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Research Paper

Eight Weeks of Endurance Training on Bax and Bcl2 in the Cardiac Tissue of Rats with Morphine Withdrawal Syndrome

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ABSTRACT

Background and Aim: Some data suggest that morphine induces apoptosis, while other evidence shows that exercise can have protective effects against cell death. For this purpose, the present study aimed to investigate the impact of eight weeks of endurance training on the levels of Bax and Bcl2 proteins in the heart tissue of rats with morphine withdrawal syndrome.

Materials and Methods: In this experimental study, 32 male Wistar rats were randomly divided into four groups, including control, withdrawal syndrome, withdrawal syndrome with endurance training, and endurance training. Two groups with morphine withdrawal syndrome were addicted to morphine sulfate 0.4 mg/dL for 21 days. To ensure morphine dependence, several animals were injected with naloxone (2 mg/kg). The training groups ran on a treadmill for 8 weeks (3 sessions per week) at a speed of 12 m/min for 20 minutes, with an increase of 5 minutes in training time and 1 m/min in speed added each weekTwenty-four hours after the last training session, heart tissue samples were collected. The levels of Bax and Bcl-2 proteins in the left ventricle tissue of the rat heart were measured by the ELISA method. Data were analyzed using a one-way analysis of variance and Tukey's post hoc test, at a significance level of $P<0.05$.

Results: Morphine led to an increase in Bax (proapoptotic) protein levels ($P=0.003$) and a decrease in Bcl-2 (antiapoptotic) protein levels ($P=0.001$) in heart tissue. On the other hand, performing eight weeks of endurance training led to a significant change in Bax ($P=0.001$) and Bcl-2 ($P=0.001$) protein levels in the heart tissue following morphine withdrawal syndrome.

Conclusion: Endurance training can play an effective role in reducing the complications of cardiac cell apoptosis in rats with morphine withdrawal syndrome.

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Introduction

Addiction is consistently recognized as one of the most significant problems in society, with the effects of drug use being chronic and recurrent over many years. Research indicates that drug use, such as morphine, leads to changes in neurotransmitter systems in different areas of the brain by arousing compromise mechanisms in the brain, ultimately leading to lasting changes in synapse function in response to opioid drugs. Hence, this makes the addict more vulnerable in the absence of drug use [1].

Morphine and its relation with oxidative stress are considered significant than those of other drugs. Morphine can increase the formation of free radicals or reduce the activity of various components of antioxidant systems in target cells [2]. The formation of active oxygen species (ROS) and reduced activity of antioxidant enzymes caused by morphine can lead to oxidative damage in various biological molecules, such as DNA, lipids, and proteins. Therefore, oxidative stress and apoptosis are among the effective mechanisms by which morphine acts on the central nervous system. In addition, morphine can initiate programmed cell death by activating opioid receptors [3]. Apoptosis is a type of cell death that causes the loss of non-functional, unnatural, or damaged cells, as well as harmful cells. However, when apoptosis is excessive, it can lead to abnormal changes in the structure and function of the heart [2]. Bcl-2 proteins are a group of proteins that include anti-apoptotic factors (such as Bcl-2 and Bcl-XL) and pro-apoptotic factors (such as Bcl-2-associated X protein, Bax). Cell sensitivity to apoptosis depends on the balance between pro-apoptotic and anti-apoptotic factors of the Bcl-2 family. The Bcl-2 protein acts as an apoptosis suppressor, while the Bax protein promotes apoptosis. Bcl-2 helps maintain the integrity of the mitochondrial membrane by associating with the mitochondrial outer membrane. In contrast, the Bax protein reduces the stability of the outer mitochondrial membrane, leading to the release of cytochrome c and the activation of the caspase cascade, ultimately resulting in apoptosis [4].

Although morphine enhances the expression of some anti-apoptotic molecules, which may be a natural reflection of cell resistance to death, the use of opium derivatives as a treatment can stimulate apoptosis in liver, brain, and heart cells in rat Jurkat cells [5].

