Effects of different exercise protocols on ethanol-induced spatial memory impairment in adult male rats

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Chronic ethanol consumption is often accompanied by numerous cognitive deficits and may lead to long-lasting impairments in spatial learning and memory. The aim of the present study was to evaluate the therapeutic potential of regular treadmill exercise on hippocampal-dependent memory in ethanol-treated rats. Spatial memory was tested in a Morris Water Maze task. Adult male Wistar rats were exposed to ethanol (4 g/kg, 20% v/v for 4 weeks) and effects of three exercise protocols (pre-ethanol, post-ethanol and pre-to-post-ethanol treatment) were examined. Results showed that ethanol exposure resulted in longer escape latencies during the acquisition phase of the Morris Water Maze task. Moreover, all three exercise protocols significantly decreased the latency to locate the hidden platform. During the probe trial, ethanol led to decreased time spent in the target quadrant. In contrast, performance on the probe trial was significantly better in the rats that had done the post- and pre-to-post-ethanol, but not pre-ethanol, exercises. These findings suggest that treadmill running can attenuate the adverse effects of chronic ethanol exposure on spatial memory, and may serve as a non-pharmacological alcohol abuse treatment.

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Introduction

Ethanol is one of the most common psychotropic drugs consumed worldwide and chronic ethanol abuse is associated with many deleterious effects (Cargiulo, 2007; Casswell & Thamarangsi, 2009). These effects are well-established in the brains of chronic alcoholics prominently in the hippocampus (Walker, King, & Hunter, 1993; White, Matthews, & Best, 2000), a structure located in the medial temporal region of the brain. The hippocampus plays an essential role in learning and memory, such as spatial learning (Lynch, 2004; Nolte, 2002), and it might be expected that chronic ethanol exposure would be associated with impairments in hippocampus-dependent learning and memory tasks. The results of behavioral studies have demonstrated that ethanol exposure induces more impairment in spatial learning than non-spatial learning, which is known to be mediated by other neural systems (Berry & Matthews, 2004; Lukoyanov & Paula-Barbosa, 2001). For instance, ethanol administration disrupts spatial memory performance in the Morris Water Maze (MWM) task (Matthews & Morrow, 2000). However, the results of studies on the cognitive consequences of chronic ethanol consumption are equivocal. Specifically, memory performance has been reported to be impaired (Farr, Scherrer, Banks, Flood, & Morley, 2005; Matthews & Morrow, 2000), unaffected (Fadda, Cocco, Stancampiano, & Rossetti, 1999; Gal & Bardos, 1994; Homewood, Bond, & Mackenzie, 1997), or even improved (Krazem, Marighetto, Higuere, & Jaffard, 2003; Robles & Sabria, 2008) in experimental animals following chronic ethanol exposure. These inconsistencies in results may be related to the type and magnitude of the neuropathological changes, which depend on the duration of ethanol treatment and the timing of its withdrawal (Lukoyanov, Madeira, & Paula-Barbosa, 1999).

The evidence demonstrates that most chronic ethanol-induced cognitive impairments are significantly reduced during the first months of abstinence (Munro, Saxton, & Butters, 2000; Sullivan, Rosenbloom, Lim, & Pfefferbaum, 2000; Sullivan, Rosenbloom, Pfefferbaum, 2000). However, spatial processing deficits are among the impairments most often described in abstinent alcoholics, and some investigations have also demonstrated that this specific deficit may not be resolved even with long-term sobriety (Crews et al., 2005; Santucci, Cortes, Bettica, & Cortes, 2008).
In contrast to ethanol, the beneficial effects of exercise on the brain functions are well-documented (Cotman & Berchtold, 2002; Cotman & Engesser-Cesar, 2002). It was shown that exercise alleviates feelings of depression and anxiety (Manger & Motta, 2005; Salmon, 2001), and improves emotional health and the sense of well-being (Manger & Motta, 2005). Furthermore, physical activity enhances cognitive function in both children (Hillman, Buck, Themanson, Pontifex, & Castelli, 2009) and adults (Barnes, Yaffe, Satariano, & Tager, 2003; Hillman, Belopolsky, Snook, Kramer, & McAuley, 2004). In elderly persons, physical activity reduces the risk of neurocognitive impairment and dementia (Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001). Also, in rodents, cognitive performance is improved following physical activity (Anderson, Eckburg, & Relucio, 2001). Also, in rodents, cognitive performance is improved following physical activity (Anderson, Eckburg, & Relucio, 2001).

