Original Article

Effects of fluoxetine on memory under forced treadmill exercise conditions in male rats

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Abstract

Background: Studies show inconsistent effects of forced exercise on cognitive processes. These differences are probably due to the stress of coercion in forced exercise. Because fluoxetine is used to treat complications caused by stress, this study aimed to evaluate the effects of fluoxetine on memory in rats under forced treadmill exercise.

Materials and Methods: Experimental groups were the control, the control exercise, the fluoxetine, and the fluoxetine exercise. The exercise program was treadmill running at 22 m/min, 0° inclination for 50 min/day, 6 days/week, for 4 weeks. Fluoxetine (5 mg/kg) was injected 30 min before treadmill. Morris water maze and passive avoidance learning tests were used for evaluation of memory. Acquisition phase of both tests were performed before interventions and memory was evaluated 1-day and 1-week after the last session of exercise and treatments.

Results: Our data showed that forced exercise impaired performance in passive avoidance learning test ($P < 0.05$ and $P < 0.01$, 1-day and 1-week after the last session of exercise and treatments, respectively). Spatial memory was only impaired after 1-week in the exercise group. Fluoxetine improved spatial memory after 1-day in the control group. However, it had no significant effects on memory in the exercise group.

Conclusion: The data correspond to the possibility that forced treadmill exercise can cause stress, and thereby cause damage to memory. The present results suggest that although fluoxetine may improve memory in intact rats but it cannot prevent damages that are caused by forced exercise.

Key Words: Fluoxetine, forced treadmill running, memory, rat

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INTRODUCTION

Exercise has positive effects on health and prevention of the disease. Exercise increases breathing, oxygen consumption by the muscles, blood flow to vital organs of the body, and boosts memory.[1] It reduces stress and oxidative stress in mitochondrial membranes of the brain, heart, liver, and kidney.[2] The effects of exercise on the brain is including the increase in synaptic plasticity, learning and memory, cognitive performance, and helping to heal the diseases of aging, such as Alzheimer's disease.[3]

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However, both in the human and animal studies conflicting effects of exercise on learning and memory were observed. This is discernible especially in complex behavioral tests as no change or impairment of learning. The variation in the results may be related to differences in the protocol (voluntary vs. forced), the intensity and duration of exercise.[4] For example, some studies have shown that treadmill exercise, a form of forced exercise, had no negative effects on the level of apoptosis in the hippocampal dentate gyrus, but also increases cell proliferation and synapses in this part of the brain and these factors will enhance and improve learning and memory.[5-7] However, some studies have not shown these desired effects; for example, when there is background of a disease like Alzheimer's or diabetes, treadmill exercise improves neurological and cognitive processes, but had no favorable effects in intact subjects.[8,9] It was also found that regular physical activity was accompanied by a positive impact on spatial learning and memory in the young rats, but without affecting in the middle-aged and elderly ones.[10] Thus, the compulsory exercises may be having different effects on neuronal functions in different situations and this may be partly due to the stress of the use of force.

There are different forms of antidepressants, which are effective in controlling depression and stress. The initial hypothesis for their action was the enhancement of some neurotransmitters levels such as noradrenaline and serotonin. However, many studies have demonstrated that cellular and molecular adaptations occur in the brain at different levels to treatment with antidepressants. It has been reported that antidepressants have neuroprotective effects.[11,12] They reduce stress-induced atrophy of hippocampal CA3 pyramidal cells[13,14] and increase proliferation of granular cells in the hippocampus.[15]

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI). It has been demonstrated that fluoxetine can prevent delayed cerebral ischemia-induced damage.[16] In addition, fluoxetine significantly decreased neuronal death, and suppressed gliosis (growth of astrocytes in damaged areas of the central nervous system) and proinflammatory markers in animal models of kainic acid-induced cell death.[12] Also, it has been shown that antidepressants such as fluoxetine, clomipramine, amitriptyline doxepin, and desipramine have anti-inflammatory effects.[17-20]

Therefore, due to the effects of fluoxetine in reducing the effects of stress and its neuroprotective effects,[12] and because of the possibility that the stress caused by force in forced treadmill exercise can impact the positive effects of exercise, the aim of this study was to investigate the effects of fluoxetine on spatial memory and passive avoidance learning in rats under forced treadmill exercise.

