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Effects of endurance, resistance, and concurrent exercise on learning and memory after morphine withdrawal in rats

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ABSTRACT

Aims: Continuous morphine consumption contributes to the development of cognitive disorders. This work investigates the impacts of different types of exercise on learning and memory in morphine-dependent rats.
Main methods: Forty morphine-dependent rats were randomly divided into five groups: sedentary-dependent (Sed-D), endurance exercise-dependent (En-D), strength exercise-dependent (St-D), and combined (concurrent) exercise-dependent (Co-D). Healthy rats were used as controls (Con). After 10 weeks of regular exercise (endurance, strength, and concurrent; each five days per week), spatial and aversive learning and memory were assessed using the Morris water maze and shuttle box tests.
Key findings: The results showed that morphine addiction contributes to deficits in spatial learning and memory. Furthermore, each form of exercise training restored spatial learning and memory performance in morphine-dependent rats to levels similar to those of healthy controls. Aversive learning and memory during the acquisition phase were not affected by morphine addiction or exercise, but were significantly decreased by morphine dependence. Only concurrent training returned the time spent in the dark compartment in the shuttle box test to control levels.
Significance: These findings show that different types of exercise exert similar effects on spatial learning and memory, but show distinct effects on aversive learning and memory. Further, morphine dependence-induced deficits in cognitive function were blocked by exercise. Therefore, different exercise regimens may represent practical treatment methods for cognitive and behavioral impairments associated with morphine-related disease.

1. Introduction

Morphine addiction is a serious health problem throughout the world [3]. Although clearly effective, morphine is useful only for the treatment of chronic pain because of the rapid development of tolerance, dependence, and addiction that occurs through neuronal and synaptic alterations in the brain, especially within the hippocampus [11]. Although morphine is widely used, information regarding the associated mental health deficits is limited [15,49].

Learning and memory are complex brain functions that are dependent upon specific central nervous system structures. In particular, the hippocampus and amygdala are critical for learning- and memory-related data processing and information storage [26]. Memory is categorized as long-term or short-term, based on the duration of memory storage. Short-term memory occurs over several minutes or less, during which information remains accessible before being either dismissed or transferred to long-term memory. Long-term memory is the brain's system for storing, managing, and retrieving information over periods ranging from several days to many years (i.e., lifetime memory) [30,39]. In recent years, the effects of morphine on learning and memory have attracted significant attention. Morphine exerts serious effects on brain regions involved in cognitive functions such as learning and memory [27]. Several studies have indicated that μ-opioid receptors in the hippocampus play a vital role in learning and memory [7,19]. Morphine preferentially binds to μ-opioid receptors, which are highly expressed in hippocampal cells [21]. According to several studies, chronic morphine administration can damage neurons by increasing oxidative stress [14,50] and reduce long-term potentiation in the hippocampus through synaptic modification [5,25]. Other studies show that disorders associated with morphine usage affect the performance of adult rats on different learning and memory tasks through unknown mechanisms [42,44].

Importantly, mental health [36] and memory acquisition [47] are affected by exercise. In contrast to morphine, exercise has been shown to

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exert positive effects on learning and [2]. Furthermore, previous studies have shown distinct impacts of different kinds of physical activity on memory and neuronal compatibility in different brain areas [22]. For example, Afzalpour et al. showed that different types of exercise exert discrete effects on the expression of brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor, inflammatory proteins, and reactive oxygen species in the rat brain [1]. Therefore, the aim of the present study is to determine which type of exercise (endurance, strength, or concurrent (combined resistance and strength)) elicits the greatest effects on learning and memory impairments induced by morphine exposure in Wistar rats. To date, no study of this type has been conducted.

2. Materials and methods

2.1. Animals

Forty male Wistar rats (150–180 g), aged six weeks, were housed at five animals per cage under a 12-hour light/dark cycle at stable room temperature (22 ± 1 °C) with 55 ± 3% relative humidity. Animals were given free access to standard mouse chow and tap water. The treatment protocols were set up in accordance with National Institutes of Health Guide for the Care and Use of Laboratory Animals as well as approved by the Institutional Animal Care and Use Committee at Hamadan University of Medical Science, Iran.

2.2. Induction of morphine dependence

Rats were handled and food intake and body weight were recorded daily prior to the experiment. On the first and second days of the experiment, 0.1 mg/mL of morphine was added to the drinking water; 0.2 mg/mL was added on the third and fourth days, 0.3 mg/mL on the fifth and sixth days, and 0.4 mg/mL on days seven through 21. Sucrose (40 mg/mL) was added to mask the bitter taste of the morphine [4].

