



The effects of voluntary exercise on learning and memory deficit in Parkinson's disease model of rats

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Abstract

Parkinson's disease (PD) is a neurodegenerative disease characterized by progressive and loss of dopaminergic neurons in the SNpc. Behavioral symptoms and cognitive impairments even dementia are common in Parkinson disease. Physical activity impacts functional recovery in humans, however, its effects in experimental animals submitted to Parkinson model have been inconsistent. The present work was focused on the neuroprotective effect of 4 weeks voluntary exercise (wheel running) against experimentally (6-OHDA) induced Parkinson's disease in rat, by analyzing the memory and learning. Morris water maze test was used for measurement of spatial learning and memory. Results did not demonstrate any main effect differences between the exercise and control groups on weight gain ($p > 0.05$). 6-OHDA injection caused a significant cognitive deficit in spatial water maze tasks and this effect was reversed in rats after receiving exercise protocol. Voluntary exercise improved the cognitive performance in both reference and working spatial memory against 6-OHDA administration ($p < 0.05$). We suggest that voluntary exercise interventions may has the potential role in promoting neuroplasticity and repair cognitive dysfunction in Parkinson's disease (PD).

Keywords Parkinson · Voluntary exercise · Learning · Memory

Introduction

Parkinson's disease (PD) is a second common neurodegenerative disease in the world. Parkinson's disease PD is a neurodegenerative disorder that affects the population over 50 years [1] that characterized by a dopaminergic neuronal loss in the nigrostriatal system [2, 3]. PD patients were consistently less physically activity and they showed motor symptoms such as resting tremor, rigidity, akinesia, and disturbances of postural reflex and sensory disorders [4].

Moreover, to the characteristic motor symptoms, many cognitive impairments such as memory and learning deficits are often found that includes attentional and working memory deficits [5, 6]. PD patients have been reported to present

visuospatial working memory deficits [7]. These problems may eventually proceed to dementia, which inability in daily activity, and decreased quality of life [6]. Recent studies demonstrated that physical exercise exerts brain plasticity, neurogenesis, and improve motor symptoms in CNS disorder patients [8–11]. A meta-analysis clarified that exercise might improve physical performance, quality of life, strength and balance of PD patients [12].

Levodopa is the common pharmacological treatment for Parkinson diseases, which has a limited time effectively, and the side effects of its such as dyskinesia and motor fluctuations currently available and controversial [13, 14]. Therefore, the researchers prefer to use the preventive strategies such as physically exercise to reducing cognitive decline and the motor symptoms in PD patients [15]. Previous surveys suggest that forced exercise can improve learning and memory in Parkinson disease [16, 17]. Recent studies have shown that voluntary physical exercise with running wheel (RW) and forced exercise with treadmill can present positive effects on motor impairments in neurotoxicant rodent models of PD such as MPTP or 6-OHDA [9–12]. The limited previous results have been inconsistent, therefore in this study, we explored whether voluntary exercise might exert

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cognitive improvement effects on the acute PD model of rats. Wheel running was used as a voluntary exercise in this study to reduce the stress of rats and free access to exercise. Therefore, the objective of the current study was to evaluate the potential effects of voluntary exercise on the cognitive deficits induced by 6-OHDA in rats.

Materials and methods

Animals

Frothy male Wistar rats weighing 250–300 g at the beginning of the experiment were used. The animals kept in a temperature-controlled room (22 ± 2 °C) on a 12-h light: 12-h dark cycle, with food and water available ad libitum. The behavior tests were conducted between 7:00 and 13:00 h. The rats were weighed every week. All efforts were made to minimize animal suffering. All experiments were performed in accordance with the National Institutes of Health ‘Guide for the Care and Use of Laboratory Animals’ and approved by the Ethics Committee of Kerman Neuroscience Research Center.

Surgical procedures

The procedure was used in this study was based on the modified method described in previously studies [18, 19]. Rats were anesthetized with a combination of ketamine/xylazine (60/10 mg/kg, i.p.), and subjected to stereotaxic apparatus (Stoelting, USA). 6-OHDA (8 µg/2 µl normal saline containing 0.01% ascorbic acid) was infused into the right medial forebrain bundle (MFB), using a 5-µl Hamilton syringe with a 27-gauge according to the coordinates in Paxinos and Watson atlas: AP: –4.4 mm, ML: ± 1.3 mm from Bregma and DV: –8.2 mm from the skull surface [20].

