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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.

Computer-based stimulation and recording was achieved using Neurotrace software version 9 and Electromodule 12 (Science Beam Institute, Tehran, Iran). For analyzing the responses, the software Potentalise from the same institute was used.

2.6. Statistical analysis

Three way repeated measure ANOVA was employed for group comparisons of overall differences in LTP time points (group, OVX and time as the factors). All comparisons among the groups of single time point were also analyzed with two-way ANOVA. When statistical significance was found between groups, a Tukey's post hoc multiple comparison test was performed to determine points of significant difference.

P values less than 0.05 were considered significant. All values were presented as means ± standard error of mean (SEM).

3. Results

To measure the effect of treadmill exercise and/or SD on basal synaptic performance, input–output (I–O) curves were plotted as changes in the slope of the field excitatory postsynaptic potential (fEPSP) against increasing stimulus intensities. On the whole, no significant difference was seen in the input/output relationship among all female rats (Fig. 1). Also, there were no significant changes in the PPF ratios of all groups ($p > 0.05$) (Fig. 2).

High frequency stimulation of the Schaffer-collaterals pathway evoked E-LTP as a marked increase in fEPSP slope which was examined for 2 h after HFS (maintenance phase of LTP). All groups revealed LTP induction (Fig. 3).

After applying HFS, the mean fEPSP slope in the SD intact female group (151.83 ± 8.28% of baseline) was significantly lower than those in the control (208.01 ± 12.1% of baseline), exercise (215.56 ± 7.45%) and exercise/SD (206.74 ± 6.53%) and wide platform (204.23 ± 6.16%) groups ($p < 0.01$) (Fig. 3A). Also shortly after HFS, the fEPSP slope in the control (207.62 ± 26.51% of baseline), exercise (207.55 ± 17.61% of baseline), exercise/SD (204.81 ± 6.21% of baseline) and wide platform (191.90 ± 14.7% of baseline) groups was significantly higher compared to the sleep-deprived group (146.92 ± 7.07% of baseline) in OVX female rats ($p < 0.05$) (Fig. 3B).

However, in the sleep-deprived intact and OVX female rats, after an initial increase in fEPSP slope, fEPSP slope approximately declined to the baseline during 2 h compared to all of the other groups (intact = 115.33 ± 10.63% of baseline, OVX = 109.40 ± 8.86% of baseline; $p < 0.001$ and $p < 0.01$ in intact and OVX female rats respectively). In contrast, 2 h after applying HFS the exercised/sleep-deprived group showed a sustained increase in the fEPSP slope (intact = 191.47 ± 14.52, OVX = 187.63 ± 16.26% of baseline) similar to those of the exercise (intact = 199.62 ± 10.46% of baseline, OVX = 188.79 ± 11.50% of baseline), control (intact = 191.26 ± 9.12% of baseline, OVX = 186.1 ± 18.92% of baseline) and wide platform (intact = 190.33 ± 11.81% of baseline, OVX = 186.09 ± 9.61% of baseline) groups (Fig. 3).

Overall, sleep deprivation induced more rapid decay of LTP maintenance in the intact ($p = 0.02$) and specially ovariectomized ($p = 0.008$) female rats in comparison with 5 min after HFS. The induction and maintenance of LTP was similar among the exercise, control, exercised/SD and wide platform (sham platform) groups of intact and OVX female rats (Fig. 3).

No differences were observed in LTP magnitude or maintenance between two control, exercise, exercise/SD and wide platform groups of intact and OVX female animals. Also SD-OVX group displayed more deficiency in LTP than intact female animals, but this difference was not significant.

