Original Article

The Effect of Preventive, Therapeutic and Protective Exercises on Hippocampal Memory Mediators in Stressed Rats

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Abstract

Background: Exercise plays a significant role in learning and memory. The present study focuses on the hippocampal corticosterone (CORT), interleukin-1 beta (IL-1β), glucose, and brain-derived neurotrophic factor (BDNF) levels in preventive, therapeutic, and protective exercises in stressful conditions.

Methods: Forty male rats were randomly divided into four groups: the control group and the preventive, therapeutic, and protective exercise groups. The treadmill running was applied at a speed of 20-21m/min and a chronic stress of 6 hours/day for 21 days. Subsequently, the variables were measured in the hippocampus.

Results: The findings revealed that the hippocampal CORT levels in the preventive exercise group had a significant enhancement compared to the control group. In the protective and particularly the therapeutic exercise groups, the hippocampal CORT levels declined. Furthermore, the hippocampal BDNF levels in the preventive and the therapeutic exercise groups indicated significantly decreased and increased, respectively, in comparison with the control group. In the preventive exercise group, however, the hippocampal glucose level turned out to be substantially higher than that in the control group.

Conclusion: It appears that the therapeutic exercise group had the best exercise protocols for improving the hippocampal memory mediators in the stress conditions. By contrast, the preventive exercise group could not improve these mediators that had been altered by stress. It is suggested that exercise time, compared to stress, can be considered as a crucial factor in the responsiveness of memory mediators.

Keywords: Stress, Exercise, Corticosterone, Interleukin-1βeta, Brain-Derived Neurotrophic Factor, Glucose

Introduction

The stress conditions have increased in societies today. They represent a collection of events which begin with a stressor and accelerate a response in the body, particularly in the brain (1). Therefore, they are one of the main factors contributing to the memory deficit (2, 3). According to our previous studies, the impairment of memory processes has been demonstrated by using chronic stress (2,3). Based on our other previous documents, exercise can be regarded as a beneficial manner in the improvement of learning and memory in stress conditions and even Alzheimer disease (4–8). These studies have confirmed that different exercise protocols ameliorate cognitive and memory function (4–6). Accordingly, exercise could alter brain functions in the stressful conditions and neurodegenerative diseases

(4–9). It is demonstrated that stress and exercise affect the secretion of glucocorticoids hormones (corticosterone in rats; CORT) from the adrenal glands (2, 10–13). In addition, glucocorticoids hormones can change some neuromodulators in the brain, such as interleukin-1 beta (IL-1β) (14), glucose (15), brain-derived neurotrophic factor (BDNF) (16), and other biochemical factors. CORT and IL-1β influence memory processing and neural plasticity and impair the memory consolidation (2, 17). On the other hand, BDNF and glucose improve memory (2, 18). BDNF has emerged as a major synaptogenesis regulator and synaptic plasticity mechanism underlying learning and memory in the brain (19). It appears that exercise, similar to stress, could be involved in regulating the levels of memory mediators. Since the effects of different exercise protocols on the levels of memory mediators in the hippocampus have not been fully clarified and the hippocampus is a main memory structure that is involved in both stress and exercise (20, 21), the present study focuses on this area. Stress and exercise can alter neurochemistry, plasticity, neurotoxicity, neurogenesis, glucocorticoid receptor regulation, and neuronal morphology in neuronal circuits of hippocampus (DG and CA1- CA4) (3, 22–24).

In human communities, different exercise protocols may be repeatedly observed in humans' lifetime. For example, an exerciser might withdraw physical activity under stressful conditions (preventive exercise). In other groups, exercise might perform during exposure to stressor (protective exercise). Even individuals may perform an exercise after stress conditions to improve the physiologic system of their bodies (therapeutic exercise). Hence, the present study investigates the effect of preventive, therapeutic, and protective exercise (exercise before, after, and during chronic stress, respectively) on the alteration of BDNF (as the main index of neurogenesis and memory), CORT, IL-1β, and glucose levels (as accessory biochemical indexes of memory) in hippocampus of rats under chronic stress.