Following injection and before being slowly withdrawn, the canal was left on the site for 5 min to allow complete diffusion of the drug. The animals were divided randomly into four groups ($n = 10$): (1) the intact animals in the control group, the Parkinson sedentary in the Parkinson control group were housed four per cage for 4 weeks. These animals received no specific training. Sham-operated group (sham) was essentially the same as voluntary exercise groups in terms of housing and exercise; however, sham rats received a saline injection instead of 6-OHDA during the stereotactic surgery. The animals in the voluntary exercise group were accessed to run on wheel running for 4 weeks.

Exercise protocols

The exercise condition consisted of 20 rats (vehicle, 6-OHDA). The rats in the wheel exercise group were

individually placed in cages equipped with a running wheel (diameter 33.3 cm; width 9 cm) for 4 weeks. The number of revolutions was recorded and wheel revolutions were counted irrespective of the direction of the wheel. All rats were allowed to habituate to the experimental environment for 30 min during 2 days before the beginning of the exercise protocol to minimize non-specific stress responses.

Morris water maze test

Morris water maze (MWM) task was used to assay spatial learning and memory [21]. The behavioral experiment was performed during the light cycle (between 8:30 and 12:00). The chamber was a black circular swimming pool of non-toxic materials (160 cm diameter, 80 cm high and 40 cm deep) and filled with water. Visual cues were placed around the chamber. This chamber was divided into four equal quadrants. A square hidden black platform (10 cm diameter) was submerged beneath (1.5 cm) the water surface in the middle of the target quadrant in the pool. The sessions were recorded with a video camera located above the center of the pool and connected to a recording system (Noldus Ethovision® system, version 5, USA).

In the spatial acquisition phase, the rats were allowed to find a submerged hidden platform during a 60-s-interval in four training trials (inter-trial interval = 60 s) repeated in three blocks (inter-block interval = 30 min). After finding the platform, the animals were allowed to rest on the platform for 20–30 s. The rats were dried with a towel and returned to their cages. After 20–30 s of rest, they were once again put in the chamber for the next trial. When a rat did not find the platform within 60 s, the experimenter would put it on the platform. On each trial, rats were randomly released into the water from one of the four quadrants of the maze with their faces toward the wall of the quadrant where they were released. Each rat had four different releasing points. Parameters such as latency and the traveled distance to find the platform were recorded in each trial.

2 h after the acquisition phase, a probe test was performed to evaluate spatial memory retention. For the probe test, the platform was removed and each rat was allowed to swim for 60 s. The time and distance spent in the target quadrant (quadrant 4) were analyzed as a measure of spatial memory retention [22].

Statistical analyses

Results were expressed as means \pm SEM. The normality of the data was assessed using the Levene test. All data had a normal distribution and the statistical analysis was performed with SPSS version 19 and one-way ANOVA followed by Tukey’s post hoc test for intergroup comparisons.

p value less than 0.05 was considered as a significant difference.

Results

All rats weighed every week. Weight of rats in PD and sham groups decreased in the week of surgery, but increased over the course of the trial; however, the trained rats weighed less than the control rats, but there was no significant difference between groups (*p*=0.35).

The mean average of daily running distance in voluntary exercise groups increased steadily in 4 weeks. However, the average daily distance run in the sham group was higher than voluntary rats in PD group; when all groups were analyzed with *t* test there were significant differences in the mean average of daily running distance between them (*p*=0.010) (Table 1).

Morris water maze test

We assessed the cognitive performance (learning and spatial memory skills) on a Morris water maze. The result of mean total distance to find the hidden platform in the Morris water maze test in all groups is shown in Fig. 1. One-way

ANOVA showed that there was a main significant difference (*p*=0.001) in spatial learning among control, sham, and, PD groups. The PD groups performed poorly and post hoc analysis determined that PD groups presented a decreased velocity, an increased time and distance traveled in zone 4, to find platform in the Morris, when compared with the control and the sham groups (*p*<0.001), (Fig. 2). Meanwhile, during the acquisition phase, animals in all groups learned to find a hidden platform as observed by the reduction in their swimming distance across blocks of training. This was also indicated by the reduction in their swimming distance increased in block 2 and block 3 compared to the other blocks. In addition, as shown in Fig. 1, the mean distance was significant increased in the parkinson voluntary exercise group compared to sham voluntary exercise and control groups, (*p*<0.05).