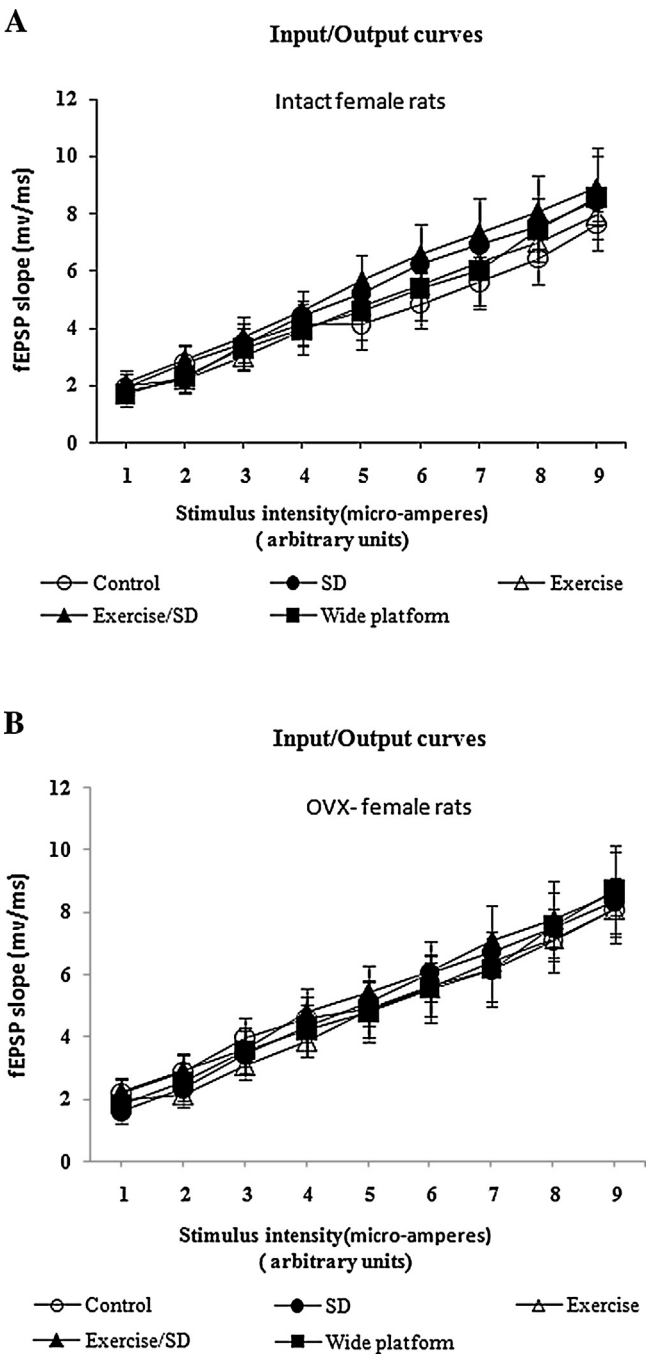

Fig. 1. Input/output curves were acquired from the field excitatory post-synaptic potential slopes to the different stimulus intensities in the CA1 area of the hippocampus in the intact (A) and ovariectomized (B) female rats. Numbers of stimulus intensity are arbitrary units where 1 is the intensity that generated the least responses, and 9 is the intensity that generated the highest responses. We used constant current stimulation and stimulus intensity was in units of micro–amperes. There were no significant differences in the input/output among all female rats ($p > 0.05$).

4. Discussion

In this study, we examined the combined effect of treadmill exercise and SD on synaptic plasticity in CA1 area of the hippocampus in the intact and OVX female rats. SD negatively affected the induction and stability of long term potentiation in intact and OVX female rats. However, the regular physical exercise alleviated SD-induced deficits of LTP in the CA1 area of the hippocampus.

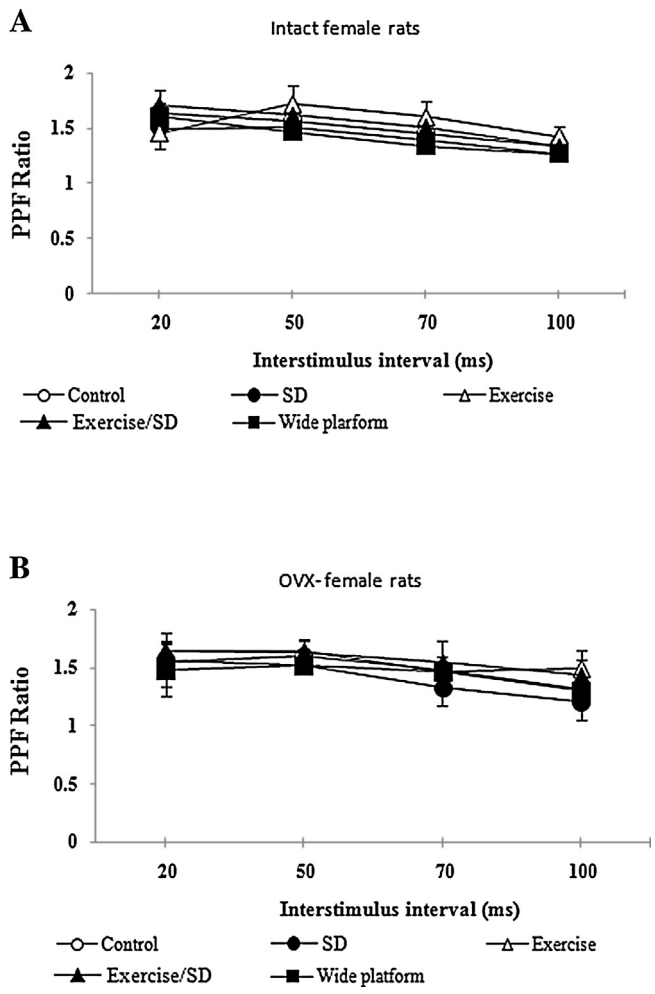

Fig. 2. The effects of sleep deprivation (SD) and exercise on paired pulse facilitation (PPF) in the CA1 area of the hippocampus were determined in the intact (A) and ovariectomized (B) female rats. PPF ratio was not significantly different among the groups ($p > 0.05$).

