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Protective effects of forced exercise against nicotine-induced anxiety, depression and cognition impairment in rat

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Abstract

Background: Nicotine is one of the psychostimulant agents displaying parasympathomimetic activity; the chronic neurochemical and behavioral effects of nicotine remain unclear. Exercise lowers stress and anxiety and can act as a non-pharmacologic neuroprotective agent. In this study, the protective effects of exercise in nicotine withdrawal syndrome-induced anxiety, depression, and cognition impairment were investigated.
Methods: Seventy adult male rats were divided randomly into five groups. Group 1 served as negative control and received normal saline (0.2 mL/rat, i.p.) for 30 days, whereas group 2 (as positive control) received nicotine (6 mg/kg/day, s.c.) for the first 15 days. Groups 4, 5, and 6 were treated with nicotine (6 mg/kg/day, s.c.) for the first 15 days and then were treated with forced exercise, bupropion (20 mg/kg/day, i.p.), or a combination of the two for the following 15 days. Between day 25 and day 30, Morris water maze was used to evaluate spatial learning and memory. From days 31 to 35, the elevated plus maze (EPM), open field test (OFT), forced swim test (FST), and tail suspension test (TST) were used to investigate the level of anxiety and depression in the subjects.
Results: Nicotine-dependent animals indicated a reflective depression and anxiety in a dose-dependent manner in FST, EPM, and TST, which were significantly different from the control group and also can significantly attenuate the motor activity and anxiety in OFT.
Conclusions: Forced exercise, bupropion, or their combination can attenuate nicotine cessation-induced anxiety, depression, and motor activity in the mentioned behavioral assay. We conclude that forced exercise can protect the brain against nicotine withdrawal-induced anxiety, depression, and cognitive alteration.

Keywords: anxiety; cognition impairment; depression; forced exercise; nicotine.

Introduction

Nicotine is one of the psychostimulant agents displaying parasympathomimetic activity. However, its pharmacological similarity to amphetamine-type stimulants makes it more liable for abuse and addiction [1]. Chronic abuse of nicotine in the form of smoke leads to physical dependency, characterized by withdrawal syndrome [2]. Upon the sudden discontinuation of nicotine administration, a number of symptoms like tremor, anxiety, depression, and cognition impairment develop [1]. Studies have established that nicotine abuse stimulates serotonergic and dopaminergic reward and generates feelings of pleasure and elation [3–5]. Investigations have confirmed that nicotine withdrawal syndrome after chronic administration and adaptations can cause increased anxiety and depression [1, 6, 7]. On the other hand, the anxiety and depression observed during nicotine withdrawal are major concerns for designing nicotine dependency treatment protocols [1, 6, 8, 9]. Taking these concerns into account, some anxiolytic and antidepressant agents are being used alongside nicotine withdrawal syndrome management [10, 11]. One of the agents which was used for the treatment of nicotine cessation is bupropion; this agent is an antidepressant characterized by norepinephrine-dopamine reuptake inhibitor. Previous studies have shown that bupropion can be used for the treatment of nicotine cessation syndrome, obesity, sexual dysfunction, and attention deficit hyperactivity disorder [12]. Moreover, many studies have shown that nicotine withdrawal is associated with a deficit in neurocognitive function including sustained attention and working memory [13]. Experimental studies have demonstrated the potential effect of nicotine on

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brain development and functional change, suggesting that chronic use of nicotine may cause neurodegeneration of some parts of the brain [14].

Previous studies have demonstrated that exercise lowers stress and anxiety and increases the secretion of endorphin in the brain [15, 16]. Furthermore, physical activity and chronic forced exercise has been seen to induce anxiolytic-like effects in some experiments [15–17]. It has also been evident that exercise can reduce depression and increase cognitive functions [18]. Similar to antidepressants, chronic exercise in mice may induce behavioral changes involving brain-derived neurotrophic factor pathways [19]. Exercise augments synthesis and the release of dopamine and promotes feelings of well-being [20]. In the present study, we have investigated the protective effect of exercise in nicotine-induced anxiety, depression, and cognitive impairment. Here, we aim to assess physical activity as an option for treating nicotine-induced withdrawal signs.