Materials and Methods

Animals

Forty male Wistar rats, with an initial weight of 250–300 g, were utilized as experimental subjects. The animals were housed under an artificial light (12-h light/dark, lights on at 7:00 a.m) and temperature (22±2°C) controlled

condition, with food and water available ad libitum. The experiments lasted 42 days. All experiments on the animals were approved by the Ethics Committee of Isfahan University of Medical Science and were performed in accordance with National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80–23, revised in 1996).

The animals were randomly divided into four groups (n=10 in each group) as follows: the control group: the rats were put on the treadmill without running for 1 hour/day. The preventive exercise group (exercise before stress): the rats were exercised for 21 days before applying the 21-day stress. The therapeutic exercise (exercise after stress) group: the rats were under stress for 21 days and then were exercised for 21 days. The protective exercise (exercise during stress) group: the rats had exercise associated with chronic stress (4–6).

Experimental procedures

Stress protocol

The rats were tightly fitted in separate flat bottom Plexiglas cylindrical restrainers (Razi Rad Co., Tehran, Iran) in medium size for the rats with a weight of 250–300 g (5 cm in diameter and 20 cm in length) for 6 hours/day (8:00–14:00) in the chronic stress model (2–5). Several holes in the walls of the cylinders provided fresh air. In addition, it was not possible for the rats to move, and the restriction of the locomotion occurred in them. Restraint stress was employed as an important common stress-inducing model of emotional stress (25–27).

Exercise protocol

In the exercised groups, the animals ran on a rodent treadmill (Technic Azma Co., Tabriz, Iran). The rats became habituated to treadmill running in order to minimise novelty stress for three days before the experiments. The exercise protocol consisted of 1 hour/day/for 6 consecutive days at 20–21 m/min and slope of 0° (5). The rats received approximately 0.3 mA electric shock at 3 seconds to sparingly promote their running from the grid located just behind the treadmill (28). After warm-up, the speed and the duration of treadmill running were kept constant at 20 m/min for 1 hour running throughout the exercise period.

Assessment of corticosterone, IL-1β, BDNF, and glucose levels in hippocampus

After decapitation and removal of the animals' brains from their skulls, the hippocampi were instantly dissected on dry ice. Each hippocampus was separately immersed in Problock™-50, EDTA free (Gold Bio Co., USA) and phosphate buffer solution (PBS buffer, 0.01 M, pH 7.4). Indeed, this solution contained complete protease inhibitor cocktail. The hippocampi were homogenised and centrifuged in a cooled centrifuge (4°C, 10000 g for 20 min). Following that, the supernatant was separated and stored at −80°C until the assessment. The commercial ELISA kit was utilised to assess the corticosterone levels in hippocampus (DRG Co., Marburg, Germany). The BDNF levels in the homogenated hippocampus were measured by the ELISA kit of BDNF (Promega Co., Sweden). Additionally, the ELISA kit (Koma biotech Co., Korea) was employed to measure the serum IL-1β level. The serum glucose level (fed glucose, not fast glucose) was measured by the glucose oxidase method (Pars Azmun Co., Tehran, Iran).

Measurement of brain and hippocampus weights

At the end of the experiments, after removing the brains and the hippocampi from the skulls, their weights were measured.

Data Analysis

All data were analysed by one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple groups. In the current study, the values are presented as mean± standard error of the mean (SEM), where $P<0.05$ is considered statistically significant.

Results

Assessment of serum CORT, BDNF, IL-1β, and glucose levels

There was a significant enhancement ($P<0.05$) in the CORT levels of the preventive exercise (exercise before stress) group when compared to the control group. Nevertheless, the CORT levels substantially decreased in the therapeutic exercise (exercise after stress) and the protective exercise (exercise during stress) groups ($P<0.001$ and $P<0.05$, respectively) compared to the preventive exercise group (Figure 1). Hence, the protective and particularly the therapeutic exercises decreased the CORT levels more than the preventive exercise.
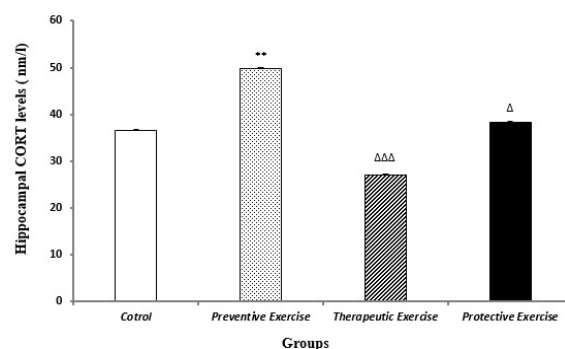