On the one hand, exercise has been introduced as a protective factor for the heart in both normal and even pathological conditions. The beneficial effects of exercise are associated with increasing antioxidant defense as well as stimulating the physiological growth of the heart through cellular mechanisms. Pre-ischemia exercise reduces the Bax/Bcl-2 protein ratio and reduces the activation of caspase 3, which is the final pathway of apoptosis [6]. Zhang et al. showed that three weeks of training on a circular wheel can reduce the Bax/Bcl-2 ratio [7]. Therefore, the hypothesis is that exercise reduces the function of addictive drugs due to the development of reciprocal tolerance between endogenous substances during exercise and externally sourced drugs. Long-term and regular exercise can activate the central opioid system, stimulate the release of endogenous opioids, and increase pain thresholds in both humans and animals. Additionally, it can release various neurotransmitters, such as dopamine, glutamate, acetylcholine, and serotonin, while also altering endogenous opioids in the brain [8].

One of the methods for treatment and prevention is regular physical activity for patients. However, the question of which sport and what kind of protocol to follow is one that researchers are continually trying to answer. According to our review, no study has been conducted on the effects of exercise training against the complications of heart damage and apoptosis caused by addiction in people with morphine withdrawal syndrome. For the first time, the present research aimed to investigate the effects of endurance training on the levels of apoptotic proteins BAX and BCL2 in the heart tissue of rats with morphine withdrawal syndrome.

Materials and Methods

The present research is applied in terms of objective and experimental/laboratory in terms of method, utilizing a post-test design with a control group. It was conducted on 32 male Wistar rats (aged eight to ten weeks with a weight range of 230±30 g) prepared from Baghiyallah University. After their acquisition, the samples were transferred to the Sara Zoology Laboratory in Tabriz City, Iran. During the research period, the rats were housed in polycarbonate cages (manufactured by Razi Company) and maintained under standard laboratory conditions (temperature 22±2 ˚C, humidity 40% to 50%, and a light-dark cycle of 12:12). During this period, the rats were fed with standard pellets for laboratory rats (Pars Animal Company) and used food and water freely.

After weighing the rats using a Sartreus model TE151502S laboratory digital scale with an accuracy of 100 g, made in Germany, the rats were randomly divided into four groups of eight: A healthy control group, a con-

Table 1. Details of the training program

Session	Training Factors	Week							
		1st	2nd	3rd	4th	5th	6th	7th	8th
1st	Speed (meter/minute)	12	13	14	15	16	17	18	18
	Period (minute)	20	25	30	35	40	45	50	50
2nd	Speed (meter/minute)	12	13	14	15	16	17	18	18
	Period (minute)	20	25	30	35	40	45	50	50
3rd	Speed (meter/minute)	12	13	14	15	16	17	18	18
	Period (minute)	20	25	30	35	40	45	50	50

trol group for morphine withdrawal syndrome, an endurance training healthy group, and a morphine withdrawal syndrome group undergoing endurance training. During the study, none of the groups experienced casualties and the number of samples remained unchanged at the end of the study.

Morphine withdrawal syndrome protocol

To induce addiction in rats in the morphine withdrawal syndrome groups, a morphine solution (Tamad Company) and 3% sucrose were used to reduce the bitterness caused by morphine. The dissolved percentages of morphine were administered in doses of 0.1, 0.2, 0.3, and 0.4 mg/mL for 48 hours, followed by a dose of 0.4 mg/mL for the remaining days until the 21st day. At the end of the 21st day, naloxone (Sigma Company; USA) at the rate of 2 mg/kg of body weight was injected intraperitoneally into the samples, and the withdrawal symptoms, such as jumping, climbing, scratching, grinding teeth, redness around the eyes, diarrhea, tremors, eyelid drooping, erection and standing on two legs for 30 minutes, were examined [9].