Materials and methods

Animals

Seventy adult male rats, with an average weight of 220 g and average age of 9 weeks, were obtained from the animal house of Iran University of Medical Sciences (Tehran, Iran) and transferred to the lab. For the following 2 weeks, the rats were kept at room temperature (22±2 °C) and provided with free access to standard food and tap water. Housing took place under a standard 12-h day/night cycle. The experimental protocol was approved by the Research Council of the Iran University of Medical sciences.

Drug

Nicotine was purchased from Shafayab Gostar Co. (Tehran, Iran), and bupropion was purchased from Abidi Pharmaceutical Company (Tehran, Iran). All solutions were freshly prepared before use.

Experimental design

Rats were assigned to one of the following groups:

- Group 1 (negative control) received normal saline (0.2 mL/rat, i.p.) for 30 days.
- Group 2 (positive controls) was treated with nicotine (6 mg/kg/day, s.c.) just for 15 days.
- Groups 3 received nicotine (6 mg/kg/day, i.p.) for the first 15 days and then were treated with bupropion (20 mg/kg/day. s.c.) for the following 15 days.
- Group 4 received nicotine (6 mg/kg/day, s.c.) for the first 15 days and then underwent forced exercise (using a treadmill) for the following 15 days.
- Group 5 received nicotine (6 mg/kg/day, s.c.) for the first 15 days and then underwent treatment with bupropion (20 mg/kg/day, i.p.) combined with forced exercise (by following protocol) for 15 days.

Between day 25 and day 30 of the experiment, a standard behavioral protocol (Morris water maze (MWM) task) was used to evaluate learning and memory in experimental animals. Between days 31 and 35, some other behavioral assays such as elevated plus maze (EPM), open field test (OFT), forced swim test (FST), and tail suspension test (TST) were used to assess anxiety and depression in these animals.

Treadmill forced exercise protocol

All animals were made to run on a motor-driven treadmill (ModelT408E, Diagnostic & Research Instruments Co., Taoyuan, Taiwan). The exercise training program for rats in groups 4 and 5 consisted of uninterrupted treadmill sessions, 6 times a week for 45 min/day. For habituation, before the main training all animals were trained 5 m/min for 3 days and then for main training. For the first week, the running speed was set at 10 m/min, and from the second week till the end of experiment, it was maintained at 15 m/min. The slope and intensity of exercise was set at 0° for the first 10 min, 5° for the next 10 min and 15° for the last 25 min.

Behavior tests

Open field test: This assay was used to evaluate anxiety and locomotor activity in experimental animals. The base of OFT apparatus was divided into 16 equally spaced squares bordered with opaque and 70 cm high walls. The whole apparatus was painted black except for the 6 mm broad white lines that divided the ground into 16 squares. This apparatus was illuminated using a 100 W bulb which focused into the field from a height of about 110 cm. Except for the open field, the entire room was kept in dark during the experiment. In order to observe subsequent behaviors for evaluating anxiety and locomotor activity, each animal was brought to the center of the setup for about 5 min. Four typical behaviors in open field test have been assessed and scored.

- Ambulation distance: Total distance of the grid lines crossed by each rat.
- Center square entries: Number of times each rat enters the central red square lines with all four paws.
- Center square duration: The time spent by each rat in the central square.
- Rearing: Frequency with which each rat stands on their hind legs in the maze.

Forced swim test: This is a behavioral test used for the evaluation of depression-like behaviors in the experimental model. The FST equipment consisted of a transparent Plexiglas cylinder (20 cm diameter×60 cm height) filled with water up to the height of 30 cm from base. A day before the test, all rats were gently placed in the cylinder and made to swim for a habituation period of 15 min. However, during experimentation, subjects were placed individually in a filled glass cylinder for a period of 5 min, and the duration of swimming was recorded for each. The swimming activity was indicative of non-depressive behavior.

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Elevated plus maze: EPM is a widely used assay to assess anxiety-related behaviors in rodents. The EPM setting consists of a plus sign apparatus; a pair of oppositely placed open arms (55×15 cm), a pair of oppositely placed closed arms (55×15 cm), and an open central squared area (10×10 cm). All the arms were kept open from the top, and the closed arms had 40 cm elevated side walls. The entire apparatus was held 50 cm above the ground by means of rods. One at a time, rats were placed in the center of the maze, and the time spent by each rat in open arms and in closed arms was recorded. The subjects were freely allowed to explore the maze for 5 min. The preference for being in closed arms over the open ones was indicative of depressive behavior.

