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Exercise improves learning and memory impairments in sleep deprived female rats

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HIGHLIGHTS

- Paradoxical sleep deprivation (PSD) impaired learning in ovariectomized female rats.
- PSD impaired short term memory in intact and ovariectomized female rats.
- Physical exercise alleviated the PSD-induced cognitive impairments in female rats.
- There was no significant change in the plasma corticosterone level of all groups.

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ABSTRACT

Inadequate sleep is a common problem in modern societies. It has been previously shown that female rats are more vulnerable to the deleterious effects of sleep deprivation on cognitive functions. Physical exercise has been suggested to attenuate the cognitive impairments induced by sleep deprivation in male rats. The objective of the current study was to investigate the effects of physical exercise on cognitive functions of female rats following paradoxical sleep deprivation.

Intact and ovariectomized (OVX) female Wistar rats were used in the present study. The exercise protocol was 4 weeks of treadmill running. The multiple platform method was applied for the induction of 72 h paradoxical sleep deprivation and the cognitive function was evaluated using Morris water maze (MWM). Plasma corticosterone level was evaluated in separate groups of study. ANOVA and repeated measures were used to analyze the data and $P < 0.05$ was considered statistically significant.

Throughout the investigation, significant learning impairment was observed in sleep-deprived OVX rats compared to the intact and the other OVX groups. Short term memory impairment was observed in both sleep-deprived OVX and intact groups. Physical exercise alleviated the PSD-induced learning and memory impairments in both intact and OVX groups. Corticosterone levels were not statistically significant among the different groups.

The results of our study confirmed the negative effects of PSD on cognitive functions in female rats and regular physical exercise seems to protect rats from these effects. Further studies are suggested to be carried out in order to evaluate the possible underlying mechanisms, and also to evaluate the possible interactions between sex hormones and PSD-induced cognitive impairments.

1. Introduction

Animal studies have demonstrated the positive effects of sleep on declarative and procedural memory in various behavioral tasks [1–4]. It has been shown that sleep contributes to the acquisition and consolidation of memory [4–6]. "Sleep" has been considered as a time window through which the acquired information is processed without any disturbance from the sensory system [2]. Sleep disorders are a common

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problem in modern societies affecting different aspects of individuals' lives and making alterations in the physiological function of both humans and animals [7,8]. Fragmented sleep and sleep deprivation, in the long period, can lead to mood changes, impaired mental ability, and disturbed performance [9–11]. It also has deleterious effects on the motor and the cognitive function [12]. Many animal studies have reported that PSD leads to impairments in hippocampus-dependent memory formation [13,14], emotional memory [15], working memory [16] and increased anxiety levels [17,18]. These pieces of evidence are partially explained based on the fact that the hippocampus is extremely vulnerable to sleep loss [14,19–21].

It seems that cognitive functions such as memory and learning [22,23] as well as different sleep aspects including its quality and pattern [24–26] are different in two genders. Changes in sleep patterns are often associated with hormonal factors — particularly estrogen level [27]. It is also noticeable that sex steroids are not only involved in the regulation of gonadal hormone secretions and reproductive behaviors, but also affect some functions such as one's cognitive performance and sleep pattern [28–30]. It has been previously shown that female rats are more susceptible to the deleterious effects of sleep deprivation on cognitive performance [31]. Female rats are also more vulnerable to stressful conditions [32].

Physical exercise has been shown to improve learning and memory in both MWM [33,34] and passive avoidance task [35] paradigms. Additionally, it has been observed that physical exercise also has multidimensional effects on brain performance, like enhancing angiogenesis [36] and neurogenesis [37,38] at the cellular level, increasing neuronal plasticity and upregulating the expression of BDNF mRNA in the hippocampus [39,40].

Exercise also plays a protective role against memory impairments observed in neurodegenerative diseases such as Alzheimer's disease [41,42]. Furthermore, it has been shown that exercise can improve memory functions during estrogen deprivation [43,44]. Previous studies have demonstrated the positive effects of physical exercise on memory impairments induced by sleep deprivation in male rats [45,46] while no study has been particularly devoted to female rats concerning this subject. Therefore, the objective of the current study was to evaluate the effects of physical exercise on the cognitive functions of sleep deprived intact and OVX female rats.