Figure 1. The comparison of different protocols of exercise on the hippocampal corticosterone (CORT) levels (nmol/L) in the different groups (n=10). Results are expressed as mean ± SEM (ANOVA test, Tukey's post-hoc test); $^{**}P<0.01$ when compared to the control group; $^{Δ}P<0.05$ and $^{ΔΔΔ}P<0.001$ when compared to the preventive exercise group.

The BDNF levels of the preventive and the therapeutic exercise groups were considerably ($P<0.01$ and $P<0.05$, respectively) different from that of the control group. Moreover, there were significant changes regarding the BDNF levels between the therapeutic and the preventive exercise groups ($P<0.001$ and $P<0.05$, respectively) compared to the preventive exercise group (Figure 2).

The BDNF level showed a significant ($P<0.01$) decrease in the protective exercise group compared to the therapeutic exercise group (Figure 2).
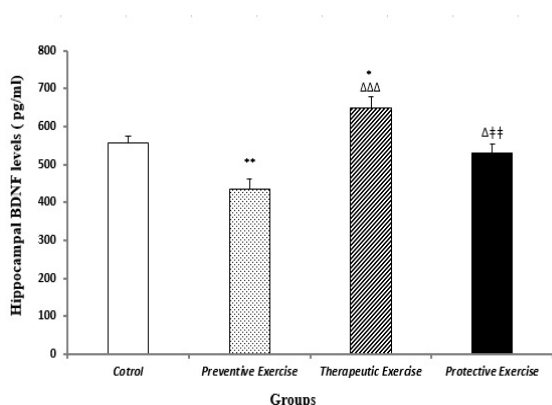
Figure 2. The comparison of different protocols of exercise on the hippocampal BDNF levels (pg/ml) in the different groups (*n*=10). Results are expressed as mean ± SEM (ANOVA test, Tukey's post- hoc test); *P<0.05, **P<0.01 when compared to the control group; $^{\Delta}P<0.05$ and $^{\Delta\Delta\Delta}P<0.001$ when compared to the preventive exercise group; $^{\Delta\Delta}P<0.01$ when compared to the therapeutic exercise group.

The IL-1ß level did not show any significant differences between all groups when they were compared to the control group and to each other. However, the IL-1ß level decreased more in the therapeutic exercise group in comparison with the other exercise groups (Figure 3).
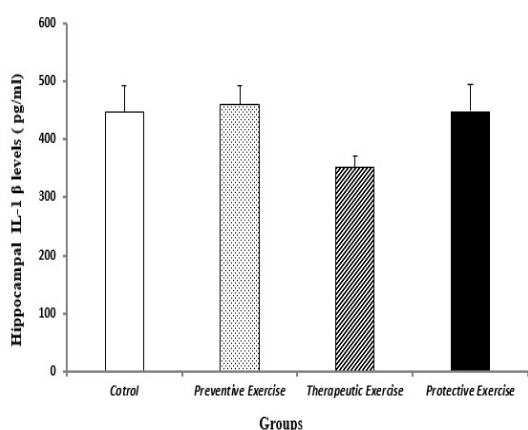

Figure 3. The comparison of different protocols of exercise on the serum IL-1ß levels (pg/ml) in the different groups (n=10). Results are expressed as mean ± SEM (ANOVA test, Tukey's post- hoc test) when compared to the control group and together. There were not significant differences between all groups.

In the preventive exercise group, the glucose level was substantially (*P*<0.05) higher than that in the control group (Figure 4).