Tail suspension test: In TST, a rat is suspended by its tail (50 cm above the ground) against a fixed metal rod with its body facing downwards. Normally, the rat tries to escape from this stressful state by trying to climb up the metal rod. However, depressed ones give up and remain immobile. Therefore, we recorded the duration of immobility in a 5-min period which was indicative of depression-like behavior.

Morris water maze: The MWM apparatus was used to assess learning and memory in rats. It consisted of a circular galvanized black steel water tank (150 cm diameter×85 cm height) placed in the center of a small room. This circular tank was divided into four quarters (north, east, west and south) and filled with 50 cm deep water. An invisible metal platform (12 cm in diameter) was submerged approximately 1 cm below the surface of the water. An automated infrared tracking system (CCTV B/W camera, SBC-300 (P), Samsung Electronic Co., Ltd., Korea) was used to record the position of the animal in the tank. The camera was mounted 2.3 m above the surface of the water and animal behavior was evaluated in three separate processes.

A. Handling
In a 4-day training session, the tank was filled with water (room temperature 25±2 °C), and the platform was submerged in one of the quarters (north-east) approximately 25 cm from the wall of the tank. At the beginning of each trial, the rat was placed into the tank, and the experimenter guided the rat to swim towards the platform placed in the specified quarter.

B. Training procedure (learning assessment)
Some distinguished landmarks (like pictures, windows, and doors) were placed in an extra maze present in the same room for spatial cues for learning of the platform's position for animals. Each animal underwent trial 4 times per day with the platform positioned in each quarter (north, east., west, and south) randomly. If the rats were unable to find the platform within 60 s, the trial was terminated automatically by the computer system. In this 4-day training procedure, two different activities were assessed:
- Escape latency: Time taken by each rat to reach the platform.
- Traveled distance: Total distance travelled by each rat to find the platform.

C. Probe testing (memory assessment)
On the fifth day (probe day), the experimenter removed the platform, the animal was randomly placed into the water tank (in the quarter other than the north-east one), and the percentage of the rats that reached the north-east was calculated.

Statistical analysis

The data were analyzed using GraphPad PRISM v.6 Software, and average values in each experimental group were expressed as mean±standard error of the mean (SEM). Differences between control and treatment groups were evaluated by one-way ANOVA. To evaluate the severity of behaviors, the differences among groups were compared using Tukey test. A p-value of <0.05 was considered statistically significant.

Results

Behavioral teratology in open field test

Assessment of open field test

Results of OFT showed that the frequency of central square entries and the time spent in the central region in the negative control group was significantly higher than the nicotine (6 mg/kg/day) treated group (positive controls) ($p<0.05$) (Table 1). Furthermore, the nicotine-dependent bupropion (20 mg/kg/day) treated group and forced exercise group showed a relatively higher frequency of central square entries accompanied with more time spent in the central region, compared to the positive control group ($p<0.05$) (Table 1). It was observed that the nicotine-dependent group which was under the treatment with both bupropion (20 mg/kg/day) and forced exercise

Table 1: Effect of forced exercise training and bupropion (20 mg/kg) on open field exploratory and anxiety-like behavior in rat under treatment with 6 mg/kg/day of nicotine.

Group	Ambulation distance	Central square entries	Time spent in central square	Number of rearings
Control	435±15	20±1	169±7	14±2
Nicotine (6 mg/kg)	380±12[a]	14±1.2[a]	113±6[a]	6±1[a]
Nicotine+bupropion (20 mg/kg)	390±19[b]	15±1.1[b]	131±10[b]	9±1[a]
Nicotine+forced exercise	400±21[b]	16±1.2[b]	136±10[b]	9±1[b]
Nicotine+bupropion (20 mg/kg)+forced exercise	420±22[c]	16±1[c]	149±12[c]	12±2[c]

[a]$p<0.05$ vs. control groups; [b]$p<0.05$ vs. 6 mg/kg of nicotine; [c]$p<0.001$ vs. 6 mg/kg of nicotine.

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showed a higher frequency of central square entries and spent more time in the central region, in comparison to the positive control group ($p<0.001$) (Table 1).

