

Research article

Treadmill exercise attenuates the severity of physical dependence, anxiety, depressive-like behavior and voluntary morphine consumption in morphine withdrawn rats receiving methadone maintenance treatment

Maryam Alizadeh^{a,b,c}, Mahdi Zahedi-Khorasani^{a,b}, Hossein Miladi-Gorji^{a,b,*}

^a Laboratory of Animal Addiction Models, Research Center of Physiology, Semnan University of Medical Sciences, Semnan, Iran

^b Department of Physiology, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran

^c Student Research Committee, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran

ARTICLE INFO

Keywords:

Morphine
Exercise
Methadone
Anxiety
Depression
Morphine preference

ABSTRACT

This study was designed to examine whether treadmill exercise would attenuate the severity of physical dependence, methadone-induced anxiety, depression and voluntary morphine consumption in morphine withdrawn rats receiving methadone maintenance treatment (MMT). The rats were chronically treated with bi-daily doses (10 mg/kg, at 12 h intervals) of morphine for 14 days. The exercising rats receiving MMT were forced to run on a motorized treadmill for 30 days during morphine withdrawal. Then, rats were tested for the severity of morphine dependence, the elevated plus-maze (EPM), sucrose preference test (SPT) and voluntary morphine consumption using a two-bottle choice (TBC) paradigm. The results showed that naloxone-precipitated opioid withdrawal signs were decreased in exercising morphine-dependent rats receiving MMT than sedentary rats. Also, the exercising morphine-dependent rats receiving MMT exhibited an increased time on open arms, preference for sucrose and a lower morphine preference ratio than sedentary rats. We conclude that treadmill exercise decreased the severity of physical dependence, anxiety/depressive-like behaviors and also the voluntary morphine consumption in morphine withdrawn rats receiving MMT. Thus, exercise may benefit in the treatment of addicts during MMT.

1. Introduction

Methadone maintenance treatment (MMT) has been widely and effectively used for opioid dependence treatment [26]. MMT dose dependently reduces withdrawal and euphoric effects from opioids and also drug-related criminal behaviors [6], and neuroendocrine abnormalities associated with heroin [28]. But, MMT is still associated with an increase in physical [20] and psychological dependence signs including anxiety and depression [22]. Also, studies have suggested that MMT may improve [29], increase craving for heroin in drug abusers [3] or may be ineffective [4]. It seems that there is a biologic basis for the development of plastic changes in neuronal circuitry following drug abuse [11], which may hinder the effectiveness of MMT to drug-seeking behaviors and relapse in addicted individuals. Thus, reversing or preventing this drug-induced neurobehavioral plasticity may prove beneficial in the treatment of relapse and mood disorders. Our previous studies have shown that the voluntary, or swimming and or treadmill exercise diminished the severity of physical dependence [7,18,19], anxiety [7,10,17,19], depression [7], and voluntary consumption of

morphine [7,10], cognitive deficits [18,19] in morphine-dependent and withdrawn rats. Given the well-known beneficial effects of exercise on the opiate-induced behavioral and cognitive deficits, the aim of this study was to investigate whether mild treadmill exercise would reduce the severity of naloxone-precipitated withdrawal signs, anxiety/depressive-like behavior and voluntary morphine consumption in morphine withdrawn rats receiving MMT.

2. Materials and methods

2.1. Animals and induction of morphine dependence

Adult male Wistar rats (200 ± 10 g, 2 months old) were housed in cages on a 12-h light/dark cycle at 22–24 °C and had *ad libitum* access to food and water. All of the experimental procedures were conducted in agreement with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Morphine hydrochloride (Temad, Iran) was injected subcutaneously at a dose of 10 mg/kg, twice per day at 12 h intervals for 14 days, as described previously [7]. The control rats were

* Corresponding author at: Laboratory of Animal Addiction Models, Research Center of Physiology, Semnan University of Medical Sciences, Semnan, Iran.
E-mail address: miladi331@yahoo.com (H. Miladi-Gorji).

treated similarly, with saline injections. Drugs were dissolved in saline and administered at a volume of 1 ml/kg.

2.2. Methadone maintenance treatment

Methadone hydrochloride (Temad, Iran) was injected subcutaneously once per day for three consecutive 2-day periods with doses of 1, 2 and 3 mg/kg, respectively. The maintenance dose of 3 mg/kg was then administered 6 days per week (to prevent the cumulative effect of methadone) until day 30 of morphine withdrawal [27]. None of methadone overdose symptoms (apnea, cyanosis, motionlessness, and irritability) [32] were not observed during the first 72 h post injection in all our experiments.

2.3. Treadmill exercise paradigm

The exercising rats receiving MMT were forced to run on a motorized treadmill (Borjsanat, Iran) for 30 min once a day, five days per week for 30 days, 30 min after methadone injection. The mild intensity exercise consisted of running at a speed of 2m/min for the first 5 min, 5 m/min for the next 5 min, and 10 m/min for the last 20 min, with no incline [8,12].

2.4. Experimental protocol

Rats were divided into eight groups ($n = 6-8$ rats per group), based on our experimental protocols (Fig. 1; Timeline of experiment) as follows: Saline/Saline/Sedentary (Sal/Sal/Sed), Saline/Methadone/Sedentary (Sal/Meth/Sed), Saline/Saline/Exercise (Sal/Sal/Exc), Sal/Meth/Exc, Dependent/Saline/Sedentary (D/Sal/Sed), D/Meth/Sed, D/Sal/Exc, D/Meth/Exc.