The result of learning velocity and escape latency to find the hidden platform in the Morris water maze test in all groups is shown in Figs. 2 and 3. The data showed that both the 6-OHDA sedentary and 6-OHDA voluntary groups scored worse than the control and sham voluntary groups in the water maze. One-way ANOVA showed a significant effect for the 6-OHDA lesion factor (*p*<0.01). The Tukey post hoc test showed significant differences between the 6-OHDA sedentary and other groups (*p*<0.05) and

Table 1 The *t* test results of daily running in 6-OHDA-treated rats

| Variable | <i>t</i> | <i>df</i> | Sig. (two-tailed) | Mean difference | 95% confidence interval of the difference | |
|---------------|----------|-----------|-------------------|-----------------|---|----------|
| | | | | | Lower | Upper |
| Daily running | 2.966 | 15 | 0.010 | 495.43750 | 139.4453 | 851.4297 |

Fig. 1 The total traveled distance to find the hidden platform in the Morris water maze test

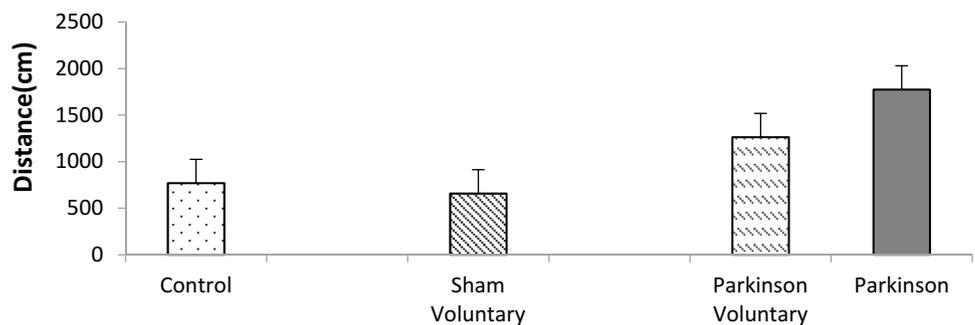
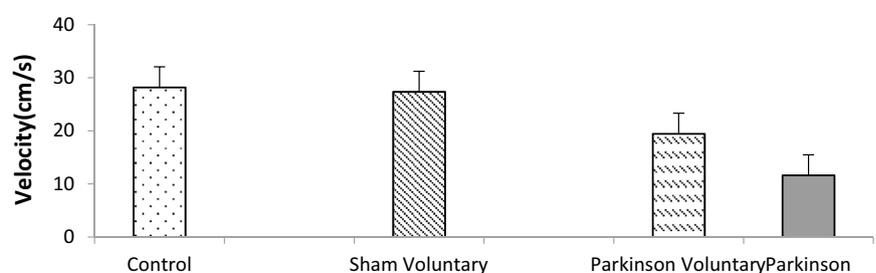


Fig. 2 Velocity in the Morris water maze test



no significant difference between the sham voluntary and 6-OHDA voluntary groups.

However, the voluntary PD group showed higher results in escape latency and lower results in velocity in learning phase than voluntary sham group (Figs. 2, 3), but there was a significant difference in velocity ($p=0.014$), and no significant difference in escape latency ($p=0.118$), among voluntary PD and sham groups (the sham surgery and control groups had similar performance in the MWM test).

2 h after the acquisition phase, a probe test was performed to determine short-term spatial memory retention. Both the 6-OHDA sedentary and 6-OHDA groups also scored worse than the control group in the cued version of the water maze. One-way ANOVA showed a significant effect for the 6-OHDA lesion factor ($p < 0.01$). The Tukey post hoc test showed significant differences between the 6-OHDA sedentary and other groups ($p < 0.05$) and no significant difference between the sham voluntary and 6-OHDA voluntary groups.

The results of ANOVA in the probe test indicated a significant difference (percent distance in the target quadrant; $p=0.013$) and for percent time in the target quadrant (zone 4); ($p=0.025$), and post hoc analysis showed that the PD groups spent less time and shorter distance in the target quadrant (zone 4) compared to the control, and voluntary exercise (sham and PD), groups ($p < 0.01$), (Figs. 4, 5, respectively), which showed short term memory deficit. Additionally, the sham voluntary group indicated the higher percent distance and higher percent time (in zone 4) in compared to the voluntary PD group, but there was no significant difference between them ($p > 0.05$) (Figs. 4, 5).

ANOVA results showed significant differences between groups ($p=0.0134$), PD groups had less frequency in entering zone 4 than other groups, but no significant differences observed among the voluntary exercise (sham and PD) groups ($p=0.196$) (Fig. 6).