So far, several biological mechanisms have been suggested to explain the effects of exercise on learning and memory. These studies suggest that physical exercise increases synaptic plasticity and stimulates neurogenesis (Hunsberger, 2007) in the areas involved in memory and learning processes, particularly in the hippocampus (Crews, Nixon, & Wilkie, 2004; Van der Borght, Havelkes, Bos, Eggen, & Van der Zee, 2007). There is a growing body of evidence demonstrating that exercise enhances hippocampal brain-derived neurotrophic factor (BDNF), which plays an important role in neuronal survival, differentiation, neuronal connectivity, synaptic plasticity (Huang et al., 2006; Vaynman, Ying, & Gomez-Pinilla, 2004), long-term potentiation (LTP), learning and memory, and even mood changes (Yamada, Mizuno, & Nabeshima, 2002). In addition, it was shown that exercise reverses memory deficits caused by ethanol. For example, wheel running can reverse alcohol-inhibited hippocampal neurogenesis (Crews et al., 2004).

Beneficial effects of voluntary exercise are well-understood on spatial learning and memory, but the effects of forced exercise are still controversial. The purpose of this study was to compare the effectiveness of three treadmill exercise protocols on the spatial memory performance in adult rats receiving ethanol.

Materials and methods

Animals

Male Wister rats (220–250 g) were provided from the university breeding stock and cared for according to the guiding principles for the care and use of animals based upon the regional ethics committee of Tabriz University of Medical Sciences. Rats were housed in pairs at 21.0 ± 2 °C and on a 12 h reverse light/dark cycle (lights on 7:00 a.m.). Food and water were provided ad libitum, and body weights were monitored daily.

Experimental design

A summary of the experimental design is provided in Fig. 1. Animals were randomly assigned to one of two treatment groups. One group received ethanol for 4 weeks, and another received saline instead of ethanol, as the control group. Each group was further subdivided into one sedentary and three treadmill exercise groups, with seven rats in each. Therefore, the experimental groups were as follows:

1. Sedentary ethanol-treated group (Sed-Eth): animals remained sedentary and received ethanol for 4 weeks.
2. Pre-ethanol exercise group (Pre-Eth/Exe): animals were run on a treadmill for 2 weeks before undergoing ethanol treatment for 4 weeks.
3. Post-ethanol exercise group (Post-Eth/Exe): animals received ethanol for 4 weeks and after its withdrawal they were run on a treadmill for 2 weeks.
4. Pre-to-post-ethanol exercise group (Pre-to-Post-Eth/Exe): animals were run on a treadmill from 2 weeks prior to ethanol treatment until 2 weeks after its withdrawal.
5. Sedentary saline group (Sed-Sal): animals remained sedentary and received saline.
6. Pre-saline exercise group (Pre-Sal/Exe): animals were run on a treadmill from 2 weeks before undergoing 4 weeks of saline treatment.
7. Post-saline exercise group (Post-Sal/Exe): animals received saline for 4 weeks and after its withdrawal they were run on a treadmill for 2 weeks.
8. Pre-to-post-saline exercise group (Pre-to-Post-Sal/Exe): animals were run on a treadmill from 2 weeks prior to saline treatment until 2 weeks after its withdrawal.

Ethanol administration

Prior to beginning the experiments, all rats were tamed by gentle handling which made them amenable to gavage. Ethanol (4 g/kg) was administrated intragastrically once a day for 28 consecutive days. The initial concentration of ethanol was 5% (v/v), and then 5% ethanol was added every 2 days to reach a final concentration of 20% (v/v). This concentration was maintained for the remaining 22 days of the experiment. Furthermore, this dose of alcohol yields a peak blood ethanol concentration of 99.80 ± 6.10 mg/dl (Husain, Vazquez Ortiz, & Lalla, 2006). Control rats received saline instead of ethanol.

