

Benefit effect of REM-sleep deprivation on memory impairment induced by intensive exercise in male wistar rats: with respect to hippocampal BDNF and TrkB

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Background: Many factors affect our learning and memory quality, but according to different studies, having a positive or negative impact pertains to their characteristics like intensity or the amount.

Purpose: The present study was conducted to investigate the effect of 24-hour REM-sleep deprivation on continuous-high intensity forced exercise-induced memory impairment and its effect on Brain-Derived Neurotrophic Factor (BDNF) and Tyrosine kinase B (TrkB) levels in the hippocampus and Prefrontal Cortex area (PFC).

Material and methods: Animals were conditioned to run on treadmills for 5 weeks then, were deprived of sleep for 24 h using the modified multiple platforms. The effect of intensive exercise and/or 24-h REM-SD was studied on behavioral performance using Morris Water Maze protocol for 2 days, and BDNF/TrkB levels were assessed in hippocampus and PFC after behavioral probe test using western blotting.

Results: After 5 weeks of intensive exercise and 24-h REM-SD, spatial memory impairment and reduction of BDNF and TrkB levels were found in hippocampus and PFC. 24-h REM-SD improved memory impairment and intensive exercise-induced downregulation of BDNF and TrkB protein levels.

Conclusion: The results of the study suggested that sleep deprivation might act as a compensatory factor to reduce memory impairment when the animal is under severe stressful condition.

Keywords: intensive exercise, sleep deprivation, spatial memory, hippocampus, prefrontal cortex, BDNF, TrkB

Introduction

Previous studies have confirmed the benefits of regular physical activity on mental function over the whole life course.¹ Still, these exercise-induced benefits are dependent on various characteristics of physical exercise such as the differences in type (aerobic vs resistance exercise),² the rate of recurrence (sessions per week),³ quantity (intensity and volume),⁴ as well as animal's health condition and the brain region. These parameters change the intracellular signaling factors and expression of different neurotransmitters mediating the effect of exercise on physical and mental activity.⁵⁻⁸ Neurobiological experiments revealed an inverted U-shaped relation between the exercise intensity and its physical and mental benefits.^{9,10}

Accordingly, emerging evidence has shown that moderate forced or voluntary activity improved cognitive functions, such as memory,^{11–13} executive function,¹⁴ mood in depression disorder,^{15,16} and increased plasticity even in late life.^{17,18} However, in response to severe exercise, disruption of hippocampal neurogenesis,¹⁹ mitochondrial dysfunction in the brain,⁶ changes in intracellular mechanism involved in neurotrophins expression²⁰ were observed as well as cognitive impairments.^{21–24} For instance, a high index of oxidative stress in the brain caused by 10-day intensive and exhaustive running program has been shown to impair hippocampus-dependent memory.²³

The areas of the brain that are most important in learning are those involved in memory, and it is thought to rely primarily on medial temporal lobe structures, including the hippocampus with its widespread functional connections to the cortex.²⁵ The prefrontal–hippocampal interactions are well known for incorporation of cognitive and emotional information for supporting adaptive actions like spatial information.²⁶

Brain-derived neurotrophic factor (BDNF), the most important neurotrophin in the central nervous system, and its main receptor, TrkB,^{27,28} influenced by various factors affecting the learning and memory²⁹ such as physical exercise^{30–32} and sleep duration^{30–34} have considered widely in animal studies to evaluate the effect of different factors on learning and memory. The binding of BDNF to its receptor tyrosine kinase, TrkB, results in the activation of cytoplasmic signaling pathways including mitogen-activated protein kinase, phospholipase C- γ , phosphatidylinositol-3 kinase (PI3-K) and Akt, a serine-threonine protein kinase that demonstrated to phosphorylate the mammalian target of rapamycin (mTOR).²⁸ Previous studies showed activation of PI3-K/Akt/mTOR signaling and protein synthesis signaling pathway induced by BDNF is important for BDNF-dependent long-term potentiation, LTP, in the hippocampus and different types of learning and memory like spatial memory.^{35,36}