Fig. 3 Escape latency (time to find the hidden platform) in the Morris water maze test

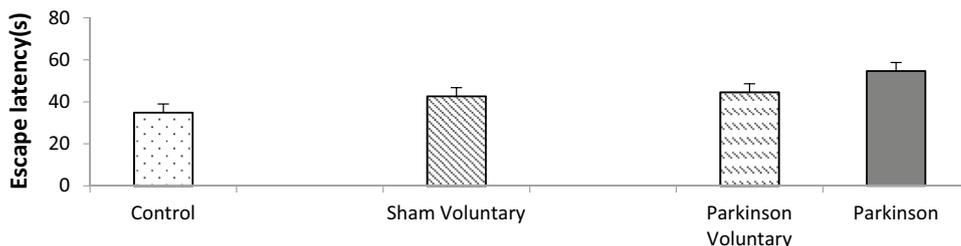


Fig. 4 The percentage of time in the target quadrant

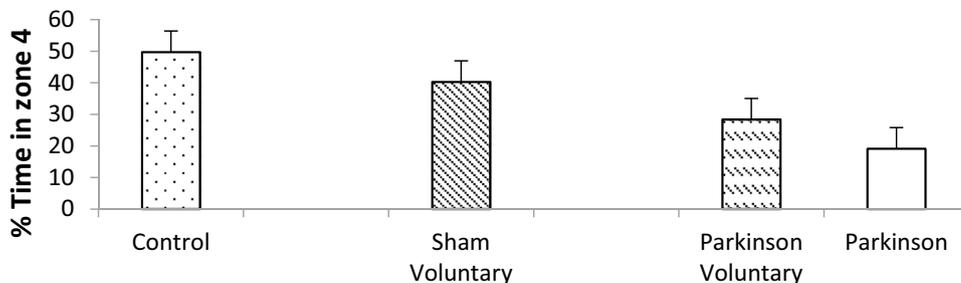


Fig. 5 The percentage of distance in the target quadrant

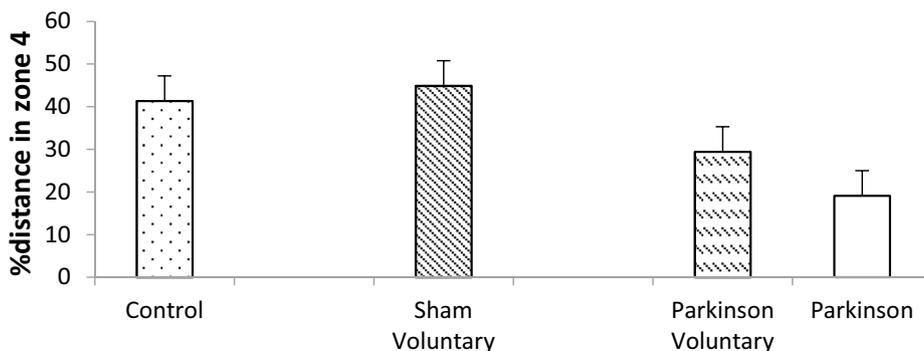
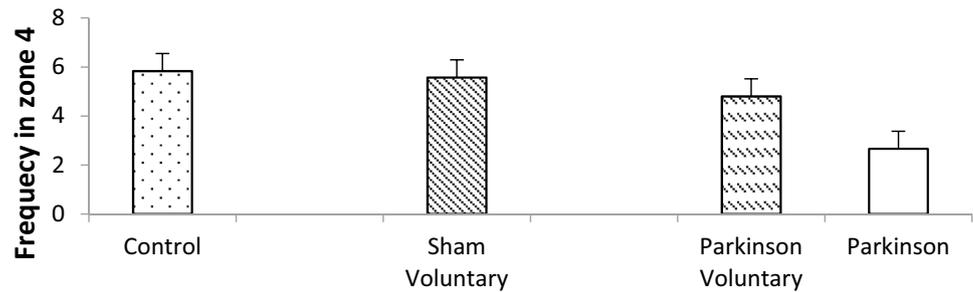


Fig. 6 The number of crossings from the platform region



Discussion

Parkinson's disease is the second most common progressive neurodegenerative disorder that is characterized by the loss of dopamine and degeneration dopaminergic neurons in the substantia nigra. Motor and behavioral symptoms and cognitive impairments even dementia are common in Parkinson disease [2–4]. These deficits caused many problems for patients and their families such as reduction quality of life and many trouble for caregivers [23]. Thus, in this study, we employ 6-OHDA infusions into the medial fore-brain bundle, which produces large, relatively uniform DA depletions across the caudate putamen [24, 25], these lesions more closely mimic the progressive dopaminergic cell loss and behavioral deficits seen clinically, and caused motor and cognitive impairment in this model of PD rats [3, 26, 27].

