Physiology and Pharmacology 27 (2023) 161-170
Original Article

Effects of swimming exercise during pre-adolescence on learning and memory in adult rats: behavioral and electrophysiological approaches

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ABSTRACT

Introduction: The positive impact of physical activity on age-related memory impairment is well documented. There is no clear report on the effects of pre-adolescent exercise on cognitive abilities in adulthood.

Methods: Male Wistar rats (4-week-old) were randomized to a non-swimmer (control, n=20) and swimmer (n=20). The swimmer group trained for 30min a day, 6 days per week, 6 weeks. After the last day, behavior (through passive avoidance learning and radial maze) and electrophysiological techniques were evaluated in rats.

Results: Swimming exercise led to a decrease in the number of trials in the passive avoidance test. In addition, swimming reduced the number of working memory and reference memory errors in the radial maze task. On the radial maze task, the two groups showed equal learning ability in finding the baited food arms by day 15. The results of the recall tests showed that the number of total memory errors and working memory errors was significantly lower in the swimmer group than in the non-swimmer group. Exercise also improved both Population spike (PS) amplitude and field-excited postsynaptic potential slope.

Conclusion: These results revealed that swimming exercise could improve memory by increasing synaptic plasticity in rats.

Keywords:
Exercise
Memory
Pre-adolescence
Hippocampus
Rat

Introduction

Adolescence is a vulnerable developmental stage characterized by critical neuronal purification, risky behaviors and emotional instability (Khani et al., 2022). This phase is a transition from pre-adolescence to adulthood (Dahl, 2004; Eiland and Romeo, 2013). Adolescence generally allocated in early, middle and late stages. In humans, around 10-14 years are considered earlier, 15-17 years middle and 18-25 years late adolescence or

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Received 7 February 2021; Revised from 14 July 2022; Accepted 24 July 2022

Citation: Shahidi S, Rafiee H, Sohrabi S, Mohebi N, Jahani M, Sohrabi F, Hakhamaneshi E, Mohamadaiazar S, Komaki A, Afshar S, Sadeghian R. Effects of swimming exercise during pre-adolescence on learning and memory in adult rats: behavioral and electrophysiological approaches. Physiology and Pharmacology 2023; 27: 161-170. http://dx.doi.org/10.61186/phypha.27.2.161

initial adulthood (Arnett, 2000). Parallel values are observed in rodents, where PNDs 28 to 42 are measured to be in early middle adolescence (Brust et al., 2015) and PNDs 42 to 55 are reflected to be in the context of overdue adolescence/advancing adulthood (Salmanzadeh et al., 2020). There are distinct physiological and behavioral traits to each of those ranges (Bogin, 1994). In addition, removal of excessive neuronal connections increases early in life, leading to reduced synaptic density in late preadolescence and late adolescence (Lenroot et al., 2007). In this growth phase, white matter integrity is also connected with the enhancement in interhemispheric transmission (Muetzel et al., 2008), inhibitory management (Liston et al., 2006) and functioning memory (Olesen et al., 2003).

Memory is a complex brain function to learn and recall new facts (Shahidi et al., 2018). Two types of memory, consisting of reference memory and working memory can be expected in spatial tasks in rodents, specifically in the Morris water maze and the radial arm maze (Shahidi et al., 2014; Shahidi et al., 2004). As part of the limbic system, the hippocampus appears to be crucial for memory function (Shahidi et al., 2018).

Exercise has positive properties on the functions of various organs in the body (Khajehnasiri et al., 2021; Sadeghian et al., 2021), including the nervous system and the brain (Molaei et al., 2020). Current studies have shown that exercise significantly facilitates the acquisition and/or retention of several hippocampus-dependent tasks in rodents (Abshenas et al., 2020; Molaei et al., 2020). Exercise improved learning and memory through hippocampal neurogenesis (Abshenas et al., 2020). In addition, exercise improves brain-derived neurotrophic factor (BDNF) levels and synaptic plasticity within the hippocampus of physically active rats (Abshenas et al., 2020; Farmer et al., 2004).

