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Research Paper: Effect of Voluntary Exercise Training on Corticosterone Level and Immobility Behavior Induced by Chronic Stress in Rats

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ABSTRACT

Background: Depression is a common mood disorder that in the long-term impairs thoughts, behavior, feelings, and health. Chronic unpredictable stress is one of the factors that can cause depression.

Objectives: To investigate the effect of voluntary exercise training on immobility behavior (caused by chronic unpredictable stress) and serum corticosterone concentration.

Materials & Methods: A total of 24 male rats were randomly and equally assigned to four groups of healthy-control, healthy-exercise, depressed-control, and depressed-exercise. Depressed-control and depressed-exercise groups were first exposed to three weeks of chronic unpredictable stress. After this period, the exercise groups performed four weeks of voluntary exercise training. Twenty-four hours after the last training session, a forced swim test was taken from the rats and their blood samples were taken 24 hours later. The obtained data were analyzed using a 2-way analysis of variance (significance level: $P<0.05$). The Pearson correlation coefficient was used to examine the relationship between study variables. All statistical analyses were performed in SPSS v. 22.

Results: Chronic stress increased immobility behavior ($P=0.001$) and serum corticosterone concentration ($P=0.001$). In contrast, exercise training reduced immobility behavior ($P=0.001$) and serum corticosterone ($P=0.001$). The immobility time ($P=0.001$) and serum corticosterone concentration in the depressed-exercise group were higher than those in the healthy-exercise group ($P=0.001$). There was a positive correlation between immobility behavior and serum corticosterone concentration ($r=0.85$ and $P=0.001$).

Conclusion: While the chronic stress increases the immobility behavior and serum corticosterone concentration, voluntary exercise training can reduce immobility behavior and serum corticosterone and adjust some depression symptoms.

Keywords: Behavior; Corticosterone; Depression; Exercise; Rats

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Highlights

- Stress increases immobility behavior and serum corticosterone concentration.
- Voluntary exercise training improves immobility behavior in depressed rats.
- Voluntary exercise training adjusts serum corticosterone concentration in depressed rats.

Introduction

Depression is a mood disorder involving impatience and reluctance to engage in pleasurable activities that negatively affect human thoughts, behavior, and emotions in the long run [1, 2].

Depression can also cause sleep and appetite disorders, fatigue, headaches, digestive problems, and heart palpitations, thus affecting physical health [2, 3].

Although statistics show that depression has a prevalence of approximately 20% in Iran, it is likely to affect at least 40% of our population. This shocking figure shows the serious social and economic damage done to the community and affected individuals. Diagnosis of depression, unlike many diseases of the body (such as diabetes, cancer, and lung disease), is not based on targeted diagnostic tests (biochemical, imaging, and biopsy) and requires a series of variable symptoms [4, 5].

Accordingly, many hypotheses have been put forward regarding the cause of depression. The basis of all hypotheses is that chronic and recurrent stress is the result of over-activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, which causes symptoms of depressive disorder at hormonal and behavioral levels. Hormonal changes in corticosteroids, especially cortisol (called corticosterone in rodents), cause changes in the levels of other hormones such as testosterone, adrenaline, estrogen, and thyroxine [6, 7].

Also at the behavioral level, despair is one of the most common symptoms in depression and leads to other problems such as suicide attempts, lack of concentration, and low ability to think. One of the valid indicators of despair in animals is immobility in the Forced Swim Test (FST) [8, 9].

So far, many studies have examined various interventions for the treatment of depression [10-12]. Various studies have shown that using different types of physical activity may be useful in treating depression [12-14]. In depression caused by inactivity, the amount of free radicals and consequently inflammation in the brain increases [15]. In other words, the brain in people with depression is attacked by reactive oxygen species. Therefore, the present study examined the use of voluntary exercise training because this training strengthens the body's antioxidant defense system. Also in this type of exercise training, the amount of free radical production is less than other types of intense training [16].

Another reason for using voluntary exercise training is that the present study seeks to examine how an active lifestyle apart from more specific exercise improves depression. According to what was discussed, the present study intends to investigate the effect of four weeks of voluntary exercise training following three weeks of chronic unpredictable stress on immobility in the FST in male rats. Changes in serum corticosterone will also be considered as a factor associated with depression.

Materials and Methods

Research design

In the present study, 24 male Wistar rats (Age: 6-8 weeks old, average weight: 220±12 g) were used. Animals were kept in an animal room with standard conditions (temperature: 22-24° C, humidity: 55%-60% and a cycle of light:darkness of 12:12 h) and in special cages whose floors were covered with clean wooden chips. The animal food was prepared in the form of pellets (Behparvar Company, Karaj). The food and water were available ad libitum except when they were submitted to chronic stress.

Rats were randomly divided into four groups (six in each group) of healthy-control, healthy-training, depressed-control, and depressed-training. At first, the depressed-control and depressed-exercise groups were exposed to three weeks of chronic unpredictable stress, and the healthy groups remained in their cages without stress for all this time.