Nicotine-dependent groups treated with bupropion (6 mg/kg/day) had a lower ambulation frequency number and rearing and shorter ambulation distances in OFT compared with the negative control group ($p<0.05$) (Table 1). However, the nicotine-dependent group treated with bupropion (20 mg/kg/day) and forced exercise showed a higher frequency of ambulation number and rearing and increased ambulation distance in OFT compared to the positive control group ($p<0.001$) (Table 1).

Assessment of forced swim test

In comparison with the negative control group, nicotine-dependent groups spent less time swimming in FST ($p<0.05$) (Figure 1). Furthermore, treatment of nicotine-dependent animals with bupropion (20 mg/kg/day), forced exercise and bupropion in combination, and forced exercise alone increased swimming time compared with the nicotine-dependent group in the FST ($p<0.001$) (Figure 1).

Assessment of elevated plus maze

When compared to the negative control group, the nicotine-dependent group appeared to spend less time in open arms in the EPM ($p<0.05$) (Figure 2). Furthermore, nicotine-dependent animals treated with bupropion (20 mg/kg/day), forced exercise, and bupropion in combination with forced exercise spent more time in open arms in comparison with the nicotine-dependent group in EPM ($p<0.001$) (Figure 2).

Assessment of tail suspension test

Immobility duration in nicotine-dependent animals was significantly higher in comparison to the negative control group in TST ($p<0.05$) (Figure 3). Treatment of nicotine-dependent animals with bupropion (20 mg/kg/day), forced exercise, and bupropion in combination with forced exercise led to a statistically significant decrease in immobility duration ($p<0.001$) (Figure 3).

Evaluation of escape latency and traveled distance during training days in the Morris water maze

Escape latency time and traveled distance during the training period in MWM for the nicotine-dependent group was significantly higher in comparison to the negative control

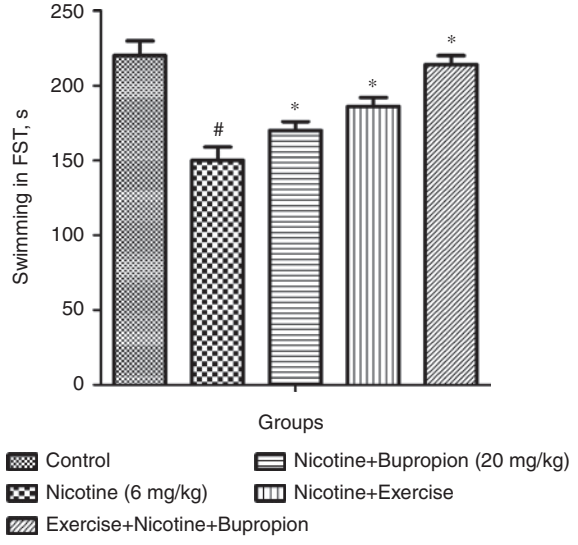

Figure 1: Swimming time (seconds) in FST in control group and groups under treatment with 6 mg/kg of nicotine and nicotine-dependent group under treatment with bupropion (20 mg/kg), forced exercise, or bupropion in combination with forced exercise.
All data are expressed as mean±SEM (n=8). #p<0.05 vs. control groups. *p<0.05 vs. 6 mg/kg of nicotine.

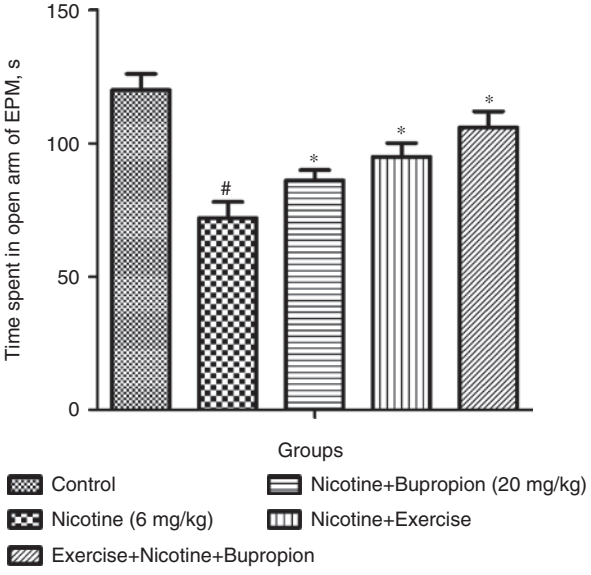

Figure 2: Duration of time spent in open arms (seconds) in elevated plus maze (EPM) test in control group and groups under treatment with 6 mg/kg of nicotine and nicotine-dependent group under treatment with bupropion (20 mg/kg), forced exercise, or bupropion in combination with forced exercise.
All data are expressed as mean±SEM (n=8). #p<0.05 vs. control groups. *p<0.05 vs. 6 mg/kg of nicotine.