The dentate gyrus (DG) is part of the formation of the hippocampus in the temporal lobe of the brain (Amaral et al., 2007). This rejoin is a useful resource in the formation of the most recent episodic memories (Hatami et al., 2018), spontaneous exploration of novel environments (Poulter et al., 2020) and other features. It is noteworthy that the presence of extensive neurogenesis in the adult human dentate gyrus was the challenge of the discussion (Hatami et al., 2018). The hippocampus consists of three main parts: the DG, the cornea ammonia (CA) 1 and 3. Information is transmitted through the entorhinal cortex to the DG, CA_1 and CA_3 (via perforant pathway fibers), DG to pyramidal neurons CA_3 (via mossy fibers) and pyramidal neurons CA_3 to CA_1 (via Schaffer collaterals). CA_1, in turn, returns to the cerebral cortex as a one-way stimulus and forms the "hippocampal trisynaptic circuit" (Avchalumov and Mandyam, 2021).

Some studies have been supported the molecular basis of long-term potential (LTP) in the CA_1 region of the hippocampus in memory consolidation for avoidance learning (Ahmed and Frey, 2005). In another study, in both hippocampal subregions, the DG and CA_1 regions, LTP was shown to be uniformly facilitated by the same novel environment (Kemp and Manahan-Vaughan, 2008; Shahidi et al.,). Many studies have shown that treadmill running leads to selective improvements in hippocampal plasticity (Abshenas et al., 2020). This study examined the effect of exercise during the pre-adolescent period on memory and synaptic plasticity in adult male rats.

Material and methods

Groups

Our research performed on 40 male Wistar rats (4-5 weeks; Purchased from the Hamadan University of Medical Sciences animal house). The animals were subjected to controlled environmental factors including: temperature of 20±2°C, light/dark cycle of 12/12 hours and relative humidity of 60±5% and had free access to food and water. After 7 days of adaptation, the rats were randomly distributed into two groups (n=20 rats/group): group 1 (non-swimmers; animals unable to swim) and group 2 (swimmer group; animals trained to swim). All experimental and animal care procedures accepted by the Hamadan University of Medical Sciences Ethics Committee (Umsha.1387.42458) and carried out in accordance with the National Institutes of Health guidelines (NIH Publication 8023, 1996) on laboratory animal care standards.

Exercise protocol

The animals were acclimated to the pool for five consecutive days (5-20min per day). After acclimatization, the trained rat swam for six consecutive days (60min per day) for two weeks. Control rats did not swim (Habibi et al., 2016). On the first day, the training sessions lasted 10min and increased by 10min every 7 days. On the ultimate day, the animals swam constantly for 20min and

on the give up of the 14th day for 30min. Daily training (30min) was maintained from day fourteen to the end of work (de Lima et al., 2012). After the last training day, each animal exposed to a series of behavioral tests.

Passive avoidance learning test (PAL)

Basically, the equipment and methods were similar to previous studies (Afshar et al., 2018). Briefly, a passive avoidance device (namely, a shuttle box) consisted of two equally sized compartments divided by a guillotine door. The walls and floor of a light compartment were made of transparent sheets and the walls of a dark chamber were prepared of dark opaque plastic. An electric shock used to be conveyed to the flooring of the darkroom by a stimulator (50Hz, 1.5s, 0.4mA intensity) (Hosseini et al., 2010).