After this period, the exercise groups performed four weeks of voluntary exercise on a wheel running, while the control groups were kept in the cages without wheel running. The FST was performed 24 hours after the last training session, and 24 hours later the rats were anesthetized and their blood samples were taken from their hearts.

Depression model

One of the most common models of depression in rats is the application of chronic unpredictable stress, which was applied in this study for three weeks. Each week of stress regime consisted of 18 h of food deprivation followed by 1 h of limited food access, 18 h of water deprivation followed by 1 h of empty bottle exposure, 21 h of the wet cage (250 mL water in sawdust bedding), two 9 h periods of 45° cage tilting, two 6-h periods of white noise (85 dB), two 6-h periods of low-intensity stroboscopic illumination (150 flashes/minute), 24 h of intermittent illumination (lights on and off every 2 h), and 24 h of no stress [17, 18].

Forced swim test

The FST was performed to measure behavioral despair and included placing the rats separately in a cylinder (clear acrylic, 20 cm in diameter and 50 cm high) containing clean water at 25° C (25 cm depth).

In the pretest phase, the rats were introduced to swimming in the cylinder for 15 minutes. One day later, during the test phase, the immobility time was recorded along 5 minutes. The immobility comprised a position in which the animal floated still on the surface of the water, making only brief movements to keep its head above water. On both days, following the test, the rats were dried with a towel and returned to the cage in a warm environment [18, 19].

Blood sampling and corticosterone measurement

Twenty-four hours after the FST, the rats were anesthetized with an intraperitoneal injection of a combination of ketamine and xylazine and their blood samples were collected from their left ventricles.

The samples were stored in tubes containing heparin at 4° C. To prepare the serum, the samples were centrifuged for 10 minutes at 3000 rpm and kept at -80°C. Corticosterone concentration was measured with a special kit and ELISA method.

Statistical analysis

The obtained data were expressed using descriptive statistics as the mean±standard deviation. The Kolmogorov-Smirnov test showed that the data had a normal distribution, so parametric statistics were used to examine the differences between the groups.

Two-way Analysis Of Variance (ANOVA) was used to evaluate the effect of stress and exercise. The Pearson correlation coefficient was used to examine the relationship between variables. P values of less than 0.05 were considered significant in all cases. All statistical analyses were performed in SPSS V. 22.

Results

The results of tow-way ANOVA showed that stress significantly increased immobility behavior in rats

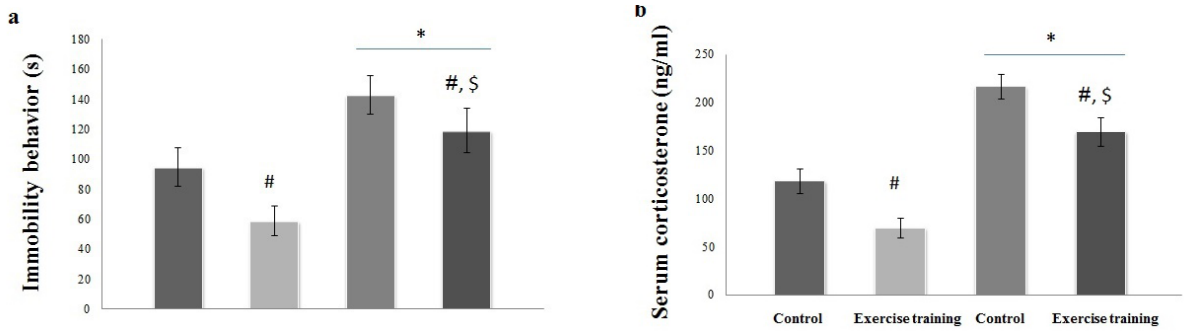

Figure 1. The results of two-way ANOVA

a. Immobility behavior(s); and b. Serum corticosterone concentration (ng/mL) in different research groups.

Data are expressed as Mean±SD in each group. There are six rats in each group; * Indicates significant differences with healthy groups. # Indicates a significant difference with the peer control group; $ Indicates a significant difference with the healthy-exercise group.

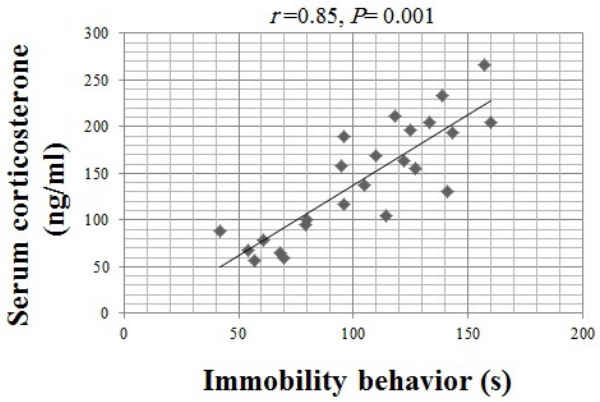

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Figure 2. The relationship between immobility behavior(s) and serum corticosterone concentration (ng/mL). There are 24 rats in each variable