As it is shown in Figure 4, the glucose levels in the therapeutic and the protective exercise groups were noticeably (*P*<0.01 in both of them) lower than that in the preventive exercise group (Figure 4).
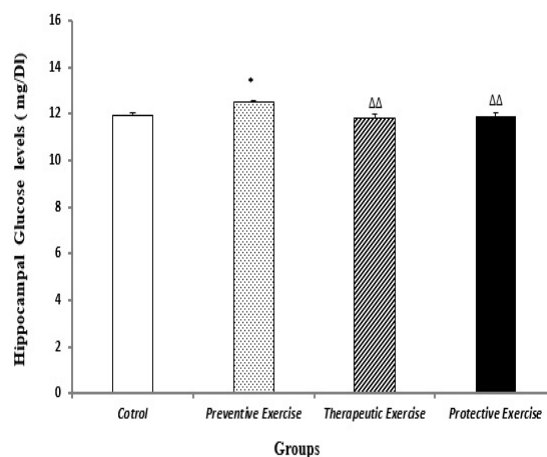

Figure 4. The comparison of different protocols of exercise on the hippocampal glucose levels (mg/Dl) in the different groups (*n*=10). Results are expressed as mean ± SEM (ANOVA test, Tukey's post- hoc test); *P<0.05 when compared to the control group; $^{\Delta\Delta}P<0.$ 01 when compared to the preventive exercise group.

Correlations between the behavioral test and the biochemical parameters

In our previous studies, memory was evaluated by the passive avoidance test in the preventive, therapeutic, and protective exercise groups (4, 6). The findings of the present study did not indicate any significant correlations between the hippocampal CORT, BDNF, IL-1ß, and glucose levels separately with memory in all of the experimental groups (not presented here as a graph).

Measurement of brain and hippocampus weights

The weights of brains and hippocampi did not show any significant differences between all groups when they were compared with the control group and with each other (Figure 5).
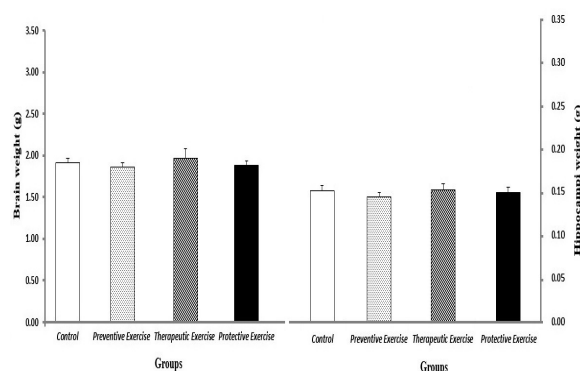
Figure 5. The comparison of different protocols of exercise on the brain and hippocampus weights (gr) in the different groups (*n*=10). Results are expressed as mean ± SEM (ANOVA test, Tukey's post- hoc test when compared to the control group and together. There were not significant differences between all groups.

Discussion

The findings of the current study demonstrated that the preventive, therapeutic, and protective exercises changed the CORT levels in the hippocampus. They also revealed that the hippocampal CORT level was higher in the preventive exercise than the other exercise protocols (Figure 1). This indicated no dominant effect of the preventive exercise on the main stress indexes such as the hippocampal CORT levels. In point of fact, the preventive exercise was not adequate for preventing the stressful challenges. Of course some previous studies reported that exercise could act as a stressor and activate the hypothalamic-pituitary-adrenal axis (29-31). In the present study, it appears that the elevated hippocampal CORT levels could result from the chronic stress induced after exercise. In other researches as well as our previous studies, it was reported that the CORT level crossed from the blood brain barrier (BBB) to brain with some limitations. Hence, the hippocampal CORT levels followed the serum CORT levels (2, 13, 32). In addition, the present findings confirmed that the protective and particularly the therapeutic exercises produced no significant decreases in the hippocampal CORT levels compared to the control group (Figure 1). Kannangara et al. reported a noteworthy reduction in the CORT levels in the central nervous system by exercise (33). Furthermore, some reports demonstrated

such different responses on the glucocorticoid levels after exercise as enhancement (34), reduction (35), and no changes (36) in the glucocorticoid levels. Consequently, this difference might be related to duration and types of exercise and probably exercise time.