Endurance training protocol

Familiarization with the treadmill was done 48 hours after the induction of acute morphine withdrawal syndrome for one week. The familiarization program included five sessions of walking and running at a speed of 5 to 8 m/min on a 0% slope for 8 to 10 minutes. Then, an endurance training program commenced, which included 8 weeks of treadmill running on 3 non-consecutive days for 20 minutes at a speed of 12 meters per minute. During the training, 5 minutes were added to the training time every week until it reached 50 minutes. Also, the speed of the treadmill was increased by 1 m/min every week until it finally increased to 18 m/min. This training program was conducted on a zero slope and included 3 minutes of warming up and cooling down at a speed of 7 meters per minute [10]. Table 1 presents the details of the endurance training program.

Tissue sampling and measurement of research variables

Twenty-four hours after the last training session, after an overnight fast, the rats were anesthetized via intraperitoneal injection of ketamine (75 mg/kg) and xylazine (10 mg/kg). Then, the chest of the animals was dissected and the heart tissue was isolated under sterile conditions and immediately stored in liquid nitrogen for further analysis. At different stages, while considering ethical issues, we made efforts to avoid any physical abuse and unnecessary methods. The samples were stored at -80 °C and subsequently sent to the laboratory for research. To measure the desired parameters, the heart tissue was first powdered using liquid nitrogen, and then 0.1 g (100 mg) of the prepared powder was homogenized with 1 mL of phosphate-buffered saline (PBS). Then, the extracted solution was centrifuged for 15 minutes at a speed of 5000 rpm and the supernatant was used to measure the considered indicators [10]. The CUSIBIO kits (USA) were used to measure the tissue levels of BAX (kit number: CSB-EL002573RA, with a sensitivity of <15.6 pg/mL) and BCI2 (kit number: CSB- E08854r EL002573RA, with a sensitivity lower than 0.078 pg/mL) according to the instructions, using the ELISA method.

Statistical method

The results are expressed as Mean±SD. For statistical analysis, after ensuring the normality of the data, the Shapiro-Wilk normality test was used, and Levene's test

Table 2. Comparing apoptotic regulatory indices in the studied groups

Variables	Control	Morphine Withdrawal Syndrome	Endurance	Endurance+Morphine Withdrawal Syndrome
BAX (pg/mL)	6.1±6.86	10±1.5	1±66.47	7.1±81.37
BCL2 (pg/mL)	127±311	13±132.9	21±555	54±302
BAX/BCL2	0±24.01	0±7.009	0±3.0007	0±26.005

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was used to check the assumption of equality of variances. After determining the normality of the data distribution and establishing the assumption of the equality of variances, one-way analysis of variance and Tukey's post hoc test (P<0.05) were used to statistically analyze the data and compare the groups Additionally, an independent t-test was employed to analyze the symptoms of morphine withdrawal syndrome. All statistical calculations were performed using SPSS statistical software, version 18.

Results

Table 2 presents the values of apoptosis regulatory indices in the study groups.

The results of the ANOVA showed a significant difference between different groups in terms of BAX levels (P=0.001, F=68.33; df=3) (Table 3). The results of Tukey's test showed a significant decrease in BAX levels between the endurance training+morphine withdrawal syndrome group compared to the control group (P=0.003 and P=0.001, respectively). Additionally, significant decreases were observed between the morphine withdrawal syndrome group and the endurance training+morphine withdrawal syndrome group compared to the endurance group (P=0.001 and P=0.008, respectively), as well as between the endurance training+morphine withdrawal syndrome group and the morphine withdrawal syndrome group (P=0.006). However, no significant decrease was observed in the endurance training+morphine withdrawal syndrome group compared to the control group (P=0.21).

