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Swimming improves the emotional memory deficit by scopolamine via mu opioid receptors

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HIGHLIGHT

- Swimming did not alter anxiety-like behaviors and improved emotional memory.
- Scopolamine (intra-CA1) reduced emotional memory but not anxiety-like behaviors.
- Swimming restored emotional memory deficit induced by intra-CA1 scopolamine.
- Morphine treatment during swimming improved the memory deficit by scopolamine.
- The previous result could be blocked by subthreshold doses of naloxone.

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ABSTRACT

Aims: The aim of the present study was to investigate the effect of swimming exercise on elevated plus-maze (EPM)-associated memory deficit induced by intra-CA1 injection of scopolamine (a muscarinic acetylcholine receptor antagonist used to model Alzheimer's disease in rodents) in male mice. In addition, involvement of the mu opioid receptors in this phenomenon was investigated.
Main methods: Bilateral guide cannulae were implanted to allow intra-CA1 microinjections.
Key findings: Data showed that mice with 10 and 20 days of swimming, only acquired the emotional memory, while 30 days of swimming exercise improved it. On the other hand, pretest intra-CA1 injection of scopolamine at the doses of 2 and 3 but not 1 μg/mouse reduced the emotional memory. Our results demonstrated that 20 days of swimming by itself and without any drug injection restored the emotional memory deficit induced by intra-CA1 injection of scopolamine, only at the dose of 2 but not 3 μg/mouse. Moreover, once daily injection of the subthreshold doses of morphine (2.5 and 5 mg/kg, i.p.) during the last 7 days of the 20 day-swimming intervention, improved the emotional memory deficit induced by scopolamine (3 μg/mouse) and this effect could be blocked by the subthreshold doses of naloxone (0.2 and 0.4 mg/kg). It was noted that all previous interventions did not alter the anxiety-like behaviors.
Significance: Swimming improved the emotional memory by itself and restored the emotional memory deficit induced by the intra-CA1 injection of scopolamine. Mu opioid receptor-dependent mechanism(s) is(are) suggested to play a role in this phenomenon.

1. Introduction

Alzheimer's disease (AD) is a disorder of advanced age followed by cognitive and non-cognitive mental declines such as impaired learning and memory, mood disorder, depression, apathy and anxiety [1,2]. Diminished hippocampal trophic factors have been proposed as a major

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contributor to atrophy and neural cell death in this disease [3]. The hippocampal neural circuits which are involved in learning and memory as well as regulation of behavior are affected in the course of AD [4,5]. Intra-CA1 injection of scopolamine (a muscarinic acetylcholine receptor antagonist) is a common method used to model AD in rodents [6,7].

Recent findings have suggested the significant role of exercise in improving physical and mental health in conditions such as diabetes [8], obesity [9] and cardiovascular diseases [10]. Exercise is shown to enhance brain plasticity [11] and hence improve the speed of learning and memory formation [4,12]. Evidence has substantiated that exercise affects various levels and stages of memory formation including encoding, consolidation and retrieval [13]. In terms of the neurobiology of exercise, a U-shaped dose–response curve is proposed, where low and high exercise load leave stimulatory and inhibitory effects, respectively [14]. Since the possible benefits of exercise in cognition depend on several variables such as the intensity, duration of exercise and the animal's health, it seems complex to draw a clear image from the so far investigations. For instance, exercise could be a negative tool when applied at inappropriate intensities [15]. Taken together, it has been postulated that 1 — low to moderate physical exercise can be a useful tool in the prevention of motor and cognitive impairments associated with the central nerves system monoaminergic depletion [16] and 2 — the antidepressant effects of the short bouts of exercise [17,18] represent a viable behavioral strategy to improve cognition and synaptic plasticity in aging rats [4].

The hippocampus is a brain region essential for memory [7,19] and long term potentiation [20]. It receives cholinergic inputs from the medial septum, meanwhile has different types of cholinergic (including nicotinic and muscarinic) receptors [21]. Some reports have shown that regular exercise may give rise to an increase in number of cells in the pyramidal and granular cell layers of CA1 and dentate gyrus, respectively [22,23], which in turn can lead to improved mental functions [24,25]. For instance, maternal swimming exercise during pregnancy potentiates the neurogenesis process in the offspring rats' hippocampus and ameliorates the short-term memory [26].

Moreover, following exercise, the activity of major classic neurotransmitters and neuropeptides which involve in learning and memory will be changed. These include cholinergic [27,28], opioidergic [29,30], adrenergic [31], GABAergic [32], glutamatergic [33], dopaminergic [34] and neurotrophic factors [35] which are known to play determinant roles in memory function.