Studies suggested that, adequate sleep has a crucial effect on different types of memory particularly hippocampus-dependent.³⁷ Experimental evidence revealed that, two main parts of sleep including non-rapid eye movement and rapid eye movement (REM) modulated the consolidation of declarative and non-declarative memories, respectively, in a different way.^{35,38} In recent years, the effect of sleep deprivation (SD) on cognitive capacity and performance has received a lot of attention. Not having enough sleep influences negatively on cognitive behaviors such as attention vigilance,³⁹ non-declarative and declarative memory,^{40–42} executive function,⁴³

decision making⁴⁴ and emotion perception.⁴⁵ Although SD may impair cognitive capability and can reduce the learning and memory, recent experiments have shown conflicting results. For instance, different types of SD, either total or partial have a fast and transient antidepressant effect⁴⁶ and they were considered as a short-term treatment for stress-induced depressive behavior.^{46–48}

The current study was carried out to investigate the effect of REM-SD on the memory impairment induced by high-intensity exercise. In addition, to support the changes of memory performance, the level of BDNF and its receptor TrkB were evaluated in the hippocampus and prefrontal cortex.

Materials and methods

Animals

Thirty-two adult male Wistar rats (Pasteur Institute, Tehran, Iran) were used in this study. The experimental protocols and procedures in this study were approved by the Research and Ethics Committee of Tehran University of Medical Sciences, and conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals (1996 revision). The animals were housed in groups of four in standard polypropylene cages. The room temperature was kept at $22 \pm 1^\circ\text{C}$. The animals were housed in a 12 hrs:12 hrs light-dark schedule (07:00–19:00) and had free access to food and water. All experimental procedures were performed between 9:00 AM and 14:00 PM.

Experimental procedure

This paradigm consists of 32 animals that distributed in 4 different groups. Animals randomly assigned to control (cont., $n=8$), 4 weeks physical exercised (Ex, $n=8$), 24 hrs of REM-sleep deprivation (SD24, $n=8$) and the interaction of exercise and sleep deprivation (ExSd, $n=8$). Animals in the control group were placed in the non-running treadmill. After 24 hrs, exercised animals in the ExSd group were gone under 24-hr REM-SD. Ex group received 5 weeks treadmill with increasing intensity. The spatial and then non-spatial behavioral tests were done for control and Ex groups 24 hrs after the last exercise procedure, but it was performed in REM-SD and ExSd groups immediately after the REM-SD procedure. All rats were used for behavioral evaluation and then were sacrificed for brain tissue collecting.

Exercise training protocol

Using a 4-lane animal treadmill (IITC Life Science Inc., USA), rats were handled and trained to familiarize with running 3 days prior to start the exercise (speed: 5 m/min, 5 mins per run). The bars at the end of the treadmill were delivered electrical shocks (1.0 mA) to the hind part of the body when the animal stops running and forced them to run forward during exercise time. After 2 rest days, the procedure was performed, one session daily, 5 days a week for 5 weeks. The main phase of treadmill training was started at a speed of 18 m/min for 30 mins and no tilt for the first week. The duration and treadmill's tilt was increased progressively, 10 mins and 5 degrees increased in each week. The speed was maintained at 18 m/min for all this period. Sedentary animals were placed on a stationary treadmill daily and were given electrical stimulation in a way identical to that used for the exercise group.⁴⁹

Induction of REM-SD

REM-SD was induced by placing four to six rats in modified water-filled multiple platforms (125 cm×44 cm) that consisted of 8 small circular platforms (6.5 cm, in diameter) which submerged to about 1–2 cm above the water surface. The platforms were located at a distance so rats could move freely from one to another and balance on the platforms. Due to natural REM's muscle paralysis, the rats would come into contact with the water and awaken. The rats had free access to clean water and food pellet baskets hanging from the aquarium cover. For the control group, using larger platforms (14 cm in diameter) caused to falling sleep without falling down.^{49,50} The REM-SD period lasted for 24 hrs.