Also, the results of the ANOVA showed a significant difference between different groups regarding BCL2 levels (P=0.001, F=49.06, df=3) (Table 4). The results of Tukey's test showed a significant increase in BCL2 levels between the endurance training+morphine withdrawal syndrome group compared to the control group (P=0.001 and P=0.043, respectively). Also, a significant increase was observed between the morphine with-

Table 3. One-way analysis of variance regarding BAx levels in the research groups

Index	Variances	Sum of Squares	df	Mean of Squares	F	P
	Intergroup	299.77	3	99.92		
BAX	Intragroup	40.94	28	1.46	68.33	0.001
	Total	340.72	31			

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Table 4. One-way analysis of variance regarding BCL2 levels in the research groups

Index	Variances	Sum of Squares	df	Mean of Squares	F	P
	Intergroup	726822.1	3	242274		
BCL2	Intragroup	138263.7	28	4937.9	49.06	0.001
	Total	865085.8	31			

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Table 5. One-way analysis of variance regarding the BAX/BCL2 ratio in the research groups

Index	Variances	Sum of Squares	df	Mean of Squares	F	P
BAX/BCL2	Intergroup	0.023	3	0.008	132.37	0.001
	Intragroup	0.002	28	0.001		
	Total	0.025	31			

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drawal syndrome group and the endurance training plus morphine withdrawal syndrome group compared to the endurance group (P=0.030 and P=0.001, respectively). In addition, a significant increase was observed between the endurance training nificant increase was observed in the endurance training plus morphine withdrawal syndrome group compared to the control group in BCL2 levels (P=0.99).

Also, the results of the ANOVA showed a significant difference between different groups in terms of the BAX/BCL2 ratio (P=0.001, F=132.37, df=3) (Table 5). The results of Tukey's test showed a significant decrease in the BAX/BCL2 ratio between the endurance training+morphine withdrawal syndrome group (P=0.001 and P=0.007, respectively). Also, a significant decrease was observed between the morphine withdrawal syndrome group and the endurance training+morphine withdrawal syndrome group compared to the endurance group (P=0.004 and P=0.001, respectively). A significant decrease was also noted between the endurance training+morphine withdrawal syndrome group and the morphine withdrawal syndrome group (P=0.001). However, no significant decrease in the BAX/BCL2 ratio was observed in the endurance training+morphine withdrawal syndrome group compared to the control group (P=0.96).

Analysis of the symptoms of morphine withdrawal syndrome (jumping, climbing, standing on two legs, and scratching) in the studied groups using an independent t-test showed a significant difference between the endurance training+morphine withdrawal syndrome group compared to the morphine withdrawal syndrome group (P=0.04) (Table 6).

Discussion

It has been shown that exercise and physical activity significantly increase the production of natural morphine in the brain, originating from beta-endorphin, half an hour after the start of exercise. By affecting brain receptors through the same mechanism, exercise produces similar pleasant effects and euphoria as those following morphine consumption or other opioids. Effective and low-cost methods to prevent harm caused by drugs can play a crucial role in treating and preventing their effects. The use of different drugs in withdrawal syndrome usually has limited effectiveness and causes the person to become dependent on new substances. Therefore, it seems that exercise is one of the effective and low-cost methods for addiction treatment [11]. It has been reported that morphine can induce oxidative stress and increase apoptosis in macrophages [12]. This study was conducted to investigate the effect of eight weeks of endurance training on Bax and Bcl2 levels in the heart tissue of rats with morphine withdrawal syndrome. The results showed a significant difference between the Bax and Bcl2 protein levels in the heart tissue of rats in the training and control groups. According to the results, the

Table 6. Independent t-test results to compare the symptoms of morphine withdrawal syndrome in the studied groups

Variables	Morphine Withdrawal Syndrome + Endurance Training	Morphine Withdrawal Syndrome	P*
Redness around the eyes	0.347	4.885	0.04
Scratching	0.491	9.206	0.05
Grinding teeth	0.732	7.213	0.04
Trembling and nervousness	0.560	12.54	0.02

*Significant difference between the morphine withdrawal syndrome group and the morphine withdrawal syndrome + endurance training group (P<0.05).