MATERIALS AND METHODS

Male Wistar rats (180–220 g) were housed 4/cage and maintained on a 12 h light–dark cycle in an air conditioned constant temperature (23 ± 1°C) room, with food and water made available *ad libitum*. The Ethic Committee for Animal Experiments at Isfahan University approved the study, and all experiments were conducted in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH publications number 80–23) revised 1996.

Animals were divided into four groups: The control, the control exercise, the fluoxetine, and the fluoxetine exercise (n = 10 for each experimental group).

Rats in the control exercise and fluoxetine exercise groups were subjected to run at the speed of 22 m/min for 50 min daily (6 days a week), for 4 weeks at 0° of inclination. To familiarize, animals were left on the treadmill for 50 min once a day for 2 consecutive days without operation of the treadmill, then from the 3rd day onward, the treadmill was switched on and the speed increased from 5 to 22 m/min and the duration increased from 10 to 50 min over the course of 5 days. Electric shocks were used sparingly to motivate the animal to run. From week 2 onward, after warm up, speed and duration were kept constant at 22 m/min and 50 min/run. The nonrunners groups were put on the treadmill without running for the same duration as the runners.

Fluoxetine (5 mg/kg; Dr. ABIDI Pharmaceutical Laboratory)[14,16,21] was dissolved in saline and was injected intraperitoneally 30 min before treadmill running.

Acquisition phases of Morris water maze (MWM) and passive avoidance learning tests were conducted before starting the exercise protocol and receiving fluoxetine. One day and 1-week after the last session of treatment and exercise retention phases of the tests were performed.

Passive avoidance learning test

The apparatus consists of two separate chambers connected through a guillotine door. One chamber was illuminated, while the other was dark. The floor of both the chambers consists of steel grids, used to deliver electric shocks. In the acquisition trail, 1-day before exercise and treatments, each rat was placed

in the illuminated chamber while its back was to the guillotine door. After 30 s of habituation, the guillotine door separating the illuminated and dark chambers was opened and the initial latency to enter the dark chamber was recorded. The guillotine door was closed immediately after the rat enters the dark chamber, and an electric foot shock (75 V, 0.2 mA, 50 Hz) was delivered to the floor grids for 3 s. Then the rat was removed from the dark chamber and returned to its cage. One day and 1-week after the last session of exercise and treatment, retention latency time to enter the dark chamber was taken in the same way as in the acquisition trail, but the foot shock was not delivered, and the latency time was recorded up to a maximum of 600 s.

Morris water maze test

The circular tank (180 cm in diameter) was filled with water (22 ± 2°C) made opaque and was surrounded by a variety of extra-maze cues. The tank was divided into four quadrants, and four start positions were located at the interactions of the quadrants. Data were recorded using custom software (Radiab1). Twenty-four hour before water maze testing, all rats were habituated to the water and apparatus. In the spatial acquisition phase, the rats learned to find a submerged platform using extra-maze cues. A transparent Lucite platform (10 cm) was submerged 2 cm underneath the water in the South-East quadrant of the tank, where it remained for all spatial trials. Each rat participated in 16 trials, which were organized into daily block of four trials (1 trial/start position within a block) for 4 consecutive days prior to the start of exercise and treatment. For each trial, the rat was given a maximum time of 60 s to locate the platform, after which the rat remained there for 30 s; if the rat did not locate the platform within 60 s, it was guided to it by the experimenter. The next trial started immediately after removal of rat from the platform. Escape latencies(s) was recorded. One day and 1-week after the last session of exercise and treatment in the retention phase, 60 s probe trial was conducted to examine how well the rats had learned the exact location of the platform. During this trial, the platform was removed from the tank. The swim time was measured inside a circular area (70 cm diameter) around the center of platform and the number of crossing the exact location that previously the plat was located (plat crossing) was counted. To test possible deficits in sensor motor processes, rats were tested in the water maze with a visible platform after probe trial.[8,22]

Statistical analysis

Data were analyzed using the SPSS version 21 for windows (IBM Corporation). The data were analyzed statistically by two-way analyze of variance (ANOVA) followed by Tukey *post-hoc* for between subjects differences and within effects, across the blocks. The data from probe trial of MWM and passive avoidance learning were analyzed by one-way ANOVA followed by Tukey. Number of plat crossing were analyzed by Kruskal–Wallis test (nonparametric ANOVA) followed by Dunn's multiple comparisons for posttest. The significant level was set at $P < 0.05$. Results were expressed as a mean ± standard error of the mean.