2.5. Withdrawal rating scale

Methadone withdrawal signs recorded and scored in morphine withdrawn rats receiving MMT, on day 45, immediately after naloxone hydrochloride (Tolidar, Iran) injection (1 mg/kg, intraperitoneally) according to a modified version of the Gellert–Holtzman scale for 30 min, as described previously [17] (Fig. 1; Experiment 1, $n = 6-8$ rats per group). Graded signs including jumps, wet dog shakes, and abdominal contractions were counted as the number of events occurring during the test time. Body weights were recorded immediately before and 60 min after naloxone injection. Checked signs including diarrhea, ptosis, erection or genital grooming, teeth chattering, writhing and irritability were counted as positive if the sign occurred at any time during the observation period and expressed as the percentage [17,18].

2.6. Anxiety measurement in the elevated plus maze test (EPM)

On day 46, all rats were tested in the EPM task after a 30 days period of treatment with methadone and exercise (Fig. 1; Experiment 2). Rats

were individually placed in the center of the EPM, as described previously [17] and allowed to explore the apparatus for 5 min. Time spent in, and entries into the open and closed arms were measured during each 5 min test by a tracking system (EthoVision, Noldus, The Netherlands). The apparatus was cleaned after each trial with water.

2.7. Sucrose preference test (SPT) to assess depressive-like behavior

All rats were maintained in individual cages for 24 h before testing. Then, on days 47–48 (Fig. 1; Experiment 2), rats were allowed access for 48 h to two bottles in each cage, one with 200 ml of 32% sucrose (w/v) and the other also with 200 ml of tap water. The positions of the bottles were changed every 12 h to avoid learning. Fluid intake and sucrose were measured every day, as our previously described [7]. After 48 h, the bottles were removed and sucrose preference was calculated as: $100\% \times \text{sucrose solution consumption (ml)}/\text{total fluid consumption (ml)}$.

2.8. Two-bottle choice (TBC) paradigm

Voluntary morphine consumption and preference ratios were quantified using modified model of two-bottle choice in rats as our previously described [7,10]. Each rat was housed individually in cages after testing of SPT with two bottles for a period of 12 days of testing, on days 49–60 (Fig. 1; Experiment 2). In one bottle, morphine sulfate was dissolved in 3% sucrose solution and also 3% sucrose solution was in control bottle as follow, respectively; On days 1–4 of test, (0.3 mg/ml morphine); On days 5–8 of test, (0.5 mg/ml morphine); On days 9–12 of test, (0.7 mg/ml morphine). Rats were allowed continuous access to both bottles. The positions of the bottles were changed at the time of daily bottle weighing to avoid learning. Fluid intake was measured by weighing the bottles between 9:00 and 10:00 am daily. Body weights of the rats were measured in the start of each period. The average morphine consumption and preference ratios (ml morphine solution consumed/total ml consumed from both bottles) were evaluated during a 4-day period.

2.9. Statistical analysis

The data were expressed as the mean \pm SEM. Data exhibited a normal distribution and were analyzed using three-way analyses of variance (ANOVA) with the fixed factors dependence \times methadone \times exercise, with repeated measures as required. Post-hoc analyses included Tukey's test. Checked somatic signs of opiate withdrawal were analyzed by the Mann-Whitney U test. Statistical differences were considered significant at $P < 0.05$.

3. Results

3.1. The severity of physical dependence

Three-way ANOVA for the total withdrawal scores (Fig. 2.) revealed significant effects of dependence ($F_{1,51} = 57.3$, $P = .0001$), methadone ($F_{1,51} = 265.6$, $P = .0001$), exercise ($F_{1,51} = 48.42$, $P = .0001$), dependence \times methadone ($F_{1,51} = 92.65$, $P = .0001$), methadone \times exercise ($F_{1,51} = 12.9$, $P = .001$) and dependence \times methadone \times exercise ($F_{1,51} = 6.3$, $P = .016$) interactions. Between groups comparisons revealed that the total withdrawal scores were significantly higher in the Sal/Meth/Sed, D/Sal/Sed and D/Meth/Sed rats than the Sal/Sal/Sed rats (all, $P = .0001$). While, the Sal/Meth/Exc ($P = .0001$), D/Sal/Exc ($P = .016$) and D/Meth/Exc ($P = .0001$) rats displayed lower levels of total withdrawal scores than the Sal/Meth/Sed, D/Sal/Sed and D/Meth/Sed rats, respectively. Also, the D/Meth/Sed rats had a higher withdrawal score than D/Sal/Sed group ($P = .002$). Among the graded signs, the D/Meth/Exc rats displayed less wet dog shakes and weight loss (both, $P = .0001$) compared to D/

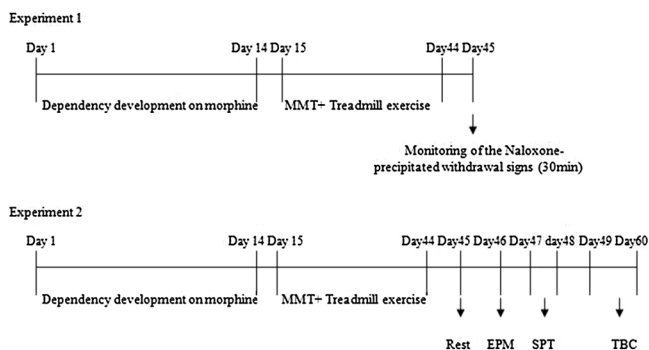


Fig. 1. Timeline of experiment (see Section 2 for details).

Download English Version:

<https://daneshyari.com/en/article/8841429>

Download Persian Version:

<https://daneshyari.com/article/8841429>

[Daneshyari.com](https://daneshyari.com)