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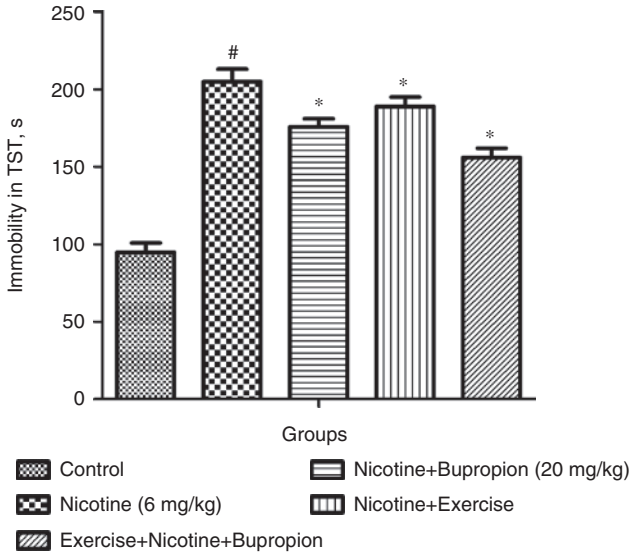

Figure 3: Duration of time stayed in immobility (seconds) in tail suspension test (TST) in control group and groups under treatment with 6 mg/kg of nicotine and nicotine-dependent group under treatment with bupropion (20 mg/kg), forced exercise, or bupropion in combination with forced exercise.
All data are expressed as mean±SEM (n=8). #p<0.05 vs. control groups. *p<0.05 vs. 6 mg/kg of nicotine.

group (p<0.05) (Figures 4 and 5). Treatment with bupropion (20 mg/kg/day), forced exercise, and bupropion in combination with forced exercise in nicotine-dependent animals reduced escape latency time and traveled distance during training period in the MWM in comparison to nicotine-dependent group (p<0.001) (Figures 4 and 5).

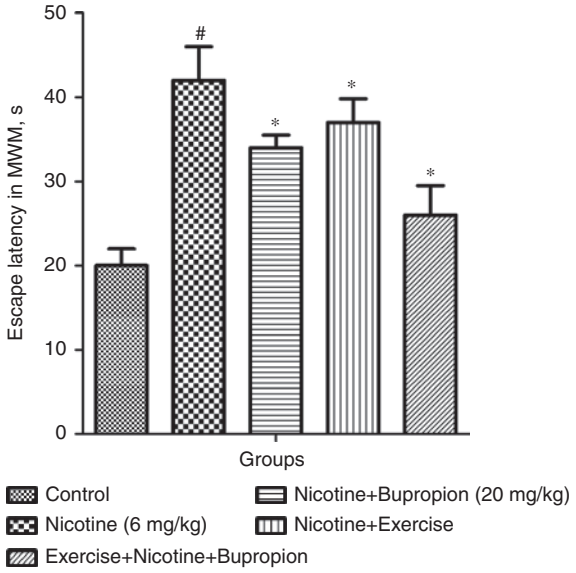

Figure 4: Average of escape latency in control group and groups under treatment with 6 mg/kg of nicotine and nicotine-dependent group under treatment with bupropion (20 mg/kg), forced exercise, or bupropion in combination with forced exercise.
All data are expressed as mean±SEM (n=8). #p<0.05 vs. control groups. *p<0.05 vs. 6 mg/kg of nicotine.