RESULTS

Passive avoidance learning test

In the acquisition trial, the mean initial latencies were same in all groups. One day after the last session of exercise and treatment, step through latency showed that forced exercise significantly impaired memory with respect to the control group ($P < 0.05$). The fluoxetine had no significant effect on memory. In fluoxetine exercise group, latency was increased and no significant differences were observed compared to the control group [Figure 1a].

One week after the last session of exercise and treatment, step through latency was decreased in

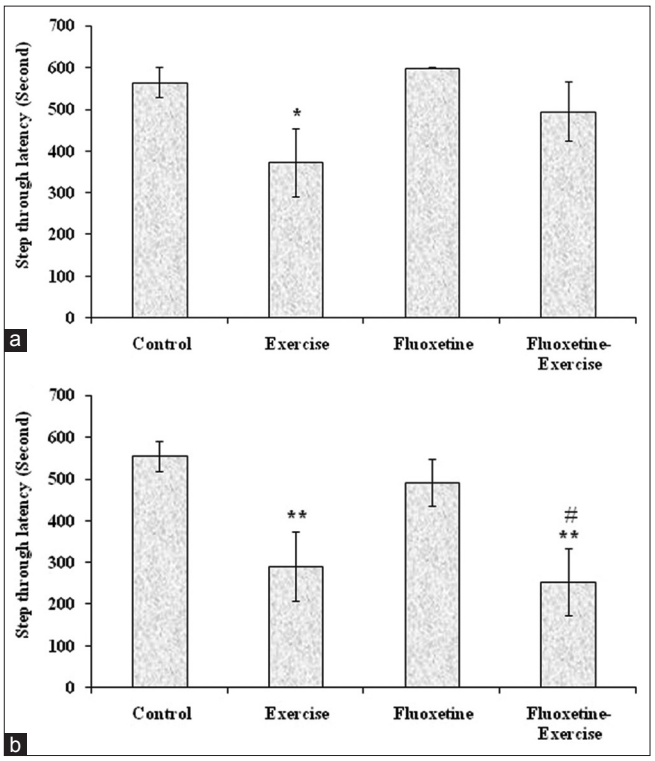

Figure 1: Effects of fluoxetine and forced treadmill running on step through latency in passive avoidance test, 1-day (a) and 1-week (b) after the last session of exercise and treatment. Data are expressed as a mean ± standard error of the mean. *$P < 0.05$ and **$P < 0.01$ with respect to the control group, and #$P < 0.05$ with respect to the fluoxetine group (n = 9–10)

the exercise group ($P < 0.01$) and fluoxetine could not prevent this decline, as there were no significant differences between the exercise and the fluoxetine exercise groups [Figure 1b].

Morris water maze test

All rats showed a reduction in escape latencies [BLOCK effect, F (3,105) =29.59, $P < 0.001$; Figure 2] across the blocks of trials, indicating spatial acquisition. The pattern of reduction in escape latencies across the blocks had no significant differences between the groups [GROUP * BLOCK effect interaction, F (9,105) = 1.03, $P = 0.42$; Figure 2]. Test of between subject effects did not show any significant difference between the groups.

For the results of probe trial 1-day after the last session of exercise and treatment, between group comparison indicated that the fluoxetine group spent more time around the area, where the platform was previously located, than the control group [$P < 0.05$; Figure 3a]. There were no significant differences between the other groups. The number of plat crossing was lower in the fluoxetine exercise group with respect to the fluoxetine group [$P < 0.05$; Figure 3b]. But, the number of plat crossing was same between the other groups.

The results of probe trial 1-week after the last session of exercise and treatment, between group comparison indicated that, the fluoxetine exercise group spent less time around the area than the control and the exercise groups [$P < 0.05$; Figure 4a]. There were no significant differences between the other groups. The number of plat crossing was lower in the exercise group with respect to the control group [$P < 0.05$; Figure 4b]. However, the number of plat crossing was same between the other groups.

