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Research report

Prior regular exercise prevents synaptic plasticity impairment in sleep deprived female rats

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ABSTRACT

Previous studies have indicated that physical exercise plays a preventive role in synaptic plasticity deficits in the hippocampus of sleep-deprived male rats. The objective of the present study was to evaluate the effects of treadmill running on early long term potentiation (E-LTP) at the Cornu Ammonis (CA1) area of the hippocampus in sleep-deprived female rats.

Intact and ovariectomiezed (OVX) female Wistar rats were used in the present study. The exercise protocol was four weeks treadmill running and the multiple platform method was applied to induce 72 h sleep deprivation (SD). We examine the effect of exercise and/or SD on synaptic plasticity using in vivo extracellular recording in the CA1 area of the hippocampus. The field excitatory post-synaptic potential (fEPSP) slope was measured before and 2 h after high frequency stimulation (HFS) in the experimental groups.

Field potential recording indicated that the induction and maintenance phase of E-LTP impaired in the sleep deprived animals compared to the other groups. After 72 h SD, E-LTP impairments were prevented by 4 weeks of regular treadmill exercise.

In conclusion, the synaptic plasticity deficit in sleep-deprived female rats was improved by regular physical exercise. Further studies are suggested to evaluate the possible underlying mechanisms.

1. Introduction

Sleep has an important role in the acquisition and retention of new information in the hippocampus. Several behavioral, physiological, cellular and molecular studies suggest that sleep plays an important role in memory consolidation (Datta, 2010; Diekelmann and Born, 2010; Gais et al., 2006) and sleep loss leads to neurocognitive impairments (McCoy and Strecker, 2011). Furthermore sleep deprivation prior to learning decreases learning ability and impairs memory, while sleep deprivation after learning disrupts memory formation (Diekelmann and Born, 2010).

Chronic sleep restriction is a growing problem in many countries and modern societies. Sleep disorder is a common complaint among women since they report more sleep difficulties in comparison with men. In addition, sleep problems are reported to be more frequent during the menopausal and post-menopausal periods compared with pre-menopausal periods in women (Dzaja et al., 2005; Luyster et al., 2012; Manber and Armitage, 1999). Some studies have suggested that level of estrogen may play a role in regulating sleep (Manber and Armitage, 1999) and cognitive functions (Kramár et al., 2013). The role of female sex steroids in sleep regulation is particularly obvious in postmenopausal women, who have low levels of circulating estrogen (Dzaja et al., 2005; Manber and Armitage, 1999) and are more vulnerable to deleterious effects of poor sleep on cognitive performance (Alhola et al., 2005).

Evidence indicated a strong correlation between sleep deprivation and cognitive impairment in humans and animals (Alvarenga et al., 2008; Curcio et al., 2006). Accordingly, sleep deprivation negatively impacts hippocampus dependent learning and memory and long term potentiation (Tartar et al., 2006), which is a form of synaptic plasticity accepted as a biological model of learning and memory (Bliss and Collingridge, 1993; Malenka and Bear, 2004). Similar studies have indicated that 24 h sleep deprivation impairs spatial

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learning and memory and induction of LTP in the hippocampus of male rats (Zagaar et al., 2012a,b)

The beneficial effects of exercise on many physiological systems, including the central nervous system and brain health, are well-demonstrated (Cotman and Berchtold, 2002). Exercise can improve learning and memory and cognitive performance (Cotman and Berchtold, 2002; Van Praag, 2009), and it can also enhance cell proliferation in the hippocampus (Jin et al., 2008).

Physical exercise can alter some forms of synaptic plasticity such as LTP (Cotman and Berchtold, 2002). Aside from enhancing LTP, exercise can also increase the level of brain derived neurotrophic factor (BDNF) (Vaynman et al., 2004).

In addition exercise plays a protective role in memory impairments (Hoveida et al., 2011) and improves LTP (Liu et al., 2011) in neurodegenerative diseases. Furthermore, it has been shown that exercise improves memory functions during estrogen deprivation (Ben et al., 2010). Other studies have indicated that regular exercise can prevent the SD-induced deficit in early LTP (Zagaar et al., 2012a) and late-LTP (Zagaar et al., 2012b) in CA1 area of hippocampus in male rats, however the effects of exercise on LTP have not been fully investigated in sleep deprived female rats. The present study was designed to examine whether regular physical exercise can attenuate SD induced E-LTP impairment in female rats.