The PAL test consists of three phases: habituation, acquisition and retention. During the habituation stage, all experimental groups underwent two tests. At first, each rat was placed in the bright compartment of the device and after 15s, the guillotine door was raised so that the rat entered the dark compartment. Then the door was closed and 30s later, the rat was taken out. After 30min, this habituation test repeated. In passive avoidance training, animal was placed inside a lighted room. Five seconds later, the door was opened and when the rat entered the dark room, the door was closed and the rat received an electric shock. The avoidance behavior was repeated until the rats did not enter the dark room within 120s. Dark section input latency (step-through latency, STLa) and number of tests to acquisition were recorded (Dehbani et al., 2019). In the retention experiment (24h after PAL acquisition), the rat was located in the lighted section and after 5s the guillotine door was raised. Step-through latency during the retention trial (STLr) and time spent in the dark compartment (TDC) recorded up to 300s. No electric shock administered in this experiment.

Radial maze

Spatial memory measured in an 8-arm radial maze. The device consisted of eight arms (50cm long, 15cm high, 10cm wide) extending from a small central platform (20cm in diameter). A feeding station was located at the end of each arm and food pellets inserted at the distal end of four arms. Several additional visual cues for the labyrinth added to the walls for orientation. The rat located in the maze and allowed to find and eat all of the food pellets for a maximum duration of 5min. All animals trained 3 trials per day, with an interval between trials of 5min and the trials were recorded by the video tracking software for 6 consecutive days. On the last day, the trial completion time and the number of food arms baited measured. A reference memory error was measured when the rat never visited baited arms, while a working memory error was calculated when a rat visited a baited arm more than once (Huang et al., 2004; Shahidi et al., 2014).

Electrophysiological study

Electrophysiological techniques previously described (Shahidi et al., 2019a; Shahidi et al., 2019b). After behavioral testing, anesthetized rats were fixed inside the stereotaxic apparatus using urethane (1.5g/kg, IP, Sigma-Aldrich, USA). An electric heating pad kept the rats' body temperature at 36.5±0.5°C. Based on the Paxinos and Watsons atlas, the position of the DG and the perforating pathway (PP) (Shahidi et al., 2021) was determined and small holes were drilled in the skull. Then the recording and stimulation electrodes were located in the DG and PP areas, respectively. In each region (DG/PP), Teflon-insulated bipolar stimulation/recording electrodes (concentric; 125m in diameter) were used (Mohammadi et al., 2019).

An input/output response curve was plotted by the intensity of a single-pulse stimulation and the average of five responses for each intensity. This recorded baseline response was considered a "0 min" time in the measurement of PS amplitude and field-excited postsynaptic potential (fEPSP) immediately before high-frequency stimulation (HFS). HFS (400Hz, excitation time of 0.2 milliseconds, 10 bursts of 20 stimuli and burst interval of 10s) induced LTP. After HFS, the proposed responses recorded at 5, 30, 60min, fEPSP and PS were measured.

Excitation parameters were set from the stimulus using eTrace software and supplied to the constant current cutoff system "A365, WPI, and Inc. USA" through a data acquisition device before being transmitted to the PP via the excitation electrode. The DG's field-induced potential response passed through the preamplifier, amplified (1000) and filtered (1Hz to 3kHz) (Karamian et al., 2015). These data were stored on a computer for future offline analysis (Salehi et al., 2015). The PS amplitude is the distance of the negative peak between two positive peaks. The slope fEPSP is that the slope of the

primary positive peak.

Statistical analysis

The data analyzed in SPSS version 16.0. Electrophysiological data, including PS amplitude and EPSP slope, analyzed using two-way ANOVA. In addition, data from behavioral examination statistically evaluated with the help of a t-test. The statistical difference was $P<0.05$. All statistics mentioned as mean±SEM.

Results

Passive avoidance learning test

As demonstrated in Figure 1A, there has been no remarkable difference within the STLa within the first acquisition trial among the experimental groups (non-swimmer: 16.3±4, swimmer: 21.6±4.8). An evaluation of the number of trials to acquisition indicated that there was a noteworthy difference between the groups (non-swimmer: 1.2±0.16, swimmer: 1±0; Fig. 1B). Especially, the number of trials inside the Swimmer group become noticeably decrease than the non-swimmer group ($P<0.05$).