Apparatus and behavioral procedure

To assess spatial learning and memory, all animals were trained in the Morris water maze (MWM), a most widely used task to assess spatial learning and memory in rodents.⁵¹ The apparatus consists of a circular, black-painted tank (pool), 150 cm in diameter and 60 cm deep, containing filled with opaque water at around 30 cm. The sufficient stressful water temperature was maintained at 20±2°C. Several distinctive, distal visual cues were placed on the walls of pool's laboratory room and their position remained unchanged to aid animals to identify their location in space. The tank was divided into four equal quadrants with four starting locations called north (N), east (E), south (S) and west (W) at equal distances on the rim.

A plexiglas escape circular platform (10 cm in diameter) was submerged 1 cm beneath the surface of the water in the center of the target quadrant (north-west quadrant). During the experiments, the images of the swimming animal were captured by a camera placed above the center of the maze, which was connected to a computer. A video tracking system (Etho-Vision XT v 8.5; Noldus Information Technology, the Netherlands) was used to measure the parameters such as the time to find the hidden platform (escape latency), path length to reach the hidden platform (traveled distance), the time spent in quadrants and the velocity of each rat in the training session.⁵²

Eight trials in a single training session with four starting points that positioned equally around the maze. Each trial was started from one of the four starting points. During 60 s of each free-swimming trial, the animal had to find a hidden platform by using distal spatial clues. If the animal stepped on the platform, he was allowed to stay there for 20 s, if not, it was guided to the platform by the experimenter and allowed to remain there for 20 s. The gap time between trials was 20 s. In each trial, escape latency (s) and traveled distance (cm) were measured to assess the development of spatial memory, and then swimming speed (cm/s) was used to evaluate motor function. Probe trial as a retrieval test session was carried out 24 hrs after the training. It applied in a 60 s free-swimming period without a platform and traveled distance and the total time spent in the main quadrant was recorded. On the last day, following probe trial, for evaluating non-spatial visibility test, the platform that covered with a piece of aluminum foil was elevated above the water in the center of the north-east quadrant. This procedure is believed to provide information on the possible non-specific effects involving motor, visual or motivational abilities unrelated to learning and memory.⁵²

Brain tissue collecting and Western blotting

After probe and non-spatial behavioral test, animals were sacrificed under CO₂ asphyxiation. Rats were decapitated and the brain was removed. Hippocampus and PFC were dissected and frozen in liquid nitrogen immediately, and stored at -80°C until needed for later analysis. We used five brain samples for each group to perform Western blotting test.

Protein concentration was measured by spectrophotometry at 230 nm using Picodrop instrument (Picodrop,

Hinxton, UK), and the results were acquired as microgram per milliliter. Samples were loaded in SDS-8% polyacrylamide gel (PH=8.3) and electrophoresis was carried out at 120 V for 120 mins, then transferred to polyvinylidene fluoride membrane (Chemicon Millipore Co., Temecula, CA, USA). To block non-specific protein binding sites, membranes were incubated in 5% skim milk (PH=8.6) for 90 mins. Then, blots were incubated overnight at 4°C with a primary antibody (Abcam, 1:1000 diluted in skimmed milk). On the next day, Tris-buffered saline and Tween 20 (TBST) were used to wash membranes three times and then blots were incubated for 1 hr, with secondary antibody (Horseradish peroxidase-linked goat anti-rabbit IgG, Abcam, 1:5000). To detect bounds, blots were exposed by enhanced chemiluminescence (ECL; Amersham, UK) and then visualized by exposure to autoradiographic film for adequate time.⁵³

All the experimental procedure part is summarized as a timetable in Figure 1.