Treadmill exercise

Rats were familiarized with the treadmill apparatus to minimize novelty stress and were randomly assigned to different experimental groups (sedentary and exercised groups). Each rat ran on the treadmill at a low initial speed followed by an increase of 5 m/min in the speed of the treadmill every 3 min until they reached their point of exhaustion (i.e., failure of rats to continue running). The time to fatigue (in minutes) and workload (expressed by velocity in m/min) were taken as indices of exercise capacity, and as a measure of maximum oxygen uptake (VO2 max) (Arida, Scorza, dos Santos, Peres, & Cavalheiro, 1999; Cechetti et al., 2012). The moderate-intensity forced-exercise training program was used, which consisted of running sessions on an adapted motorized rodent treadmill at 60% of each rat’s maximal oxygen uptake (Brooks & White, 1978).

Animals in the exercise groups were trained on a treadmill (0° inclination) for 60 min/d, at a treadmill speed of 17 m/min, for 5 d/week. In order to encourage rats to run forward, the front end of the treadmill was covered with a dark cloth. Furthermore, a shock grid at the back of treadmill provided a mild shock (0.75 mA, 500 ms duration, 0.5 Hz rate) to prod rats to run if the pace of the animals slowed below the treadmill rate. Actually, very few shocks were applied in the first few minutes of the exercise and most animals ran voluntarily without using shocks. Animals that were not able to perform the exercise were excluded from the sample. At the same time of the day, the sedentary rats were placed on a stationary treadmill, with the shock grid turned off, for the duration of the treadmill training session.

Morris Water Maze

Two weeks after the ethanol withdrawal, spatial learning and memory were assessed using a Morris Water Maze (MWM) task.
A black circular water pool (with a diameter of 200 cm and a depth of 60 cm) was filled with water at 23°C and situated in a room with many visual cues on the walls. The pool was conceptually divided into four equal quadrants and had four points designed as starting positions (N, S, W, or E) (Pereira, Strapasson, Nabinger, Achaval, & Netto, 2007). The behavior of each rat was tracked with a camera that was placed directly above the pool and connected to a computer.

Prior to assessing animals in the MWM, rats were allowed to swim in the water for 1 min, in order to familiarize them with the task and its environment. One day after the familiarization session, rats were tested in the MWM task. First, all animals were submitted to a visible platform task to test eyesight and swimming ability. A black escape platform (10 cm diameter) was placed in one quadrant region in the pool such that its top surface was 1 cm above the water level. A large visual cue was attached to the platform to increase its visibility. Animals were initially placed on the platform for 30 s to familiarize them with the cue. Each rat was given four trials in which they were allowed to search for the platform for a period of 60 s. The rat's starting position remained constant throughout the visible testing, but the platform location was randomized among trials to overcome any residual preference for the previous location of the platform. Escape latency (the time to find the platform) and swim speed for the four trials were averaged to obtain each animal’s visible task score.

The next day after the visible platform task, rats were trained on the hidden platform task to assess spatial acquisition. In this task, the platform was submerged 2 cm below the water surface and remained in the same location for all trials. The animals received three blocks of training, each consisting of four trials (12 trials in total). Each block was considered as a separate test session and the blocks of trials were separated by 30 min. All training was completed in a single day and took place during the light cycle. In each trial, rats were placed into the water, facing the wall of the pool, in one of the four starting locations (N, S, W, and E) and were permitted to swim up to 60 s to find the escape platform. At the end of 60 s, if the animals failed to find the platform within the allotted time, they were gently guided to the platform by hand and were allowed to remain there for 15 s. The next trial was started immediately after their removal from the platform. After completion of the fourth trial of the block, rats were removed from the pool and placed in a temporary holding cage under a heat lamp.

Spatial memory retention was evaluated in a 60 s probe trial that was carried out 24 h after the last acquisition trial. The platform was removed from the pool, and rats were placed into the water in either the adjacent right or the adjacent left quadrant with respect to the training quadrant. The percentage of time spent in each quadrant was recorded.