Figure 1 showed the consequences of the retention phase in the PAL test. Our results showed no remarkable difference in STLr between groups (non-swimmer: 195.2±43, swimmer: 163.1±32; Fig. 1C). Furthermore, no significant differences in TDC were observed between the experimental groups (non-swimmer: 36.1±12, swimmer: 47.1±14; Fig. 1D).

Radial maze

As indicated in Figure 2, there have been no significant differences within the trial termination times [non-swimmer: 105.35±12, swimmer: 105.10±15] between the two groups on the last day of training. According to the results, there was a significant difference in the number of references [non-swimmer: 2.4±0.16, swimmer: 2±0.1] and working memory errors [non-swimmer: 0.85±0.2, swimmer: 0.35±0.1] between two experimental groups. Figure 3 showed that the number of reference memory errors in the Swimmer group significantly decreased compared to the non-swimmer group ($P<0.01$). It also found that the number of working memory errors in the Swimmer group considerably reduced compared to the

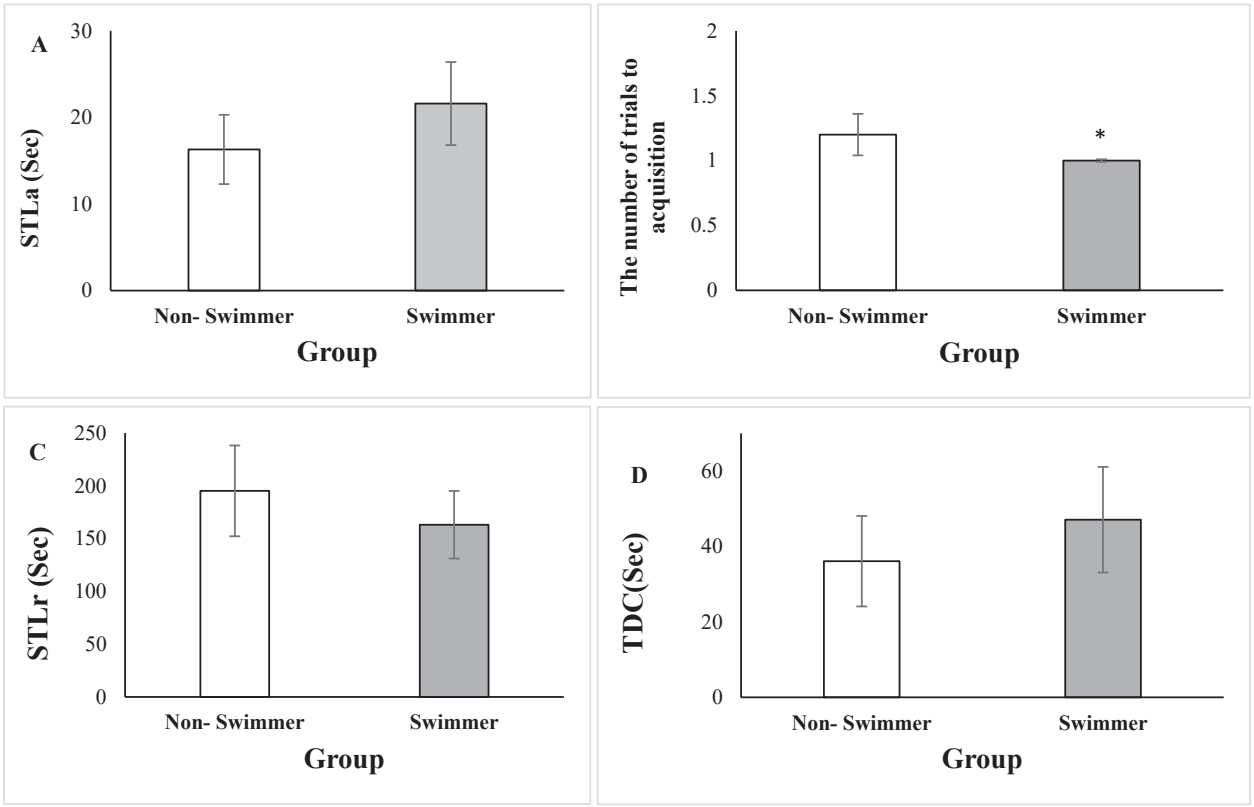

FIGURE 1. Results of the passive avoidance learning (PAL) test among the experimental groups: swimmer and non-swimmer (n=20 per group). Step through latency in the acquisition stage (STLa) (A), the number of trials to acquisition (B), step-through latency during the retention trial (STLr) (C), and the time spent in the dark compartment during the retention trial (TDC) (D). $^{*}P<0.05$ as compared to the non-swimmer group.

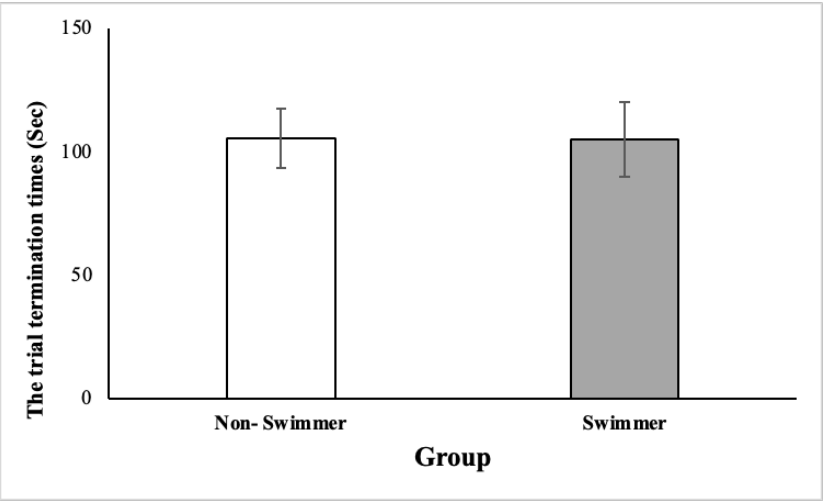

FIGURE 2. Effect of swimming exercise on the trial termination time on the radial maze task (n=20 per group).

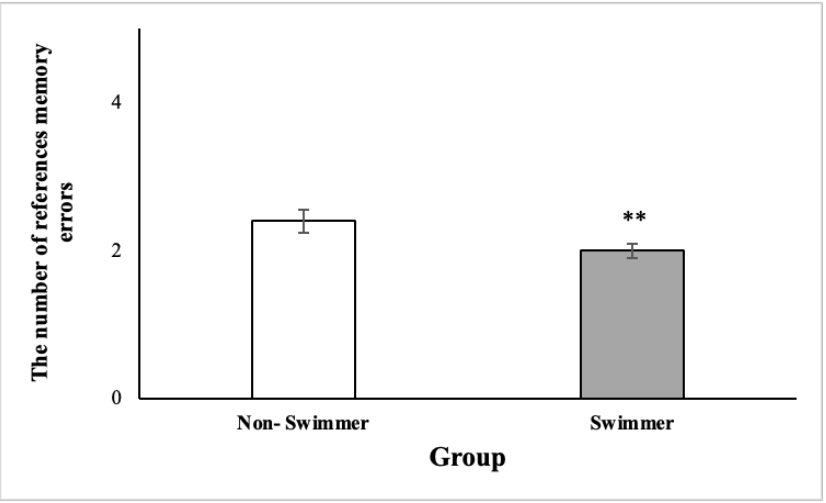

FIGURE 3. Effect of swimming exercise on the number of reference memory errors on the radial maze task (n=20 per group). $^{**}P<0.01$ as compared to the non-swimmer group.