Statistical analysis

SPSS (Version 23) was used for this study. For trial sessions, repeated measures ANOVA was used for data analysis. In this test Ex, SD24 and ExSd groups are measured versus the control group. Data were obtained in the probe session and non-spatial test analyzed by one-

way ANOVA. To comparison differences between groups, post-hoc (Tukey) test was done. For analyzing Western blotting data, Image J software was used to densitometry of bonds. After that, data obtained with Image J were subjected to one-way ANOVA analysis using SPSS. Post-hoc (Tukey) test was used for within-subject comparisons. In all comparisons, the *p* -values 0.05 and less were considered as statistically significant. Data were analyzed by two people individually but blinded for one of them. We did it to ensure the accuracy of the analyzing.

Results

Behavioral experiment

Twenty-four-hour REM-SD made better high-intensity exercise-induced spatial memory deficit.

For testing the effect of REM-SD on long-term memory deficit induced by high-intensity exercise, we used a 2-day MWM protocol, where all groups went through eight trials in 1 day. Instantly after the last trial, the SD24 and ExSd24 rat groups were put down in the modified multiple platform aquarium for 24 hrs. Immediately after that, probe test was done for assessing the long-term memory. Figure 2(A–C) shows that there was no significant difference in escape latency [$F(21, 196)=0.467, p=0.904$], traveled distance

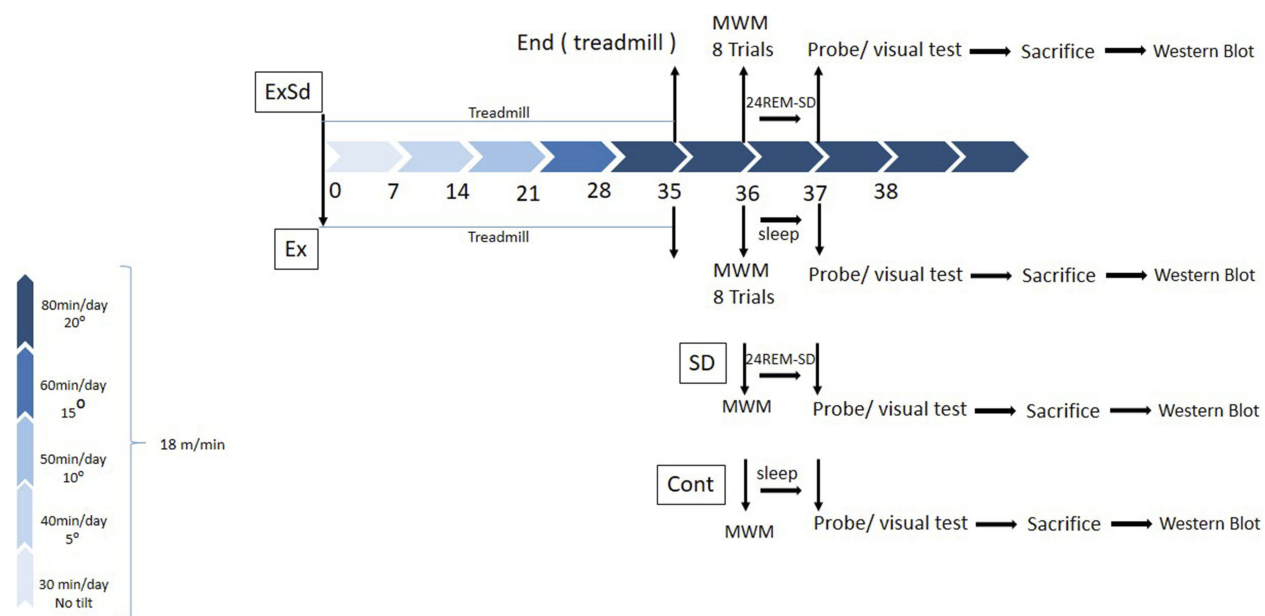


Figure 1 The schematic timeline for study design. Two groups of animals received 5 weeks of physical exercise with a gradual increase in intensity (5 weeks, 5 days in a week); one of these groups (ExSd), 1 day after the last session of exercise received 24-hr REM-SD and other one went for MWM test. SD24 received 24-hr REM-SD after trial day of MWM and then probe test was performed. Control animals received nothing but MWM test. All animals were sacrificed after the visual test and their brain was collected for Western blotting test.