The results showed that the weight of lesion group dropped after surgery. This result was similar to previous studies [28], it is due the surgical procedure and stress effects but in next weeks the weight gain returned to a steady increase. We found no significant differences in weight gain between groups, this logic results because all groups had a standard and similar condition laboratory and food. However, the final weight in control group is higher than exercise groups, Gorton et al. [29] found similar results as our finding, and it was due to the fact that exercise groups had more activity.

The average running distance and the duration of daily exercise in all exercise groups increased during the study period. This founding was similar to previous studies [29–31], In the present study, the average daily running distance that the voluntary rats ran in the 4 weeks in the wheel running, was approximately between 900 and 1200 m, whereas in the previous studies, the distance that rats ran 3–4 km in 4 weeks [31, 32]. This difference might be due to the variation in lesion place or dose of 6-OHDA used or the variation of wheel running between the studies [33]. In addition, there is no correlation between running distance and weight, also in Howell et al. [30] study, however, previous studies found a correlation between them [21, 34], suggesting that the weight of the rats and the duration of study were within a range that did not influence their correlation.

In the present study, we found that 6-OHDA lesioned rats in MFB caused the learning and memory deficits. This is in agreement with the previous studies reporting impairment of the learning ability of 6-OHDAP-lesioned rats in MWM.

Consistent with previous findings [21, 35], the results of Morris water maze test showed that PD groups presented a poor performance in the Morris as indicated by a reduction in velocity in learning and memory phase, percent time spent in zone 4 and distance traveled in zone 4, in comparison to sham or control group, this result indicated the active role of 6-OHDA lesion on cognitive deficits in an animal model of Parkinson's disease [36]. The inability to perform the memory task in cued version of the water maze after 6-OHDA injection could be due to the lesion of the nigrostriatal pathway [37] and hypokinesia and motor weakness (power and strength) in Parkinsonism rats to some extent, this confirms preliminary findings in the previous study [29].

Increasing the overall distance in the Parkinson's group compared to the control group resulted from 6-hydroxy dopamine injections in the Parkinson's rats group and impairment in learning. This has been confirmed in previous studies [5, 7]. In this study, considering the significant decrease in the time needed to find the platform in the training group rats, compared with the Parkinson's group and a significant decrease in the distance traveled to find the platform in the rats of the training group than the Parkinson's control group, The neuroprotective effect of exercise on memory function has been studied before [38], and our findings strongly suggest that voluntary exercise plays a significant role in the cognitive and behavior deficits in an animal model of Parkinson's disease; this result was consistent with published data [39, 40].

In the study of the effect of exercise, Vučković et al. showed that the effect of running high treadmill exercises in Parkinson's Rats led to an increase in the production of dopamine receptor in the dentin [41]. Aguiar et al. (2009) showed that physical activity increased levels of neutrophins and improved cognitive function (learning and memory). Mabandla et al. [42] showed that 4 weeks of training led to an increase in BDNF levels [43]. Learning skills and working memory are dependent to the basal ganglia and SNC and the decrease of dopaminergic efferents of the striatum

[38]. Recently, it has been suggested that the positive effect of training on learning and memory processes, due to its antioxidant activity and angiogenesis, upregulation of DA receptors, hippocampal BDNF and its receptor TrkB, DJ-1 in muscle and brain [39, 40], seems to be the increase in dopaminergic neurons and the increase of dopamine as an effective substrate in the memory process [44, 45]. In forced exercise *Stress reduces the neuroprotective effect of exercise* [25], it is possible that the difference in our result with other studies may have been due to some small variations in the model of wheel running (size and ...), exercise protocol, intensity and duration of the exercise, in dosing of 6-OHDA injection, place of injection.

One limitation of our study is that we did not have a histological or motor control study, so further research focusing on the historical and motor performance be suggested, also studies with longer time are needed to discern the effect of different duration and intensity exercise on cognitive impairments in PD diseases.

Conclusion

Physical exercise can improve the cognitive impairments in the MFB-lesioned rats via increasing the learning and spatial memory skills. The results suggest that voluntary exercise can be helpful in management of PD treatment.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval All experiments were performed in accordance with the National Institutes of Health ‘Guide for the Care and Use of Laboratory Animals’ and approved by the Ethics Committee of Kerman Neuroscience Research Center.

Informed consent For this type of study the formal informed consent is not required.

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