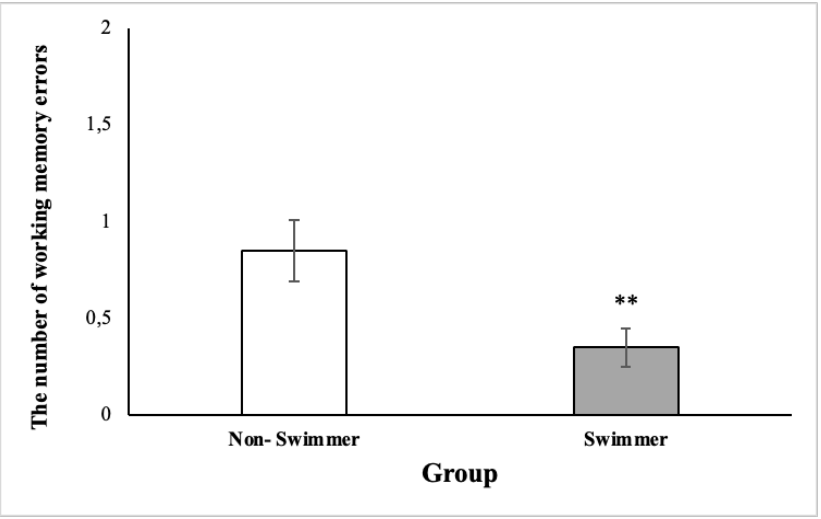

FIGURE 4. Effect of swimming exercise on the number of working memory errors on the radial maze task (n=20 per group). $^{**}P<0.01$ as compared to the non-swimmer group.