Abbreviations: SD, sleep deprivation; MWM, Morris water maze.

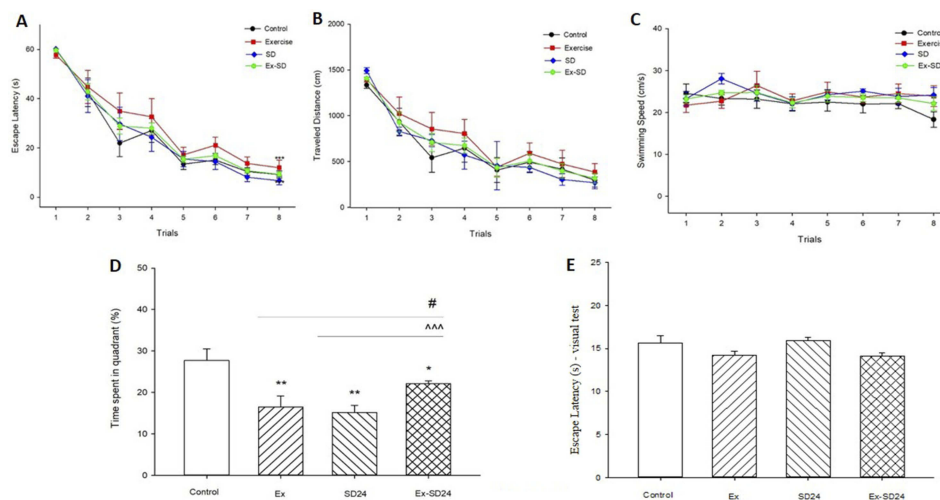


Figure 2 Effect of 24-hr REM-SD on memory impairment induced by intensive exercise. After 5 weeks of intensive exercise, ExSd group of animals received eight trials in a day and immediately went under 24-hr REM-SD. **(A)** Escape latency, **(B)** traveled distance and **(C)** swimming speed across eight trials. Values are given as mean±SEM for each experimental group. Probe test was done immediately after the 24-hr REM-SD. **(D)** Percentage of time spent in target quadrant. Data are shown as mean±SEM. * $p < 0.05$ and ** $p < 0.01$ different from the control group. # $p < 0.05$ different from the Exercised group. ### $p < 0.001$ different from the 24h REM-SD group. Each bar represents mean±SEM per group. **(E)** Escape latency during non-spatial visible platform test. $p > 0.05$ NS (not significant).

Abbreviations: Ex, Exercised group; SD24, 24-hr REM-sleep deprivation; ExSd, Exercised-Sleep deprivation group; REM-SD, REM Sleep Deprivation.

[$F(21, 196)=0.314$, $p=0.993$] and velocity [$F(21, 196)=0.769$, $p=0.692$] between REM-SD, Ex and ExSd groups compared with the control group in the learning stage. As is shown in **Figure 2D**, one-way ANOVA shows a significant difference between groups in the total time spent in the main quadrant over the probe test [$F(28, 3)=7.631$, $P=0.0008$]. Post-hoc Tukey analysis showed differences for Ex ($p < 0.01$), REM-SD ($p < 0.01$) and ExSd ($p < 0.05$) in comparison with the control group. One-Way ANOVA revealed there is no significant difference between groups and control for non-spatial test (**Figure 2E**), [$F(28,3)=2.932$, $p=0.0508$].