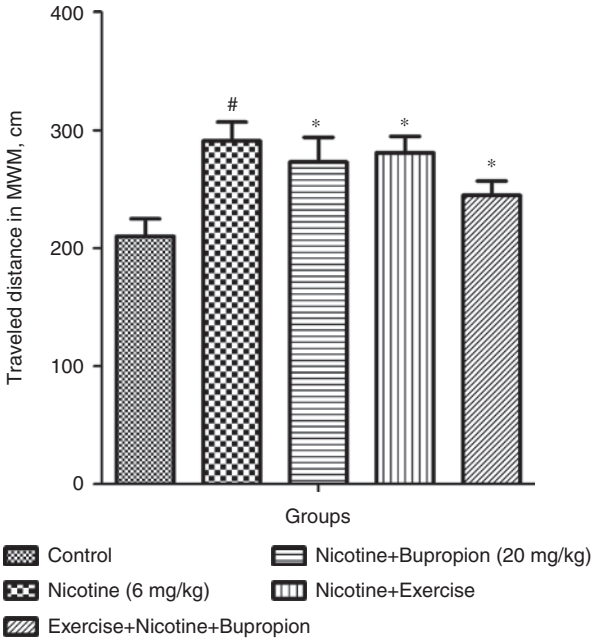

Figure 5: Average of traveled distance in control group and groups under treatment with 6 mg/kg of nicotine and nicotine-dependent group under treatment with bupropion (20 mg/kg), forced exercise, or bupropion in combination with forced exercise.
All data are expressed as mean±SEM (n=8). #p<0.05 vs. control groups. *p<0.05 vs. 6 mg/kg of nicotine.

Evaluation of swimming speed during training period

There was no alteration found in the swimming speed training trials in any of the animal groups, suggesting that exposure to nicotine dependency and our treatment protocol in the experimental group did not cause any motor disturbances involvement in the performance tests (Figure 6).

Evaluation of percentage in target quarter in probe trial

The data showed that there was a significant decrease in the percentage of the presence of animals in the target quarter in nicotine-dependent group in comparison with negative control groups (p<0.05) (Figure 7). Treatment with bupropion (20 mg/kg/day), forced exercise, and bupropion in combination with forced exercise in

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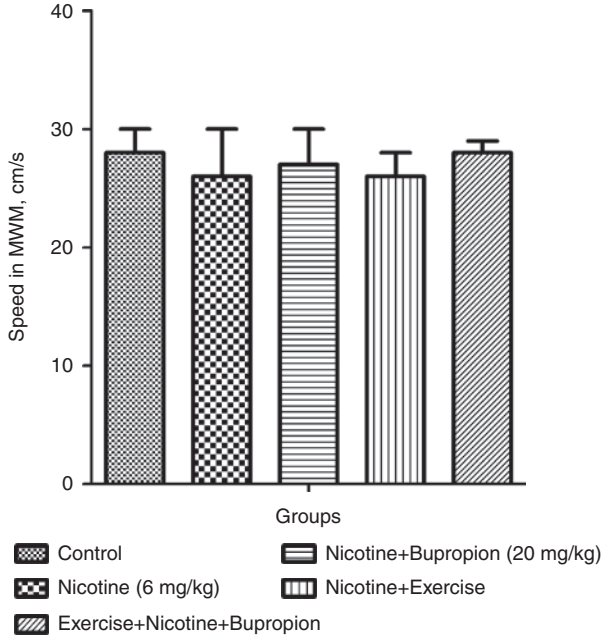

Figure 6: Average of swimming speed in control group and groups under treatment with 6 mg/kg of nicotine and nicotine-dependent group under treatment with bupropion (20 mg/kg), forced exercise, or bupropion in combination with forced exercise.
All data are expressed as mean±SEM (n=8). #p<0.05 vs. control groups. *p<0.05 vs. 6 mg/kg of nicotine.