2. Materials and methods

2.1. Animals

Female Wistar rats (weighing 200–250 g) were used for the current study. Animals were caged in groups of four with access to food and water ad libitum. The temperature was controlled ($23 \pm 1\,^{\circ}C$) and they were also housed under a 12-h light–dark cycle (lights on: 07:00–19:00 h). Two groups of intact and ovariectomized (OVX) rats were randomly selected, and the following subgroups were formed: control (stayed in home cages), SD, exercise, exercise/SD and wide platform (sham platform). All procedures were performed in compliance with the National Research Council's Guide for the care and use of laboratory animals and on approval of the Ethics Committee of Kerman Neuroscience Research Center (Ethics Code: KNRC-92-33).

2.2. Surgical procedures

All of the operations were carried out under general anesthesia using a mixture of ketamine and xylazine (60 mg/kg, i.p. ketamine and 10 mg/kg, i.p. xylazine). Both ovaries were removed by a small mid-abdominal incision under aseptic conditions. All of the ovariectomized rats were put in a special room for one month after operation (Ben et al., 2010).

2.3. Treadmill exercise

For four weeks from Saturday to Wednesday, the exercise groups had force exercise sessions (at 0° inclination) during the light cycle which started from 9:00 till 14:30 (they received a mild shock, 0.25 mA, whenever they stopped running). They 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 included the following stages: 30 min for the first two weeks (at 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 5 min break (Zagaar et al., 2012a).

2.4. Induction of sleep deprivation

We used a multiple platform apparatus to induce SD. This apparatus (90 cm × 50 cm × 50 cm) included 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), this was to allow rats to jump from one platform to another. The cage mates (4 rats) were put together in a 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 present research, SD was induced for 72 h, as previously explained (Hajali et al., 2012). Animals were kept under standard conditions [12:12-h light–dark cycle at a controlled temperature ($23 \pm 1\,^{\circ}C$)] in the sleep deprivation period (72 h).

We carried out the SD paradigm for 24 h after performing the last exercise session in the exercise/SD groups. The possible effects of novel environmental stress were evaluated by putting the control (sham platform or wide platform) groups in a similar chamber but with wider platforms (10 cm high, and 15 cm in diameter). The platforms were large enough so that the rats would not fall into the water during their sleep period (Hajali et al., 2012).

2.5. Electrophysiological study

In vivo electrophysiological recording of field excitatory post synaptic potentials (fEPSPs) from CA1 area was performed according to Zagaar et al. (2012a). For electrophysiological recordings, the female Wistar rats were anesthetized with urethane (1.2 g/kg) (Sigma–Aldrich) and placed in a stereotaxic apparatus. Their skulls were exposed and two holes were drilled, under sterile conditions, to place stimulating and recording electrodes according to the atlas of Paxinos and Watson (2006). The rectal temperature was kept at $36.5 \pm 0.5\,^{\circ}C$ throughout the period of the experiment (Harvard Apparatus).

For field potential recording from area CA1, a concentric bipolar stimulating electrode (stainless steel, 0.125 mm diameter, Advent, UK) was placed in the ipsilateral Schaffer collateral pathway (AP = 3 mm; ML = 3.5 mm; DV = 2.8–3 mm), and a stainless steel recording electrode was lowered into the stratum radiatum of area CA1 of right hippocampus (AP = 4.1; ML = 3 mm; DV = 2.5 mm).

The stimulating electrode was connected to a stimulator and the recording electrode was connected to an amplifier. A maximum fEPSP slope was acquired by stimulating the Schaffer collateral pathway and recording in area CA1. After a 30-min stabilization period, we obtained input–output (I/O) curves by gradually increasing the stimulus intensities with constant current (input) and recording fEPSP (output). Extracellular field potentials were amplified and filtered (1 Hz to 3 KHz band pass) using a differential amplifier. A baseline was established by giving a test stimulus every 10 s for 20 min at a stimulus intensity of which 50% was required to elicit a maximum response. Paired pulse facilitation (PPF) experiments were conducted in rats which were afterwards used for LTP experiments. PPF was measured by delivering ten consecutive evoked responses of paired pulses at 20, 50, 70 and 100 ms inter pulse interval (IPI) to the Schaffer collateral pathway at a frequency of 0.1 Hz (10 s interval). The fEPSP slope ratio [second fEPSP slope/first fEPSP slope; fEPSP2/fEPSP1] was measured at different inter-stimulus intervals.

E-LTP was then evoked by applying a train of high frequency stimulation (HFS: 10 pulses at 400 Hz/7 s repeated for 70 s). The maintenance of LTP was measured for 2 h after the HFS by giving a test stimulus every 10 s. The values of the slope of the fEPSP at each point in the graphs were averaged from 10 consecutive traces.