The effect of the combination of high-intensity exercise and REM-SD on hippocampal/prefrontal BDNF levels

Figure 3A–B shows that there is a significant difference between groups versus control in BDNF levels in the hippocampus [$F(16, 3)=21.06$, $p < 0.0001$] and prefrontal cortex [$F(16, 3)=18.6$, $p < 0.0001$]. Post-hoc Tukey analysis showed that there were significant differences in the level of TrkB in the hippocampus between Ex and SD ($p < 0.001$), and ExSd ($p < 0.01$) groups in the hippocampus as compared with the control group. In addition, ExSd group showed an enhancement in BDNF level in comparison with the Ex ($p < 0.001$) and the SD ($p < 0.01$) groups in the hippocampus. **Figure 3B** illustrates that BDNF level in

PFC is significantly lower in the Ex ($p < 0.01$) and SD ($p < 0.001$) groups when compared with the control group; however there is no significant difference between ExSd and control group. Following the intervention of Ex and SD, BDNF was upregulated when compared with the Ex ($p < 0.001$) and SD ($p < 0.0001$) groups.

The effect of the combination of high-intensity exercise and REM-SD on hippocampal/prefrontal TrkB levels

Figure 3C–D shows that there is a significant difference between groups versus control in TrkB levels in the hippocampus [$F(16, 3)=10.806$, $p < 0.0001$] and prefrontal cortex [$F(16, 3)=6.187$, $p=0.0023$]. Post-hoc Tukey analysis showed that there were significant differences in the level of TrkB in the hippocampus between Ex and SD ($p < 0.001$) and ExSd ($p < 0.05$) groups as compared with the control group. In addition, ExSd group showed no significant difference in TrkB level in comparison to the Ex and the SD groups in the hippocampus. **Figure 3D** illustrates that the level of TrkB in the PFC was significantly lower in the Ex ($p < 0.01$) and SD ($p < 0.05$) groups when compared with the control group; however, there is no significant difference between ExSd and control group. Following the intervention of Ex and SD, TrkB was upregulated when compared with the Ex ($p < 0.001$) and SD ($p < 0.0001$) groups.