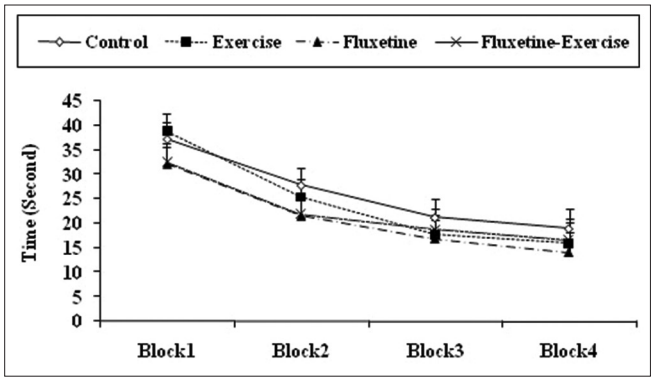

Figure 2: Effects of fluoxetine and forced treadmill running on the escape latency at different blocks to reach the platform during the spatial acquisition of Morris Water Maze test in rats. Each point represents amean ± standard error of the mean of 4 swims. Lower numbers indicate better performance (n = 9–10)

DISCUSSION

The results showed that forced treadmill running damages memory. Although fluoxetine in intact animals could enhance memory somewhat, but when it used during forced exercise could not prevent the damages.

Despite the positive effects of voluntary exercise that has been shown in human and animal models,[23-25] our results show that forced exercise can cause damages in the nervous system. These results are in line with studies that did not show any positive effects of treadmill running in rats.[26] Studies have shown that forced exercise compared to voluntary exercise, has minimum priority, high levels of stress and low levels of brain-derived neurotrophic factor (BDNF) in the brain.[27] A study that compared low intensity (the speed of 10 m/min) and high intensity (the speed of 21 m/min) of forced exercise have shown that high intensity of forced exercise leaded to considerable impairment in spatial memory acquisition and concluded that this was probably due to high stress at high intensity of forced exercise.[28]

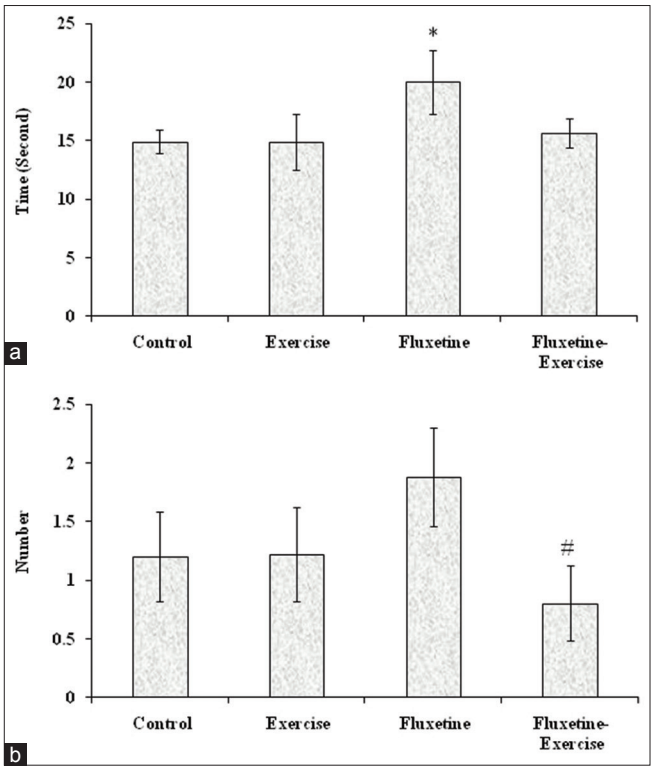

Figure 3: Effects of fluoxetine and forced treadmill running on performance during the probe trial 1-day after the last session of exercise and treatment, as measured by the mean time spent inside a circular (70 cm diameter) around the center of platform (a) and the number of crossing the exact location that previously the plat was located (plat crossing) (b). Data are expressed as a mean ± standard error of the mean. *$P < 0.05$ with respect to the control group, and #$P < 0.05$ with respect to the fluoxetine group (n = 9–10)