On the other hand, the reduction and enhancement of hippocampal BDNF levels were observed in the preventive and the therapeutic exercises, respectively, compared to the normal condition. Additionally, the protective exercise had an intermediate condition in the hippocampal CORT and BDNF levels compared to the other exercise protocols in stressful conditions in the current study (Figure 2). Previous studies reported a relationship between the enhancement of glucocorticoid levels and the reduction of BDNF mRNA as well as their involvement in memory functions of rat's hippocampus (2, 37-39). However, although the results of this study demonstrated this relationship, there is no significant negative correlation between the hippocampal CORT and BDNF levels in the preventive, therapeutic, and protective exercises in the stressed rats.

Initially, it appears that the preventive exercise may protect the hippocampus against the reduction in the hippocampal BDNF level; nonetheless, the present findings did not confirm the useful effect of the preventive exercise on the BDNF levels. Exercise increases the hippocampal BDNF levels in hippocampus compared to the normal condition (40, 41). The present findings could explain some of the mechanisms underlying the beneficial effects of the protective and particularly the therapeutic exercises on reducing stress and probably memory functions. Therefore, it appears that the protective and the therapeutic exercises can probably affect synaptogenesis, plasticity, dendrite proliferation, and neurogenesis in the hippocampus (42).

Other comparisons of the preventive, therapeutic, and protective exercise illustrated that different exercise protocols did not change the IL-1β level in hippocampus (Figure 3). Some studies reported that stress increased the central IL-1β level (43, 44). On the other hand, it was also demonstrated that IL-1β is an important neurochemical mediator in the stress-induced stimulation of the hypothalamic-pituitary-adrenal (HPA) axis and the secretion of adrenocorticotropin (ACTH) and corticosterone (CORT) (45, 46). Hence, the present findings suggested that the exercise before, after, and during stress could keep the balance of hippocampal IL-1 β level in the stress conditions.

Conversely, Barrientos et al. reported that exercise had no effect on the basal hippocampal IL-1β level (44).

According to other our present data, the hippocampal glucose level increased in the preventive exercise and decreased in the therapeutic and the protective exercise groups (Figures 3 and 4). Accordingly, all of the current data suggested that the changes in the hippocampal BDNF and glucose levels followed the hippocampal CORT levels. In contrast, the inflammatory factor such as IL-1ß level did not follow the changes in the CORT levels of hippocampus in the present study.

In our previous studies, memory was assessed in the preventive, therapeutic, and protective exercise groups by passive avoidance test (4, 6). In these studies, memory functions at the end of the experimental period did not show any significant differences in the preventive and the protective exercise groups (5, 6). However, memory improved in the therapeutic exercise group (6). In the present study, the findings did not indicate a significant correlation between the hippocampal CORT, BDNF, IL-1ß, and glucose levels separately with memory in all experimental groups. Therefore, the correlations between memory functions and memory mediators proposed that multiple factors (such as hippocampal CORT, IL-1ß, BDNF, glucose, and perhaps many other factors) may, together but not alone, synergistically affect the memory in the interaction exercise with stress.

Conclusion

The therapeutic exercise had been the best exercise protocol in reducing the harmful effects of psychological stress on memory mediators in the hippocampus. It appears that the therapeutic exercise had neuroprotective properties and could reverse the harmful effects of stress in the hippocampus. However, the preventive exercise could not improve the alteration induced by the chronic stress. This suggested that the exercise time, with respect to stress conditions, is an important factor for the responsiveness of memory mediators in the hippocampus. Accordingly, evaluating other factors and gene expression involved in the stress and the exercises is highly recommended.

Conflict of Interest

The authors declare that they don't have any conflict of interest.

Authors' Contributions

Conception and design: MR, HA
Analysis and interpretation of the data: MR, NH
Drafting of the article: MR, NH, HA, MRS
Critical revision of the article for important intellectual content: MR, NH, HA, MRS
Final approval of the article: MR, NH, HA, MRS
Provision of study materials or patients: MR, HA
Statistical expertise: MR
Administrative, technical, or logistic support: MRS

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