Statistical analysis

Data from the four trials of each block were averaged and analyzed as a three-factor analysis of variance (ANOVA) [2 treatment groups (ethanol and saline) × 4 exercise groups (3 exercises and 1 sedentary) × 3 training blocks]. Due to unequal variances, a weighted least-squares method was performed for the latency time to find the hidden platform during the training blocks. Data from the visible platform task and the probe trial were analyzed as a two-way ANOVA (treatment groups × exercise groups). All analyses of variances were followed by the Tukey's test for multiple comparisons, whenever appropriate. Differences with \( p < 0.05 \) were considered statistically significant.

Results

In the present study, the rats were evaluated in the MWM to assess the effects of ethanol exposure and forced treadmill exercise on spatial learning. The three-way ANOVA revealed a significant main effect of the training block on escape latency \( F(2,59) = 443.17 \), etc.
indicating that all rats improved their spatial learning across the three training blocks (Fig. 2A). There was also a significant effect of ethanol exposure \(F(1,59) = 88.85, p < 0.001\), suggesting that the ethanol treatment affected the time latency compared to saline treatment (Fig. 2B). The ethanol-treated rats took a longer time to find the hidden platform compared to the saline-treated rats. In addition, there was a significant effect of exercise \(F(3,59) = 30.50, p < 0.001\), indicating that the exercise significantly decreased the time taken to locate the hidden platform (Fig. 2C). Moreover, a significant treatment group \(\times\) exercise interaction was found \(F(3,59) = 11.49, p < 0.001\), demonstrating that exercise improved performance primarily among ethanol-treated rats (Fig. 3). However, the block \(\times\) treatment group \(\times\) exercise interaction was not significant for spatial acquisition \(F(6,59) = 0.30, p > 0.05\).

Tukey’s post hoc test revealed significant differences between the sedentary and all exercise groups \(p < 0.0005\), suggesting that all three exercise protocols improved acquisition of spatial memory (Fig. 2C). Post hoc analysis also showed a significant difference between the pre-to-post-ethanol/saline and the pre-ethanol/saline exercise groups \(p < 0.05\). The pre-to-post-ethanol/saline exercise led to significantly shorter latency to find the hidden platform in the MWM compared to the pre-ethanol/saline exercise. However, no significant differences were found between the pre-ethanol/saline and post-ethanol/saline groups, and between the pre-to-post-ethanol/saline and the post-ethanol/saline exercise groups.

The three-way ANOVA analysis of swim speed revealed no main effects of block \(F(2,144) = 2.39, p > 0.05\), ethanol \(F(1,144) = 3.52, p > 0.05\), exercise \(F(3,144) = 2.10, p > 0.05\) and their interaction, indicating that neither ethanol nor exercise had any significant effect on swimming speed.

On the probe trial, a two-way (treatment group \(\times\) exercise) ANOVA revealed a significant effect of ethanol treatment \(F(1,48) = 10.33, p < 0.01\) on the time spent in the target quadrant, indicating that the ethanol treatment decreased the searching time in the target quadrant (Fig. 4). However, the number of platform crossings was not significantly affected by ethanol treatment \(F(1,48) = 0.59, p > 0.05\). The analysis also showed significant effects of exercise on the time spent in the target quadrant \(F(3,48) = 13.61, p < 0.001\), and on the number of platform crossings \(F(3,48) = 7.54, p < 0.001\), suggesting there are beneficial effects of treadmill exercise on spatial memory retention (Fig. 5A).
and B). The treatment group × exercise interaction was not significant for the time spent in the target quadrant \( [F(3,48) = 1.77, p > 0.05] \), and for the number of platform crossings \( [F(3,48) = 0.28, p > 0.05] \).

Tukey's post hoc test revealed that both the post- and pre-to-post-ethanol/saline, but not pre-ethanol/saline, exercise groups spent significantly more time in the target quadrant during the probe trial than the sedentary ethanol/saline-treated rats \( (p < 0.05) \) (Fig. 5A). This test also showed the pre-ethanol/saline exercise group significantly spent less time in the target quadrant than both the post-ethanol/saline and pre-to-post-ethanol/saline exercise groups \( (p < 0.05) \). Additionally, there was a significant difference in the number of platform crossings between the pre-to-post-ethanol/saline exercise rats and both the sedentary ethanol/saline-treated and pre-ethanol/saline exercise groups \( (p < 0.05) \) (Fig. 5B). However, no significant differences were observed between the sedentary ethanol/saline-treated and pre-ethanol/saline or post-ethanol/saline exercise groups.