(F=98.92, P=0.001) (Figure 1A). In contrast, exercise significantly reduced immobility in rats (F=30.34, P=0.001) (Figure 1A). Immobility time in the depressed-exercise group was significantly longer than that in the healthy-exercise (P=0.001) (Figure 1A). The results of 2-way ANOVA also showed that stress significantly increased serum corticosterone concentrations in rats (F=101.26, P=0.001) (Figure 1B). In contrast, exercise significantly reduced serum corticosterone concentrations in rats (F=23.60, P=0.001) (Figure 1B). Serum corticosterone concentration in the depressed-exercise group was significantly higher than that in the healthy-exercise (P=0.001) (Figure 1B).

The results of the Pearson correlation coefficient showed a positive and significant correlation between immobility behavior and serum corticosterone levels (r=0.85, P=0.001) (Figure 2).

Discussion

Overall, the findings of the present study showed that chronic unpredictable stress significantly increased immobility behavior and serum corticosterone concentration in rats. In contrast, voluntary exercise training significantly reduced immobility and corticosterone in rats. The immobility time and serum corticosterone concentration in the depressed-exercise group were significantly higher than those in the healthy-exercise group.

According to these findings, chronic unpredictable stress has affected animals and caused depression in them. After that, voluntary exercise partially improved depression. There have been many studies on the effect of exercise on depression and several mechanisms are involved in this regard [13, 14].

In general, physical activity increases neurotrophins such as Brain-Derived Neurotrophic Factor (BDNF), which increases the neurotransmitters such as serotonin and dopamine. Physical activity also changes the hippocampal structure including volume, dendritic hypertrophy, and neurogenesis, and increases euphoria and social dependence through beta-endorphins [13, 20, 21].

Chronic stress disrupts the physiological homeostasis of the brain. The response to physiological stress involves neuronal and hormonal mechanisms that re-establish homeostasis. One of these mechanisms is the activity of the HPA axis [7, 22]. In this way, the hypothalamus enhances the production of corticotropin-releasing factor, which in turn stimulates the hormone adrenocorticotropin in the pituitary gland [7, 22]. It then instructs the adrenal glands to release the hormone cortisol (corticosterone in rodents). Normally, when the stressors stop or pose a threat to the organs of the body, an integrated system of negative feedback loops stops the production of the hormone cortisol.

However, exposure to real and long-term stressors leads to persistent corticosterone production and disruption of the negative feedback system, which in turn leads to neuronal death, inflammation, decreased hippocampal volume, and decreased cognition, and finally depressive behaviors [23-25]. It seems that chronic unpredictable stress in the present study caused depression through this mechanism, also there is a positive and significant relationship between serum corticosterone concentration and depressive behavior. Among nervous system-secreting factors, BDNF is one of the most important mechanisms for changes caused by chronic stress and exercise on depression [4, 13, 14, 26].

The central nervous system forms a major part in the control of neural or neuronal plasticity (the ability of the neural network to modulate its structure and function to adapt to environmental inputs), especially during the depression by BDNF. This neurotrophic factor in the peripheral nervous system appears to be essential for the survival of neurons. This ability promotes neuronal growth and differentiation; increases axonal and dendritic branching; and stabilizes synaptic connections, long-term potentiation, and neurogenesis in the central nervous system [27, 28].

Extensive research has shown that in depression and other stress-related disorders, BDNF levels in the hippocampus would decrease. However, treatment with chemical antidepressants, electric shock, and exercise increases BDNF [4, 13, 14, 26, 29, 30]. One of the limitations of the present study was the lack of measurement of related variables such as BDNF. Thus, it is suggested that future studies examine this variable. However, the present study showed the final changes in the behavior of rats that can occur for any molecular reason, and this is one of the strengths of the present study.

Conclusion

The results of the present study showed that chronic unpredictable stress can lead to depressive-like behaviors. In contrast, exercise could alleviate the symptoms of depression such as immobility behavior, and also reduce serum corticosterone concentration. Therefore, an active lifestyle seems to be very important in improving depression, but it may not be enough, and medical considerations should be considered, too.

Ethical Considerations

Compliance with ethical guidelines

The present study was conducted based on the guidelines published by the National Institutes of Health (NIH) and considered all ethical principles regarding laboratory animals, including storage conditions, access to water and food, slaughter, and so on. The present study has received an ethical code from the Islamic Azad University, Gachsaran Branch (IR.IAU.IAUG.REC.1399.017).

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Authors contributions

Conceptualization, methodology, investigation and funding acquisition: Ayyub Babaei; Writing the original draft: Ayyub Babaei and Zahra Entezari; Supervision, writing, review, and editing: Saleh Rahmati-Ahmadabad; Resources: Ayyub Babaei, Zahra Entezari, and Saleh Rahmati-Ahmadabad.

Conflict of interest

The authors declared no conflict of interest.

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