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levels of Bax and the ratio of Bax to Bcl-2 decreased in both the endurance training group and the endurance training group with morphine withdrawal syndrome, while the level of Bcl-2 increased. Consistent with these results, in the research by Qajari et al., eight weeks of endurance training caused a significant increase in Bcl-2 levels and a decrease in Bax levels in cardiac muscle [13]. Chengji et al. found that 12 weeks of aerobic exercise training increased the heart weight of diabetic rats and, by enhancing antioxidant enzymes, increased Bcl-2 while inhibiting caspase-3 related to endoplasmic reticulum stress, thereby reducing apoptosis [14]. Ham et al. stated that aerobic exercise caused a significant increase in Bcl-2 levels and a significant decrease in Bax levels [15]. Jafari et al. also showed that 12 weeks of endurance training reduces apoptosis by reducing the Bax/Bcl-2 ratio in rat hearts [16].

Heo et al. showed that eight weeks of running on a treadmill decreases the expression of the *Bax* gene and caspase-3 while increasing the expression of the *Bcl-2* gene in the hearts of old diabetic rats [17]. Also, according to Delfan and Afrasiabian, it seems that endurance training (at an intensity of 60%-65% of VO2peak, five days a week, and running on a treadmill for four weeks) combined with Yari probiotic supplementation is effective in reducing plasma glucose, decreasing *Bax* gene expression, and increasing *Bcl-2* gene expression [18].

On the other hand, Kashani et al. reported that high-intensity interval training does not affect the BAX protein levels, which may be attributed to differences in training protocol, training intensity, or sample type. However, training and curcumin supplementation increases Bcl-2 protein levels and neutralize the effects of BAX. Curcumin supplementation combined with intense intermittent exercise resulted in synergism and reduced programmed cell death [19]. Haji Khani et al. concluded that six weeks of endurance, resistance, and especially combined exercise training improves glycemic indices and decreases BAX protein levels compared to the non-exercise group, although Bcl-2 protein levels remain unchanged. Therefore, it would be beneficial to investigate and compare other exercise models regarding the apoptosis of the heart in diabetic rats [20]. Tanversaz et al. showed that eight weeks of aerobic exercise improves glucose metabolism and insulin sensitivity, but does not cause a change in Bcl-2 levels in cardiomyocytes of diabetic rats, which may be due to differences in training protocol, training intensity, type of sample, and measured tissue [21]. In Karimi et al.'s study, the expression of *BAX* and *Bcl-2* genes did not change significantly; however, caspase-3 activity showed a significant increase in the liver of diabetic rats after treatment with aqueous garlic extract [22]. At least part of the discrepancy between the results appears to be due to the use of garlic supplements and the type of sampled tissue.

Considering that the two proteins Bcl-2 and Bax play a crucial role in modulating cell death processes, any factor that changes the ratio of Bax to Bcl-2 or vice versa shifts the environment toward apoptosis or anti-apoptosis. The process of *Bax* gene changes is not entirely certain; however, it has been shown that an increase in *Bcl-2* gene expression is one of the main mechanisms for the suppression of the *Bax* gene [23]. The increase in *Bcl-2* gene expression by interfering with Bax oligomerization strengthens the mitochondrial wall, prevents the release of cytochrome c, and regulates the release of calcium from the endoplasmic reticulum, thereby preventing apoptosis [23]. It has been reported that endurance training plays a role in reducing apoptosis by inhibiting hydroxyl and superoxide radicals and preventing the release of cytochrome c. Also, protein kinase B, through the phosphorylation of Bcl-2 and the inactivation of Bax, or by directly inhibiting caspase activity, blocks apoptotic pathways. Sports training may also enhance antioxidant defense by increasing ATP utilization and activating protein kinases, thereby reducing apoptosis [24]. In addition, it seems that endurance training activates this signaling pathway by increasing the levels of AKT protein or by regulating and modulating growth factors, such as insulin and IGFI, which play a role in eliminating disorders within this signaling pathway. In addition, it seems that endurance training reduces the ratio of Bax/Bcl-2 by reducing the expression of Bax protein and increasing the expression of Bcl-2 protein, which can inhibit apoptosis mitochondria-induced apoptosis [25].