Finally, in the visible platform task, no significant main effects of ethanol treatment and exercise on the escape latency as well as swim speed were observed (data not shown). Moreover, there was no statistically significant interaction between treatment group (ethanol and saline) and exercise for these parameters. Therefore, the ethanol treatment and treadmill exercise had no effect on the sensorimotor functions and motivation.

**Discussion**

We investigated the effects of ethanol and forced treadmill training on the spatial learning and spatial memory of adult male Wistar rats. To our knowledge, this is the first study that has compared the efficacy of three forced-exercise protocols (pre-ethanol, post-ethanol and pre-to-post-ethanol administration) on spatial memory in the ethanol-exposed rats using the MWM task, which is a reliable method to assess hippocampus-dependent spatial learning and memory in rodents (Clark, Broadbent, & Squire, 2007; Ibi et al., 2008). Our findings indicated that performance in the MWM task was significantly impaired by ethanol treatment, and that the impairment was diminished by treadmill exercise.

Chronic ethanol exposure significantly impaired performance during the acquisition phase (spatial learning) of the MWM task, as evidenced by increases in escape latency. Ethanol treatment also caused significant deficits in spatial memory retention. Ethanol treatment decreased the time spent in the target quadrant during the probe trial. Our results agree with previous studies that demonstrated impairment of spatial memory by ethanol in rats (Acheson, Ross, & Swartzwelder, 2001; Crews et al., 2005; Farr et al., 2005; Matthews & Morrow, 2000; Rajendran & Spear, 2004; Robles & Sabria, 2008). Ethanol treatment did not alter the time taken to find the platform or the swim speed in the visible platform task, indicating that impairments in the spatial memory were not due to sensorimotor or motivational alterations. Also, such impairments were
unlikely because of ethanol withdrawal. The deficits were observed 14 days after the final exposure to ethanol, and behavioral consequences of ethanol withdrawal usually peak within the first 48–72 h after the last ethanol exposure (Roberts, Heyser, Cole, Griffin, & Koob, 2000; Valdez et al., 2002).

These observations provide evidence that chronic ethanol administration impairs spatial memory in rats. Consistent with previous studies (Crews et al., 2005; Krazem et al., 2003; Robles & Sabria, 2008; Santucci et al., 2008), it can be suggested that chronic ethanol exposure can produce spatial learning and spatial memory impairments which persist long after cessation of ethanol exposure.

Ethanol-related deficits in spatial memory presumably reflect dysfunction of the hippocampus, a cerebral structure closely involved with spatial memory (Lynch, 2004; Nolte, 2002). Place cells are specific hippocampal cells, which help animals navigate better through their environment (Doeller, Barry, & Burgess, 2010). Damage to the hippocampus alters the spatial processing of place cells, which produces impairment in spatial navigation (Squire, 1992). It was suggested that ethanol exposure impairs spatial navigation by altering spatial processing of the place cells (Matthews, Simson, & Best, 1996; White & Best, 2000), and therefore leads to impaired performance in hippocampus-dependent memory tasks including the MWM task (Baydas, Yasar, & Tuzcu, 2005; Berry & Matthews, 2004; Herrera et al., 2003).

Exercise has been shown to offer significant neuroprotection in many neurodegenerative conditions (Briones, 2006; Briones, Suh, Hattar, & Wadowska, 2005; Griffin, Bechara, Birch, & Kelly, 2009; Hayes et al., 2008; O’Callaghan, Ohle, & Kelly, 2007). Also, the beneficial effects of exercise on cognitive function are well documented (Anderson et al., 2002; Hillman et al., 2004, 2009). In the present study, ethanol-treated rats that had received treadmill exercise showed significant decreases in escape latency during acquisition trials, when compared to sedentary ethanol-treated rats. This provides evidence that the treadmill running attenuated the ethanol-induced impairment of spatial learning.

Our findings also showed that all three exercise protocols (pre-, post- and pre-to-post-ethanol) had a positive impact on performance in the MWM task, although this effect was more pronounced in the pre-to-post-ethanol exercise group compared to the pre-ethanol exercise group. Furthermore, retention of spatial memory in the MWM task was enhanced by both the post- and pre-to-post-ethanol, but not the pre-ethanol, exercises.