2. Material and methods

2.1. Animals

All experimental protocols and treatments were approved by the Ethics Committee of Kerman Neuroscience Research Center. We attempted to minimize the discomfort for the animals at all stages of the study (Ethics Code: KNRC-9-33). Female Wistar rats (3–4 months old, weighing 200–250 g) were used for the current study. Animals were caged in groups of four with ad libitum access to food and water. They were housed under controlled temperature (23 ± 1 °C) and 12-h light–dark cycle (lights on: 07:00–19:00 h).

Two sets of animals including intact and ovariectomized (OVX) were randomly allocated into the following subgroups: control (maintained in home cages), PSD, wide platform (Sham platform), naïve exercise, sham exercise and exercise + PSD. A sham surgery (sham ovariectomy) was also performed on a separate group of rats. All OVX and sham surgery (submitted to surgery without removing the ovaries) groups underwent ovariectomy surgical procedure (n = 8 for each group).

2.2. Surgical procedures

All surgical operations were performed under general anesthesia with a mixture of ketamine and xylazine (60 mg/kg, i.p. ketamine and 10 mg/kg, i.p. xylazine). Both ovaries were removed through a small mid-abdominal incision under aseptic conditions. After the operation, all rats were kept in the animal room for one month [43].

2.3. Exercise protocol

The rats in the exercise groups underwent forced exercise sessions (at 0° inclination) during the light cycle between 9:00 and 14:30, for four weeks, from Saturday to Wednesday (they received a mild shock (0.25 mA) whenever they stopped running). These rats were allowed to adapt to treadmill environment for 30 min during 2 consecutive days before the commencement of the exercise protocol, this was to eliminate the possible stress of the novel environment.

The exercise protocol was as follows: 30 min for the first two weeks (at a 10 m/min speed), 45 min for the third week and 60 min for the fourth week (both at 15 m/min speed). Every 15 min during each session, the animals were given a five minute break. Rats in the sham exercise groups were left on the treadmill, without running (0 m/min) for the same number of sessions and the same amount of time as those in the exercise groups [45].

2.4. Induction of paradoxical sleep deprivation (PSD)

A multiple platform apparatus was used for the induction of PSD. The apparatus (90 cm × 50 cm × 50 cm) contained 10 columns (10 cm high, 7 cm diameter located 2 cm above the surface of the water) which were arranged in two rows and spaced 10 cm apart (edge to edge), to allow rats to jump from one platform to another. In this paradigm, cage mates (4 rats) were placed together in the chamber to maintain social stability.

The rats had free access to clean water bottles, and food pellet baskets were always hanging from the top of the chamber. In the current study, PSD was induced for 72 h, as previously described [31]. PSD paradigm was carried out 24 h after the last exercise session in the exercise/PSD groups.

During the sleep deprivation period (72 h), the temperature (23 + 1 °C) and light/dark cycle were both maintained under controlled conditions.

We also tested the possible effects of novel environmental stress by placing the control rats in the similar chamber with wider platforms (sham platform) (10 cm high, and 15 cm in diameter), since it was large enough for the rats to sleep in without falling into the water.

2.5. Spatial learning and memory

As previously mentioned, MWM task was used to assay spatial learning and memory [31]. Rats became fully trained in approximately 3 h, as this was required to determine the effects of PSD on memory performance. In fact, the classic version of MWM (within 5 days of the training period) was not applicable for 72 h pre-training PSD.

The behavioral experiment was performed during the light cycle (between 8:30 and 12:00) 30 min after the PSD paradigm. The testing chamber was a black circular swimming pool which was painted with nontoxic materials (160 cm diameter, 80 cm high and 40 cm deep) and filled with water. Visual cues were placed around the chamber. The test chamber was divided into four equal quadrants. A square hidden black platform (10 cm diameter) was submerged beneath (1.5 cm) the water surface in the middle of the target quadrant in the pool. The sessions were recorded with a video camera located above the center of the pool and connected to a recording system (Noldus Ethovision® system, version 5, USA).

In the spatial acquisition phase, the rats were allowed to find a submerged hidden platform during a 60-second-interval in four training trials (inter-trial interval = 60 s) repeated in three blocks (inter-block interval = 30 min). After finding the platform, the animals were allowed to rest on the platform for 20–30 s.