On the other hand, morphine is the main ingredient of opium latex. Its excessive consumption has adverse effects, such as depression and respiratory destruction, addiction, coma, and death. Additionally, it promotes the production of free radicals and ultimately lipid peroxidation through the inhibition of antioxidant enzymes. Free radicals can lead to cell membrane destruction and DNA fragmentation. It has also been shown that morphine induces apoptosis in body cells through the production of reactive oxygen and nitrogen species [26]. Previous studies have found that patients dependent on morphine have left ventricular systolic dysfunction and reduced overall heart function. In this regard, Mesripour et al. found that dependence on morphine increases oxidative stress and ultimately leads to undesirable remodeling of the ventricle of the heart [27].

A balance is normally established between inhibitory factors and apoptotic stimulators; however, this balance can be disrupted in various situations, including morphine consumption. It has been reported that long-term morphine treatment is associated with an increase in FAS (TNF receptor superfamily member 6) receptors (pro-apoptotic) and a decrease in Bcl-2 protein (anti-apoptotic), ultimately leading to apoptosis in the brains of laboratory rats [28]. Boronat's study showed that the increase in apoptotic factors due to morphine can be caused by the activation of opioid receptors. As it has been proven in past research, morphine can trigger programmed cell death by activating opioid receptors [28].

Evidence shows that exercise has incentive effects in rats, which is mediated through the opioid system. Also, exercise activates at least some of the same pathways activated by morphine and other opioids. Therefore, it is possible that the decreased desire to use morphine due to exercise, which was shown in the present study, may be related to the activation of the androgen opioid system [28]. Ahmadi et al. suggest a potential effect of aerobic exercise in preventing the desire to consume morphine and in reducing withdrawal symptoms, given that the dopaminergic system plays a crucial role in addiction and the reward system. Aerobic exercise may exert its effects in this manner and could serve as an effective supportive factor in improving the condition of individuals with addiction [29]. In the study by Heidarianpour and Nazari, six weeks of endurance training on a treadmill increased the pain threshold of addicted rats with withdrawal syndrome. The mechanism that can be proposed for the observed effect of exercise is its interference with the dopaminergic system and the alteration of dopamine levels in various brain regions [30]. The integrity of the dopaminergic system in morphine dependence has also been shown in several studies. Dopaminergic pathways are involved in creating reward and reinforcement responses, as well as in physical activity and drug abuse [29].

One of the limitations of the present study is the lack of measurement of other effective factors in the apoptotic pathways, such as caspase-3 and the release rate of cytochrome c. If these variables were measured, more complete results would be obtained. Also, the length of the training period is another limitation of the current research. Longer periods of exercise would provide a more accurate assessment of exercise-induced adaptations in cardiac apoptotic pathways. In addition, due to the presence of oxidative stress and its effect on apoptosis, it is suggested that this research be conducted with the inclusion of an antioxidant supplement. It is also suggested to use other factors involved in apoptosis to investigate apoptosis more precisely.

Conclusion

According to the results of the present study, performing eight weeks of endurance training significantly increases the Bcl-2 anti-apoptotic protein levels while simultaneously decreasing the Bax apoptotic protein levels. Also, the ratio of Bax/BcL-2 decreased in the training groups, which confirms a reduction in apoptosis and an increase in the survival of healthy cells in the heart tissue of rats following morphine addiction. In addition, endurance training can reduce physical and psychological dependence on morphine in rats. Therefore, sports training may be considered as one of the treatment methods by reducing some of the behavioral effects caused by morphine addiction.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Islamic Azad University, Borujerd Branch (Code: IR.IAU.B.REC.1401.029).

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Authors' contributions

All authors contributed equally to the preparation of this article.

Conflict of interest

The authors declared no conflict of interest.

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