In the pre-ethanol exercise protocol, the animals were tested in the MWM 6 weeks after the last session of exercise. Therefore, the lesser amount of beneficial effects of pre-ethanol exercise may be due to the fact that the benefits of exercise are reversible and can return to baseline levels several weeks after the end of exercise. In other words, just 2 weeks of forced exercise is not sufficient to

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**Fig. 5.** The effect of treadmill exercise on memory retention during the probe trial, for the ethanol-treated rats. Performance on the probe trial was significantly improved by exercise. Panel A shows the percentage of time spent in the target quadrant. Panel B shows the number of platform crossings. Data are means ± SEM. SEMs were calculated using the error mean square in the ANOVA. * = significantly different from sedentary group (Tukey’s post hoc test: p < 0.05). # = significantly different from pre-ethanol/saline group (Tukey’s post hoc test: p < 0.05).
produce enduring residual effects on the spatial memory. Consequently, a regular exercise regimen may be particularly important to maintain the beneficial effects on cognitive functions. Consistent with our results, Radak et al. (2006) also reported that beneficial effects of exercise on passive avoidance tasks are reversible and are lost 6 weeks after detraining. Moreover, Van der Borght et al. (2009) revealed that increased dentate gyrus vessel density and hippocampal cell proliferation following 3–10 days of exercise, return to the baseline 24 h after cessation of the physical activity.

Consistent with our results, several previous studies have reported benefits of treadmill running on spatial memory in ethanol-treated rats (Crews et al., 2004; Heller, Goodlett, Greenough, & Klintsova, 2009; Kim, Yang, Chang, & Kim, 2011). However, in these studies, animals were exercised on a treadmill either simultaneously with ethanol exposure or after its withdrawal (Crews et al., 2004; Heller et al., 2009; Kim et al., 2011). In contrast, our study design helped us to compare the neuroprotective effect of treadmill exercise on spatial learning and memory when it was administered pre-, post-, and pre-to-post ethanol exposure.

It has been suggested that treadmill running plays a neuroprotective role and is more restorative in the face of impairments such as exposure to ethanol (O’Callaghan et al., 2007), morphine (Miladi-Gojji et al., 2011), and brain injury (Hayes et al., 2008). Additionally, physical activity was shown to reverse some of the deleterious morphological and behavioral consequences of aging (Garza, Ha, Garcia, Chen, & Russo-Neustadt, 2004; van Praag, Shubert, Zhao, & Gage, 2005) and to attenuate the harmful consequences of acute stress exposure (Pietropaolo et al., 2008).

There are a variety of potential mechanisms that can cause the exercise-induced improvements in learning and memory. The beneficial effects of exercise could be due to an exercise-induced increase in hippocampal neurogenesis (Fabel & Kempermann, 2008; Kim et al., 2004; Uda, Ishido, Kami, & Masuhara, 2006). Neurons in the hippocampus are maintained by proteins called neurotrophins, particularly BDNF, which help to sustain the structural and functional integrity of the hippocampus. BDNF is an important factor in neurogenesis (Rossi et al., 2006; Zhao, Deng, & Gage, 2008) and synaptic processes such as LTP (Barco et al., 2005). It also plays an essential role in performance on hippocampus-dependent learning and memory tasks. Moreover, the physical exercise alters neurotransmitter levels and neuronal metabolism in a rat's hippocampus. It was reported that activation of cholinergic fibers increases acetylcholine release and produces vasodilatation in rat hippocampus, resulting in the increased cerebral blood flow in the hippocampus during exercise (Nakajima, Uchida, Suzuki, Hotta, & Aikawa, 2003). Nakajima et al. (2003) demonstrated that the increase in cerebral blood flow in the hippocampus during walking is at least partly responsible for the improvement in spatial learning ability associated with hippocampal activation or hippocampal neurogenesis.

In conclusion, the present study demonstrated that 4-week ethanol exposure caused obvious spatial learning and memory impairments in adult rats, while treadmill running could significantly prevent or even reverse these deficits. This reinforces the therapeutic potential of forced treadmill exercise in treating ethanol-induced cognitive impairment.

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