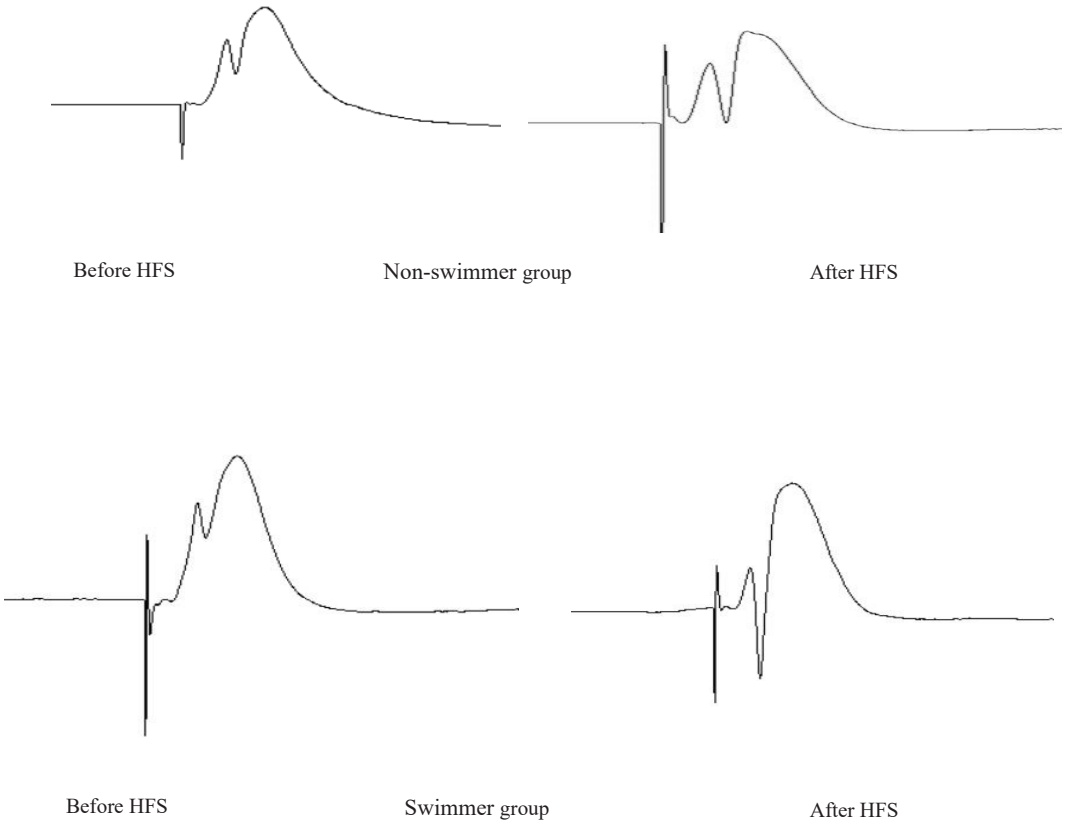

FIGURE 5. Stimulated field potential sample traces in the dentate gyrus region in groups before and after high-frequency stimulation.

non-swimmer group (P<0.01, Fig.4).

Effect of swimming exercise on the amplitude of PS of the granular cell of DG

Figure 5 showed sample trace responses in groups. Two-way ANOVA revealed remarkable differences in the PS amplitude experimental groups and time points (5, 30, 60 and 120min). In addition, the PS amplitude of the swimmer group was remarkably higher at 30 (P<0.05), 60 (P<0.05) and 120min (P<0.01) than that of the non-swimmer group, as shown by Student'st-test (Fig. 6).

Effect of swimming exercise on the EPSP slope of the granular cell of DG

Figure 7 indicates the effects of swimming on the fEPSP slope in the DG granular cell synapses. Consistent with PS amplitude, there was a significant effect of treatment and time points in the EPSP slope of DG granule cells. Our results revealed that the fEPSP slope was considerably increased in the swimmer group at 60 and 120min compared to the non-swimmer group (P<0.05).

Discussion

The main findings of this study consist of: (1) Swimming exercise reduced the number of passive avoidance test trials; (2) Swimming exercise enhanced retrieval of spatial memory by decreasing the number of working memory and reference memory errors, and (3) Swimming exercise increased hippocampal PS amplitude and fEPSP slope.

The present study demonstrated that swimming exercise improves learning as measured by the PAL test. In addition, swimming improved both spatial reference and working memory in the radial maze task. Since Da Cruz et al. (2012) reported that swimming exercise increased non-spatial memory in the novel object test. Several studies have shown that swimming exercise improves new object recognition memory in rats (Cechella et al., 2014; O'Callaghan et al., 2007). Another study in-

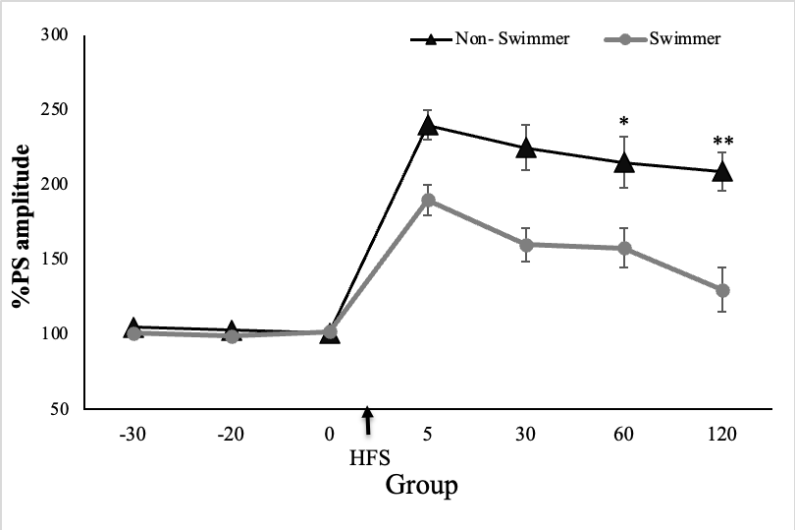

FIGURE 6. The effect of swimming exercise on the PS LTP of DG granule cells following a 400-Hz HFS applied to the PP. Data are expressed as mean±SEM % of baseline. LTP of the PS amplitude in area DG granular cell synapses of the hippocampus are significantly different between groups. $^{**}P<0.01$ and $^{*}P<0.05$ as compared to non-swimmer group.