There are evidence suggesting the effects of vitamin E supplementation and physical exercise (40 days of swimming) on the primary enzymes of aging cerebral cortex and the cholinergic neurotransmitter system upon spatial memory tasks in aging rats [36]. In addition, 10 weeks of unceasing exercise has significantly altered the dose response curves induced by scopolamine [37].

Some studies have shown that exercise not only increases the release of acetylcholine in the dorsal hippocampus [27,38], but also the endogenous opioids such as endorphin, enkephalin and dynorphin [39,40]. It has also been made clear that endogenous opioids can suppress learning and memory formation in the hippocampus [41,42] and this can be blocked by naloxone (an opioid receptor antagonist) [43,44]. Based on some recent investigations, voluntary (wheel running) and forced (running on an automated treadmill) exercise can ameliorate the spatial [45] and non-spatial [46] memory deficits induced by chronic morphine treatment, respectively.

Adding to the above, we have recently demonstrated a possible close relationship between mu opioid and muscarinic acetylcholine receptors of the CA1 region of the dorsal hippocampus in modulation of behavioral performance [43].

Referring to some investigations (i.e. behavioral, physiological, pharmacological, and genetic) suggesting a close relationship between memory and anxiety [47,48](although this relationship does not follow a consistent synergistic rule), and with the view of the exercise-related increase in the activity of cholinergic and opioidergic systems, the aim of the present study was to investigate the effect of swimming exercise on the altered exploratory-like behaviors induced by the intra-CA1 injection of scopolamine (animal model for AD) in the EPM test–retest task in mice. We further tried to investigate the potential involvement of mu opioid receptors in this phenomenon.

2. Materials and methods

2.1. Subjects

Male mice bred in the neuroscience lab animal house of the Institute for Cognitive Science Studies (ICSS, Tehran, Iran), weighing 25–30 g on first examination day were used. Mice were kept four per cage, in a room with a 12 h light/dark cycle (lights on 07:00 h) and controlled temperature (22 ± 2 °C). They had access to food and water ad libitum and were allowed to adapt to the laboratory conditions for at least 1 week prior to the first day EPM test. Each mouse was handled about 3 min each day prior to the behavioral testing. All EPM experiments on mice were carried out between 9:00 h and 15:00 h and each mouse was tested once only. Each control or experimental study arm comprised 8 mice. Animal treatment and maintenance were conducted in accordance with the Principles of Laboratory Animal Care (NIH publication No. 85–23, revised 1985) and the Animal Care and Use Guidelines of Tehran University of Medical Sciences.

2.2. Drugs

For animal anesthesia, we used ketamine and xylazine (Alfasan Chemical Co, Woerden, Holland). Morphine sulfate (mu opioid receptor agonist) and naloxone (mu opioid receptor antagonist) were used for intraperitoneal (i.p.) injection (Temad Co, Tehran, Iran) and scopolamine (as a muscarinic acetylcholine receptor antagonist) for intra-CA1 injection (Sigma, Poole, UK). All drugs were dissolved in sterile 0.9% saline just before the experiments. Control mice received saline.

2.3. Swimming arena

Animals were generally divided into two groups i.e. control (sedentary mice) and exercised (swam). The exercised group mice were trained in a progressively increasing moderate swimming program with no weight loading, in free style as validated by previous experiments [49–51]. Daily swimming exercise was performed in a plastic tank 50 cm high and 60 cm in diameter with a heating device maintaining the water temperature between 30 and 32 °C. To allow acclimatization, the swimming program comprised two phases, adaptation and training. During the first week (adaptation), the length of swimming time was gradually (10 min at a time, per day) increased from 20 min in the beginning to 60 min by week 2. During weeks 2–6, mice swam continuously for 60 min (training). This swimming program lasted 5 days per week for a total of 2–6 weeks. In order to prevent drowning, fifteen mice were placed at the same time to swim. Mice which were unable to keep swimming and failed to stay on the surface were immediately removed from water. Each mouse was towel-dried after the training session.

2.4. Elevated plus-maze (EPM) apparatus

Our EPM was made of Plexiglas consisting of two opposite open-arms (40 × 7 cm) surrounded by a 0.3 cm high ledge, and two closed-arms (40 × 70 × 10 cm), set 50 cm above the floor. The junction area of the four arms (central platform) measured 7 × 7 cm [52,53].

2.5. Stereotactic surgery and drug infusion

Animals were anesthetized using the intra-peritoneal injection of ketamine hydrochloride (50 mg/kg) plus xylazine (5 mg/kg), and