2.3. Withdrawal rating scale

One day after the completion of morphine treatment, naloxone hydrochloride (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in 0.9% saline and injected intraperitoneally (1 mg/kg) into all rats in a random sequence to examine morphine dependence. Immediately after injection, rats were taken to a quiet, isolated room with moderate illumination, and their behavior was observed for 30 min and scored using a modified version of the Gellet-Holtzman scale [12].

2.4. Experimental design

One day after the naloxone test, the animals were withdrawal score matched and randomly divided into tentative groups: sedentary-dependent (Sed-D, N = 10), Endurance exercise-dependent (En-D, N = 10), strength exercise-dependent (St-D, N = 10), and concurrent exercise-dependent (Co-D, N = 10). Ten healthy, non-morphine-dependent rats were used as the Control group (Con). Experimental timeline is shown in Fig. 1.

2.5. Exercise programs

2.5.1. Endurance exercise

A motorized treadmill with eight individual lanes was used for aerobic exercise, according to the protocol published by Ranjbar et al. [37]. The program included two periods: an adaptation period and an exercise period. Training began at 10 m/min with a 5° incline for 10 min per session to allow gradual adaptation to exercise-induced stress. The time and speed were then gradually increased to 30 m/min with a 12° incline for 60 min per session (5 days/week) within 10 weeks.

2.5.2. Strength exercise

Rats in this group underwent 10 weeks (5 days/week) of progressive resistance training. Rats climbed a 1 m ladder with an 85° incline 12 times in each session. Weights inside a cloth bag were fastened to the tail with a band; weights initially consisted of 50% of the animal's body weight and were gradually increased to 130% over 10 weeks (first and second weeks: 50–60%; third through fifth weeks: 70–90%; sixth through eighth weeks: 100–110%; ninth and tenth weeks: 110–130%). Each training session consisted of three sets of four repetitions each, with 15 s intervals between repetitions and 3 min intervals between sets. This exercise protocol was adapted from that of Philippe et al., with minor modifications [35].

2.5.3. Concurrent exercise (combined resistance-aerobic training)

Rats in this group completed half of each of the sessions described above on each day of exercise. Thus, these animals performed 2 sets of 3 ladder-climbing repetitions each, with 15 s intervals between repetitions and 3 min intervals between sets, followed by 30 min of exercise on the treadmill at 30 m/min. Running time and intensity and climbing weight were gradually increased each week, as described above [38].

2.6. Spatial and aversive learning and memory tests

The Morris water maze (MWM) and shuttle box tests were used to evaluate the spatial and aversive learning and memory (acquisition and retention), respectively, in morphine-dependent rats after completion of exercise programs.

2.6.1. Morris water maze test

The MWM [20] consisted of a circular black pool (180 cm in diameter and 60 cm high) that was filled to a depth of 25 cm with water (22 ± 1 °C). The pool was placed in a dimly lit, sound-insulated room with various visual cues. The pool had four wards with four starting lines named north (N), east (E), south (S) and west (W) and an invisible Plexiglas platform (10 cm diameter) was centrally located 1 cm beneath the water in the quadrant N. The training of animals lasted for 4 days at nearly the same time (10:00–12:00 a.m.), and each day had two blocks with four trials (90 s). There was a 30 second gap between two trials on the platform and the rest time was 5 min between two consecutive blocks. While, for recording the time spent to reach the hidden platform a video camera was set up (Nikon, Melville, New York, USA) which was connected to a computer directly above the pool (the escape latency). One day after the spatial acquisition phase (i.e., on day five of MWM

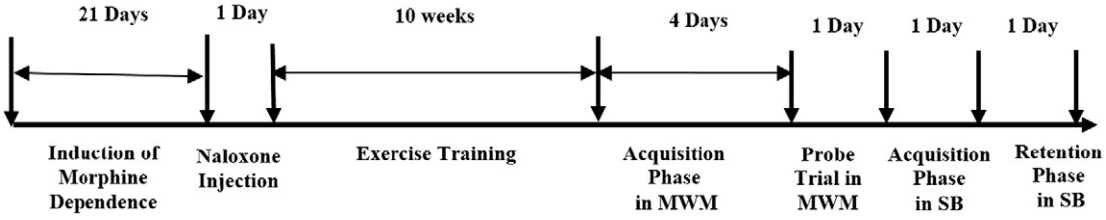

Fig. 1. Experimental timeline.