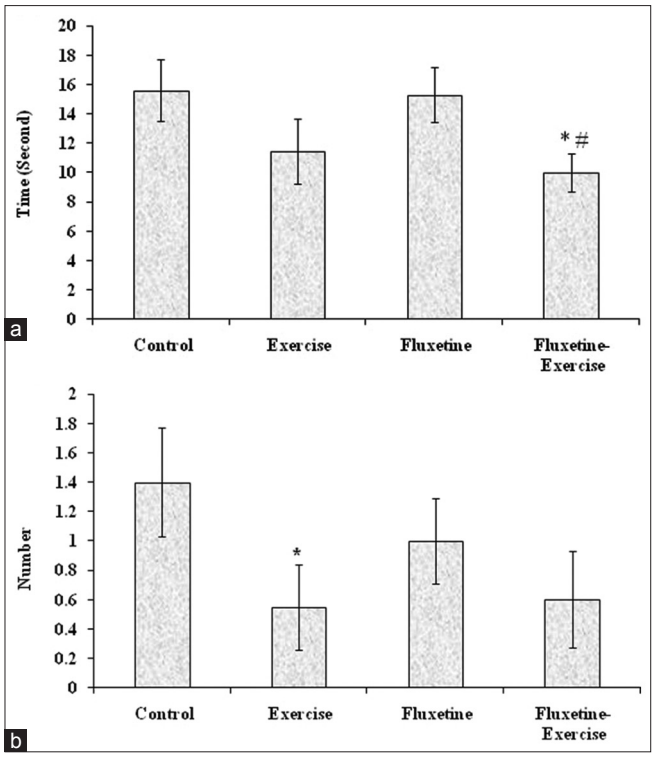

Figure 4: Effects of fluoxetine and forced treadmill running on performance during the probe trial 1-week after the last session of exercise and treatment, as measured by the mean time spent inside a circular (70 cm diameter) around the center of platform (a) and the number of crossing the exact location that previously the plat was located (plat crossing) (b). Data are expressed as a mean ± standard error of the mean. $^{*}P < 0.05$ with respect to the control group, and $^{\#}P < 0.05$ with respect to the fluoxetine group (n = 9–10)

In this study, a day and a week after the last session of exercise, passive avoidance learning was damaged in the exercise group. But 1-day after the last session of exercise no significant change was observed in spatial memory and just over a week, plat crossing was significantly decreased. The reason could be that in the short-term, until the rats have exercised, favorable effects of exercise counteracted the effects of coercion-induced stress somewhat, but a week later the lasting effects of stress could damage the memory.

Forced treadmill exercise can cause some stress responses, because in this type of activity, time, duration, and intensity of exercise is determined by the experimenter and the animal is forced to run by a mild electric shock.[29] Although, to manage stress, the rats in the control group placed on the treadmill in the same conditions while the power is off, but, these animals quickly become familiar with the device and avoid from the electric shock that is, on. They moved freely on the treadmill, and even sometimes slept. However, the rats in the exercise group, if did not run, were permanently at the risk of electric shock. In addition, the rats were exposed to stress that is due to intensity, time of day and duration of exercise, as well as.

Hippocampus is a part of the limbic system, which is involved in learning and memory.[30,31] Studies have shown that this region is damaged after repeated stress.[32] Stress increases the adrenal steroids and steroids affect the hippocampus and inhibit proliferation of granular cells in dentate gyrus.[33-35] It has been demonstrated that adrenal steroids can cause deformation of dendrites in the hippocampus and damage to cognitive functions such as learning and memory.[35,36] However, favorable effects of forced exercise on learning and memory have been shown.[37] These differences may be due to differences in the intensity of exercise, differences of race and age of animals, which are known influencing factors.[38]

Secondarily, we observed that fluoxetine improves memory in normal rats somewhat. Fluoxetine is a SSRI that modulates long-term neural functions in different structures of the brain.[39] Different studies showed the neuroprotective and proliferative effects of fluoxetine.[40,41] Fluoxetine can protect neurons after transient ischemic damage. Such effects are likely related to adjust and change in neurotrophic factors and antioxidant enzymes.[42] Fluoxetine increased BDNF expression that is an important factor for activate and strengthen the neural Plasticity.[43,44] In this study, it was observed that fluoxetine increases the memory in normal rats. However, 1-week after discontinuation of fluoxetine, memory declined to the initial level and got similar to the control group. These results suggest that short-term use of fluoxetine has temporary effect on memory and it is not associated with lasting changes. However, some studies have shown that long-term use of fluoxetine can have reversible devastating effects on memory.[39]

Although, fluoxetine temporarily improved memory in intact rats, but had no significant effects on memory in the exercise group. Therefore, the stress caused by the forced exercise and its neurologic complications are not preventable by fluoxetine, and for appearance of its therapeutic effects, more time is probably needed; because, there is a 2–3 weeks delayed phase between initiation of treatment and the clinical protests of the therapeutic effects of antidepressants.[45]

Our results show that forced treadmill running can cause damage to memory. It seems that this damage is likely caused by stress that is a result of coercion.

However, there may be other factors that require further study. Also, despite that fluoxetine improves memory in intact rats, it could not prevent the damages caused by the forced exercise.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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