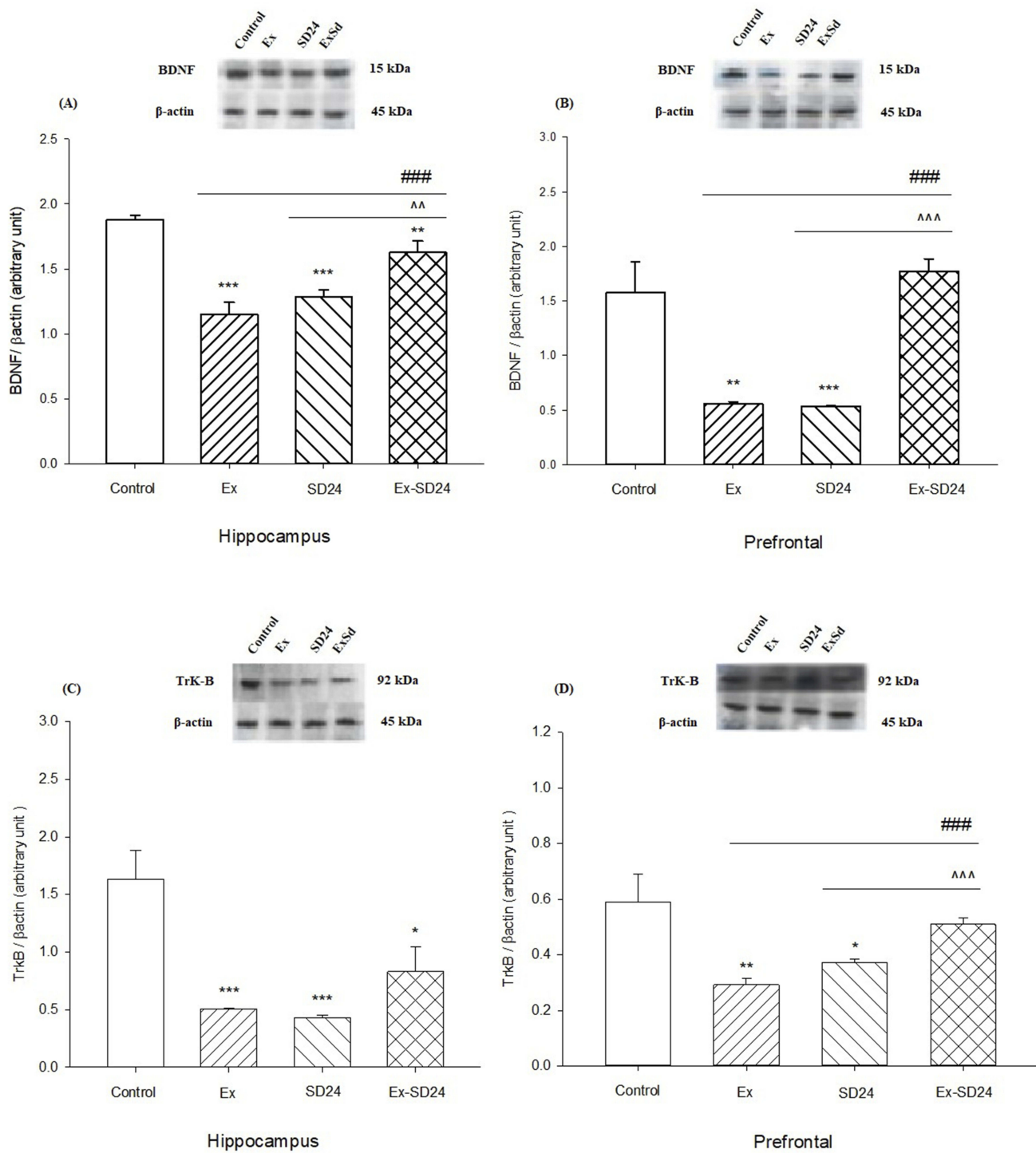


Figure 3 Effect of 24-hr REM-SD on the level of BDNF in the Ex group in the (A) hippocampus and (B) prefrontal cortex. Values are expressed as the means \pm SEM (n=5 for each group); effect of 24-hr REM-SD on the decreased level of TrkB in Ex group in (C) hippocampus and (D) prefrontal area in the rat. * P < 0.05, ** P < 0.01 and *** P < 0.001 versus control, ^ p <0.01, ^^ p < 0.001 versus SD24 group and #### p < 0.001 versus Ex group.

Abbreviations: Ex, exercised group; SD24, 24-hr REM-sleep deprivation; ExSd, Exercised-Sleep deprivation group; BDNF, brain-derived neurotrophic factor; TrkB, Tyrosine kinase B.

Discussion

There is a complex relationship between the exercise and its effect on the cognitive ability, depending on different characteristics of exercise, such as the intensity, duration and type of exercise. The exercise intensity may influence brain oxygen utilization,⁵⁴ the formation of mitochondrial ROS,^{5,6} inducing antioxidant imbalance and disturbance of the cellular signaling,⁵⁵ spatial memory impairment, object recognition disruption^{56–58} as well as reduction in arousal level by intensive exercise and reaching to the optimal level after medium intensity.⁵⁹ Therefore, in relation to the complexity of the exercise biology, inverted U-shaped dose–response curves were defined, where low doses are stimulatory and high doses are inhibitory.¹⁰ In our study, the combined effect of SD and intense exercise on hippocampus-dependent learning and memory was investigated. Results displayed that, a 5-week gradual high-intensity training exercise may cause a decrease in the total time in the target zone of MWM test with corresponding reductions in the expression of hippocampal and prefrontal BDNF and TrkB level represented to reduce memory performance. Physical fatigue and exhaustion,⁶⁰ excessive blood lactate,⁶¹ decreased glucose uptake,^{19,62,63} changes in metabolism⁶⁴ and oxidative stress,^{65,66} altered inflammatory cytokine expression⁶⁷ and increased susceptibility to infection⁶⁸ might be the explanations regarding the adverse effect of intensive exercise. However, the most important issue in the cognitive impairments induced by intense physical exercise might be exhaustion,⁶⁹ increasing free radical and ROS levels.^{66,70} Brain with high mitochondrial energy metabolism and poor antioxidant defenses could be affected by oxidative damage induced by high ROS levels⁷¹ which, in turn, results in a decrease in the BDNF levels⁷² and an increase in the neuron degeneration.⁷³