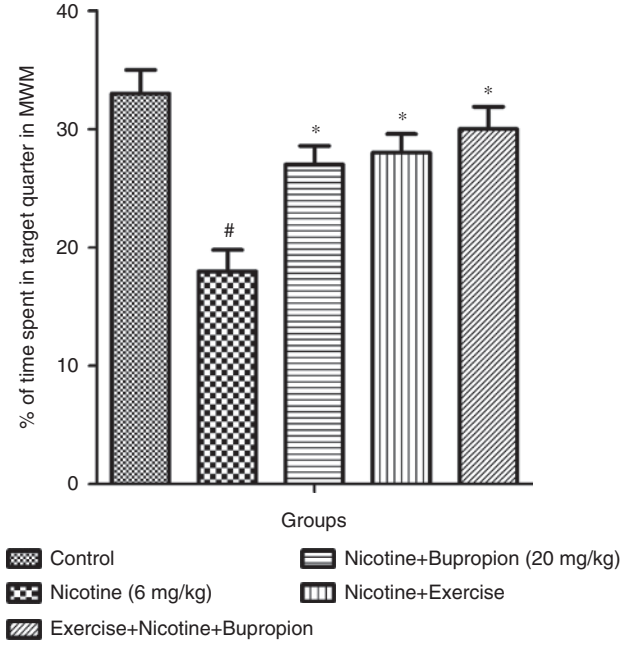

Figure 7: Percentages of time spent in target quarter in probe trial in control group and groups under treatment with 6 mg/kg of nicotine and nicotine-dependent group under treatment with bupropion (20 mg/kg), forced exercise, or bupropion in combination with forced exercise.
All data are expressed as mean±SEM (n=8). #p<0.05 vs. control groups. *p<0.05 vs. 6 mg/kg of nicotine.

nicotine-dependent animals increased the time spent by animals in the target quarter in comparison to the nicotine-dependent group (p<0.001) (Figure 7).

Discussion

The current study shows that physical activity in the form of exercise can decrease nicotine dependency and withdrawal syndrome inducing anxiety, depression, and cognitive deficits. We have found that nicotine dependency causes significant changes in behavioral markers in FST (swimming and immobility) and EPM (open arm and close arm entry). Furthermore, nicotine dependency and its withdrawal also alters behavioral parameters in OFT (central area entry, central area duration, ambulation, and rearing) and TSS (immobility). Interestingly, cessation of nicotine suppresses cognitive behavior such as learning and memory in MWM [8]. Nicotine abuse in the form of smoke leads to physical and physiological dependency which is characterized by withdrawal and cessation syndrome [6]. Upon the sudden discontinuation or attenuation of nicotine intake, a number of symptoms such as restlessness, anxiety, depression, and cognition impairment develop [1, 21].

Previous studies have indicated that exercise lowers anxiety and stress levels and triggers the release of opioid-like peptides in the brain [15, 22]. Physical activity can attenuate the severity of withdrawal symptoms by reducing depression and reducing anxiety and thereby facilitating the patient to regain a state of well-being [22, 23]. Many studies have confirmed that exercise can aid in this recovery process [22, 24, 25]. Moreover, physical activity helps reduce the risk of drug abuse relapse. Many studies have confirmed that exercise is beneficial in decreasing the rewarding effects of some agents like cocaine and morphine. This is evident by increased synthesis and release of dopamine and serotonin, which in turn stimulate neuroplasticity and promote feelings of well-being [26, 27].

The present study indicates that nicotine discontinues with doses of 6 mg/kg causes a remarkably decreased swimming time in FST. In addition, our results have indicated that nicotine abuse induces depression-like behavior in animals. Nicotine abuse and withdrawal can alter brain monoamines to induce anxiety and depression [28]. Previous findings suggest that nicotine abuse in humans induces persistent changes in behavior [28]. On the other hand, our data indicate that bupropion (20 mg/kg), forced exercise, and forced exercise in combination with bupropion diminish depression-like behavior induced

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by nicotine cessation in FST. Many previous studies have demonstrated that bupropion acts as an effective agent against nicotine withdrawal signs [29]. Our results based on exercise are in accordance with the previous study, which indicates that physical activity can modulate depression and anxiety [15, 17, 24].

Our data suggested that withdrawal from nicotine can reduce the time spent in open arms in EPM. Additionally, we have also shown that bupropion (20 mg/kg), forced exercise, and forced exercise in combination with bupropion can reduce depression-like behavior in nicotine-dependent rats in FST. Our previous study showed that chronic use of nicotine causes anxiety and fear-like behavior in rats. Based on our results from the current study, forced exercise can abolish these effects of nicotine withdrawal and increase the time of animal presentation in open arms in EPM. Also, forced exercise can potentiate bupropion activity during nicotine withdrawal syndrome management [29]. It has previously been shown that nicotine abuse can augment anxiety, which is associated with the neural sensitization of anxiety-related behavior in EPM test after a sudden cessation of nicotine [30]. Our previous study showed that forced exercise can activate brain reward system and diminish alcohol withdrawal syndrome, thereby abolishing anxiety and depression-like behavior in rodents [16]. Previous studies demonstrated that the most important neurotransmitter in the reward pathway is dopamine, which in normal conditions controls individuals' responses to natural rewards, such as food, sex, and social interactions, and is therefore an important determiner of motivation and incentive drive. Simply put, activation of the pathway tells the individual to repeat what they just did to get that reward. Recent research has shown that forced exercise can activate this dopaminergic pathway and increase subject pleasure and leisure [31, 32].

