observed in the open field arena (Table 2).

In the olfactory discrimination test, MANOVA revealed no significant effect for the condition [Wilks  $\lambda$   $F_{5,43} = 2.04$ ,  $P = 0.14$ ], for the treatment [Wilks  $\lambda$   $F_{5,43} = 0.56$ ,  $P = 0.45$ ], or for the interaction factor [Wilks  $\lambda$   $F_{5,43} = 1.05$ ,  $P = 0.35$ ] on the percentage of time spent in the correct quadrant. Thus, all groups were able to discriminate between the familiar and the non-familiar compartments, spending much more time in the familiar compartment (Table 2).

Fig. 2B illustrates the results for the effects of physical exercise (RW and treadmill) on the investigation time of reserpine-treated (1.0 mg/kg, s.c.) rats, when the same juvenile was re-exposed at 30 min later. Rats from all groups did not differ in their social investigation time during the first presentation of the juvenile. MANOVA revealed a significant effect for the interaction factor between condition and treatment [Wilks  $\lambda$   $F_{5,94} = 7.15$ ,  $P \leq 0.05$ ] on the investigation time during the second presentation of the famil-

iar juvenile. Post hoc comparisons indicated that adult rats injected (s.c.) with the control solution, when re-exposed 30 min later to the same juvenile, spent less time investigating it than upon the first exposure ( $P \leq 0.05$ , SNK post hoc test). Post hoc comparisons also indicated that reserpine injection significantly increased the investigation time during the second presentation of the familiar juvenile, indicating a disruption of the social recognition memory. More importantly, RW and treadmill exercises improved the social recognition memory deficits induced by reserpine, as indicated by a significant reduction ( $P \leq 0.05$ , SNK post hoc test) in the investigation time during the second encounter (Fig. 2B).

## 4. Discussion

The present study provides new evidence that low to moderate physical exercise plays an important role in improving motor and cognitive impairments associated to CNS monoaminergic depletion. The present training programs consisting of 4 consecutive weeks on the RW or the treadmill attenuated the motor disruption induced by a high reserpine dose (5.0 mg/kg, s.c.) in rats, corroborating previous observations that physical exercise ameliorates motor performance in rodents submitted to neurotoxicant models of PD, such as 6-OHDA [20,32] and MPTP [11,24]. More importantly, the present findings demonstrate, for the first time, that physical exercise improved selectively social recognition memory deficits induced by a low reserpine dose (1.0 mg/kg, s.c.) in rats, reinforcing the cognitive enhancing properties of physical exercise.

The systemic administration of reserpine to rodents is a simple pharmacological model widely used for investigating symptomatic anti-parkinsonian treatments [6,12]. Reserpine interferes with the storage of dopamine (and of noradrenaline and 5-hydroxytryptamine) in synaptic vesicles, leading to depletion of dopamine in nerve terminals. Previous studies [5,15] have demonstrated that a single injection of the same doses of reserpine (5.0 or 1.0 mg/kg, s.c.) that were utilized in the present study reduced extracellular dopamine levels, respectively, to 4% and 10% of control levels at 24 h post-injection. Although the use of reserpine as model of PD shows a good face and predictive validity, it is important to emphasize that reserpine presents some limitations because it does not induce progressive degeneration of the dopaminergic nigrostriatal pathway. Moreover, since the animals trained on the RW were placed isolated from each other at night and we did not quantify the amount of exercise, we cannot discard completely a possible influence of social stress [21] and inter-rat differences in the use of RW in the present findings, and this constitutes a very interesting field that requires additional research.

In accordance with an extensive literature [6,12,23], we observed that the exploratory activity and motor coordination were highly reduced in reserpine-treated (5.0 mg/kg, s.c.) rats. It must be

conceded that the learning curve observed in the rotarod could confound partly the interpretation of the results of this study. Of high interest, both types (RW and treadmill) of exercise induced a full recovery of the locomotor performance of reserpinized animals in the open field and rotarod tests. Moreover, physical exercise also restored the normal pattern of vertical exploration, with the number of rearings similar to those of control animals.

The positive effects of exercise on motor function seem to be mediated, at least in part, by adaptive changes of the dopaminergic system in the basal ganglia and motor circuitry. For instance, Petzinger et al. [24] have recently published a highlight study demonstrating the increase of striatal dopamine release as well as the downregulation of both dopamine transporter (DAT, a protein responsible for the uptake and clearance of dopamine from extracellular space) and tyrosine hydroxylase (TH, an enzyme responsible for the rate-limiting step in dopamine biosynthesis) of MPTP-treated mice submitted to treadmill for 28 days. Alternatively, it has been reported that reserpine treatment induces an increase in the striatal oxidized glutathione/reduced glutathione ratio (GSSG/GSH) [2]. Interestingly, Teixeira et al. [31] have recently demonstrated that chronic moderate physical exercise attenuates reserpine-induced orofacial dyskinesia and striatal oxidative stress in rats.

Additionally, several lines of evidence strongly suggest the involvement of monoamines in learning and memory processes. For example, studies using reserpine [4,28] MPTP [22,26] or 6-OHDA [30] to mimic PD in rodents have shown procedural and working memory impairments analogous to those observed in the earlier stages of PD [9,19]. Confirming our previous study [28], the present findings demonstrate that the acute treatment with a low reserpine dose (1.0 mg/kg, s.c.), 24 h before the experiments, induced pronounced deficits in the social recognition memory in rats. This response cannot be attributed to non-specific effects (such as locomotion or olfactory deficits) of the tested dose of reserpine that could confound the interpretation of the results of this study, since no alteration in the open field and olfactory discrimination tests was observed.

The social recognition is a particular model of short-term working memory based on the olfactory discrimination ability of rats [8]. It can be facilitated by memory-enhancing drugs and disrupted by pharmacological and pathophysiological models known to impair memory in rodents [27]. The present results are in accordance with previous studies showing the importance of monoamines for the social recognition ability in rats. Griffin and Taylor [13] have previously demonstrated that social memory for a conspecific juvenile can be enhanced or disrupted, respectively, by a drug-induced elevation or depletion of norepinephrine in the central nervous system. Furthermore, Letty et al. [18] have demonstrated the improvement of social recognition memory by serotonin in rats through the activation of 5-HT<sub>4</sub> receptors. Corroborating these findings, a previous report from our group showed that a single administration of the dopamine D<sub>2</sub> receptor agonist quinpirole reversed the reserpine-induced deficits in social recognition memory in rats [28].

As outlined in the introduction, the benefits that physical exercise can produce on the cognitive function are well documented in both human and rodents [16,29,33]. These exercise effects seem to be associated with adaptive responses in the CNS such as the upregulation of neurotrophic factors [3,7] and neurogenesis [33,34]. Here, we extended these results demonstrating that the prophylactic engagement of exercise ameliorates the deleterious effects of reserpine in the short-term social memory in rats. Certainly, additional research is needed to clarify the exact mechanisms underlying the exercise modulation of the social memory and whether the efficacy of reserpine in depleting monoamines is altered by exercise in comparison to sedentary rats.

## 5. Conclusion

In conclusion, the present study provides new evidence that low to moderate physical exercise represents a useful tool in the prevention of rodent behavioral impairments associated to CNS monoaminergic depletion. More importantly, our findings reinforce the cognitive enhancing properties of exercise that may be of interest in the management of learning and memory deficits associated to diverse disorders with the dysregulation in dopamine neurotransmission.

## Conflict of interest

The authors declare that they have no competing financial interests.

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