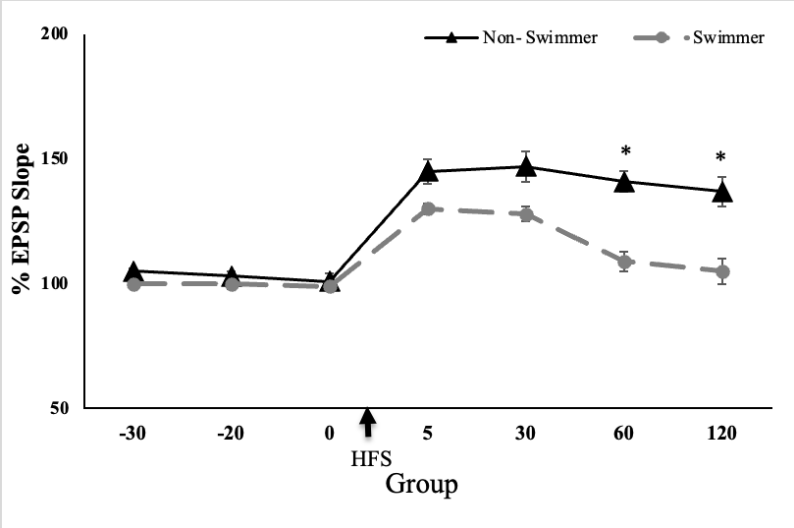

FIGURE 7. The effect of swimming exercise on the fEPSP LTP of DG granule cells following a 400-Hz HFS applied to the PP. Data are expressed as mean±SEM % of baseline. LTP of the EPSP slope in area DG granular cell synapses of the hippocampus was significantly different between groups. $^{*}P<0.05$ as compared to non-swimmer group.

dicated that training improved the learning and memory of sleep deprivation rats in the Y maze test (Zhang et al., 2017). Accumulating evidence demonstrated that treadmill exercises enhanced memory in the PAL and MWM tests (Abshenas et al., 2020). There is evidence-based physical activity such as running and swimming can increase BDNF expression in the rat hippocampus and increase cognitive function (Abshenas et al., 2020; Zhang et al., 2017). Regular physical activity seems to enhance educational and work performance in children, young adults and the elderly, with or without cognitive impairment (Raichlen and Alexander, 2017).

Surprisingly, benefits were associated with time spent on physical activity (Raichlen and Alexander, 2017). These enhancements frequently paired with anatomical and functional changes in the brain. Extension of part of the brain (Sexton et al., 2016), improved brain connectivity (Li et al., 2017) and increased blood flow in the cerebral and hippocampus (Steventon et al., 2020) are among these changes, which are combined with neurogenesis (Abshenas et al., 2020). The molecular bases of these adaptations attributed mainly to neutrophils, par-

ticularly BDNF (Abshenas et al., 2020).

Our findings showed that swimming exercise increased EPSP slope and PS amplitude. Similarly, a significant enhancement LTP following training was observed by O'Callaghan et al. (2007). In another study, voluntary training improved synaptic plasticity disorders in sleep-deprived female rats (Rajizadeh et al., 2020). Consistent with our results, exercise enhanced long-term potentiation in mice (Liu et al., 2011; Van Praag et al., 1999). Based on these findings, exercise can improve synaptic plasticity and LTP, up-regulation of BDNF expression and improve cognitive tasks.

Conclusion

Our results demonstrated that swimming exercise improved learning in the PAL test and memory in the radial maze task. Moreover, swimming improved hippocampal LTP in rats. Further studies such as histology and molecular experiments should be focused to regulate the mechanistic pathways of exercise.

Acknowledgments

A grant number "4245" funded this project at Hamadan University of Medical Sciences.

Conflict of interest

NO

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