In OFT, our data indicate that nicotine abuse causes decrease in ambulation distance which is a behavior marker indicative of motor activity. On the other hand, treatment with bupropion, forced exercise, and a combination of both can neutralize this effect of nicotine and increase motor activity in nicotine-dependent animals in OFT. These results are in accordance with previous studies showing that nicotine dependency alters motor activity in experimental subjects [33, 34]. Therefore, it can be indicated that nicotine dependency can disturb the motor activity by altering the reward system and motor activity controlling center. On the contrary, nicotine dependency can cause repeated stimulation and consequence depletion of dopamine vesicles in the reward system, which motivates subjects to increase doses to obtain more pleasure. But this defective cycle exacerbates the condition and disturbance of the reward system and causes behavioral symptoms such as anxiety, depression, and cognition impairment, resulting in a disturbance called withdrawal syndrome [32].

Moreover, physical activity can diminish the side effects of nicotine and can boost the effect of bupropion for the recovery of nicotine-dependent subjects.

Our data have also demonstrated that nicotine dependency can decrease central square entries, time spent in central square, and rearing frequency in OFT. In contrast, treatment of nicotine-dependent rats with bupropion, forced exercise, and their combination can significantly increase the central square entries, time spent in central square, and rearing frequency. As mentioned above, based on previous studies, we can conclude that nicotine dependency can increase anxiety and fear by altering the reward system. On the other hand, exercise can reduce these side effects by increasing dopamine and serotonin levels and opioid-like peptides in the brain and potentiate the bupropion effect on the recovery of nicotine-dependent subjects [35]. Overall, according to FST, EPM, and OFT assessment, nicotine dependency and its withdrawal can induce depression and anxiety-like behaviors which can be remodeled with exercise by activation of the reward system. We can discuss this effect through the mentioned concept above which highlights that nicotine dependency can cause disturbance of the dopamine pathway and decrease pleasure, but exercise and physical activity can modulate and activate the dopamine neurons and circuits, abolish nicotine abuse side effects on the reward system, and normalize the reward system functions.

In TST, nicotine withdrawal causes an increase in immobility time, which in turn is reduced by bupropion treatment, physical activity, and a combination of both. The results of TST confirm the results of other behavioral assays and verify that nicotine dependency causes depression and anxiety and physical activity can normalize these effects.

MWM was used to assess spatial learning and memory. In MWM, nicotine dependency caused the increment in escaped latency time and traveled distance. However, bupropion, forced exercise, and a combination of both caused significant reduction in escaped latency time and traveled distance. Many previous studies have demonstrated that forced exercise can enhance learning activity in amphetamine-type stimulant-abused animals [36]. Interestingly, it has been shown that bupropion activates learning and memory in nicotine-dependent subjects. In MWM, during probe day, our data showed that

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nicotine dependency and its withdrawal causes decrease in percentage of time spent in target quarter (quarter in which the platform was inserted), and this attenuation was statistically significant in comparison to the control group. Furthermore, our exercise protocol was beneficial in improving memory. Likewise, it has been indicated that nicotine dependency can alter brain monoamines which are important in cognition, learning, and memory. One of the major benefits of physical activity is seen as cognitive improvement. Forced exercise has been seen to increase brain adrenaline, which is important in long-term potentiating and stability of learning and the memory [36, 37].

Conclusions

The present study shows that bupropion in combination with exercise forms a better protocol for attenuation of the withdrawal syndrome and assists patients to break free from nicotine dependency with less undesirable effects. Furthermore, exercise can be an accessible nonpharmacologic therapeutic option for patients with abuse which can be used as an adjunct therapy in combination with the standard pharmacologic protocols.

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