Moreover, chronic and daily foot shock, not single dose, as a stressful experience has been shown to negatively influence the hippocampal neurogenesis. In our study, changes in the BDNF and TrkB levels in the brain were in agreement with the behavioral data. These molecular reductions in the hippocampus and the PFC were associated with impairment of spatial memory.^{74,75} In the animal models of stress and depression, production of ROS increased in the PFC and hippocampus.^{73,74} The enhancement of the ROS level in the PFC might be one of the critical factors in decreasing BDNF expression and induction of depressive-like symptoms.⁷⁶ Stress could also

alter the brains' chemical components such as BDNF, cAMP response element-binding protein, extracellular signal-regulated kinases (ERK1/2) levels^{73,77–79} in the hippocampus consequently promoting oxidative stress-induced depression-like behaviors and causing memory impairment in rats.⁸⁰

The destructive effect of sleep deprivation on the cognitive function is generally accepted.^{81–83} However, one of the controversial findings in the recent studies is the different action of sleep deprivation on the cognitive capability and expression of some neurochemicals in different parts of the brain and then applying these benefits to help cure some cognitive diseases like depression^{84–86} and mood disorders.^{87,88} In our study, disturbance of memory function after intensive exercise was ameliorated by subsequent 24-hr REM-SD. In parallel, results also revealed a rise in the levels of BDNF/TrkB within the hippocampus and PFC.

SD for one night subtracted depressive symptoms in 40–60% of cases;⁸⁹ furthermore, a higher decrease was observed in depressive symptoms by a reduction in REM sleep phase.⁹⁰ However, previous researches showed different results regarding total sleep deprivation or REM-SD on memory performance and hippocampal BDNF level. For instance, 8 hrs of total sleep deprivation showed no changes in BDNF level⁹¹ but short-term REM-SD caused an increase in the BDNF level in the rats' hippocampus.⁴⁷ However, Fujihara et al⁹² showed 1–2 hrs SD induced an increase in the BDNF level but 8 and 48 hrs of SD decreased BDNF level in the hippocampus.⁹³ Some studies showed that, extended wakefulness might result in an increased level of BDNF in the hippocampus.⁹⁴

However, because of partial non-REM deprivation based on our SD protocol,⁹⁵ REM deprivation and then an increase in wakefulness state, it is not clear which part is mainly responsible for elevation of BDNF/TrkB expression. Furthermore, the proposed mechanisms related to SD that might elevate the BDNF level in rats' hippocampus are: 1) sleep homeostatic and circadian mechanisms referring to the two process models of sleep regulation;⁹⁶ 2) monoaminergic mechanisms referring to a significant role of monoamines between SD and antidepressants;⁹⁷ and 3) glutamatergic mechanisms and synaptic plasticity referring to a suggested role for the glutamate and its interplay with monoamine neurotransmitters in the fast antidepressant consequence of SD.⁹⁸

In this study, the memory performance and BDNF/TrkB levels significantly increased in ExSd group compared to Ex and 24h SD groups, yet their decrease was still less than the control group. Said differently, REM-SD just caused the BDNF expression notably better and not restored it completely.

Disclosure

The authors report no conflicts of interest in this work.

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