Sleep deprivation was induced using multiple platform method which depends on the losing of muscle tone during REM (rapid eye movement) sleep. Although this technique is effective in suppressing about 95% of REM sleep, it can also interfere with NREM sleep (Machado et al., 2004).

This method also eliminates both the isolation and immobilization stress associated with the other methods (Suchecki and Tufik, 2000). To increase the accuracy of this experiment, we subjected the rats to wider platforms columns to control aquarium environment which permitted them to sleep relatively uninterrupted. Our experiments suggested that the cognitive ability of rats which were kept on the wide platforms in the aquarium for 72 h was not significantly different from home cage matched controls of intact and OVX female rats. Also the previous study in our laboratory indicated that the difference of corticosterone levels was not significant among the control, sham (wide platform) and SD groups (Hajali et al., 2012). It appeared that cognitive impairment in sleep-deprived rats on the narrow platforms was largely the result of sleep loss and not from stresses of the aquarium. These results are consistent with previous reports (Alhaider et al., 2010; Zagaar et al., 2012a,b).

Several lines of evidence have demonstrated that sleep plays a vital role in learning and memory (Diekelmann and Born, 2010). However, sleep deprivation impairs learning and memory consolidation in several paradigms such as Morris water maze (Hajali et al., 2012) and radial arm water maze (Zagaar et al., 2012a,b) tasks. It has been reported that SD impairs LTP induction within the CA1 region of the hippocampus in male rats and after applying HFS, the fEPSP slopes in SD groups were approximately diminished to baseline levels (Kim et al., 2005; Davis et al., 2003). Additionally, the negative effect of the SD on LTP and synaptic plasticity is thought to be due to deleterious changes in intracellular signaling molecules (Zagaar et al., 2012a) and receptors such as NMDA(N-methyl-D-aspartate) (Ravassard et al., 2009)and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors (Hagewoud et al., 2010).

Our previous finding indicated that sleep deprived OVX female rats had significantly more impaired spatial learning and memory ability than sleep deprived intact female animals (Hajali et al., 2012).

There are also some human studies reporting the increased susceptibility of postmenopausal women to the deleterious effects of poor sleep on physical (Goldman et al., 2007) and cognitive performances (Blackwell et al., 2006). Based on mentioned findings, it seems that depletion of endogenous sex steroid hormones is the main candidate for mediating the more sensitivity of OVX female rats to the adverse effects of sleep loss on cognitive and synaptic functions.

The results of the present study indicated that SD caused impairment of hippocampal E-LTP in all female rats, however, SD-OVX group displayed more deficiency in LTP than intact female animals, but this difference was not significant. Although, a milder sleep deprivation procedure (less than 72 h) or sleep restriction rather that sleep deprivation might reveal differences. Further studies are required to evaluate the effects of shorter deprivation period or sleep restriction on synaptic plasticity in female rats.

However, in the present study we indicated that 4 weeks of regular exercise prevented the deleterious effect of SD on E-LTP in CA1 region of the hippocampus. In addition, our results showed that regular exercise alone had no significant impact on LTP magnitude or maintenance in normal rats. These results support our view that our forced exercise exerts its positive effects only in the presence of cognitive impairment.

Other studies suggested that treadmill exercise had neuroprotective effects on deleterious behavioral, synaptic and molecular changes induced by paradoxical sleep deprivation (Fernandes et al., 2013; Zagaar et al., 2012a,b). These investigations revealed that the benefits of exercise at the cellular level may be due to its capability to increase the production of BDNF and other signaling molecules in sleep-deprived male rats (Zagaar et al., 2012a,b).

However, it has been widely reported that running exercise ameliorates various brain injury-induced neurological impairments; facilitates functional recovery, and increases resistance to brain insult (Ang and Gomez-Pinilla, 2007; Ding et al., 2004), though the underlying mechanisms are poorly understood. One possible explanation is that exercise enhances the cell proliferation, long-term potentiation (Van Praag et al., 1999), and synaptic plasticity (Aguiar Jr et al., 2011; Liu et al., 2011) in the hippocampus. These advantages have been best defined with respect to the elevated expression of neurotrophic factors, including the BDNF (Griesbach et al., 2009; Vaynman et al., 2004).

We did not focus on the role of signaling molecule in the present experiment. It seems that further studies are required to examine the effect of physical exercise on the expression of BDNF mRNA and other signaling molecules in female rats following SD.

Although some evidences have indicated the significant promotion of cognitive performance, learning and memory by physical activities (Ang and Gomez-Pinilla, 2007; Cotman and Berchtold, 2002; García-Capdevila et al., 2009; Leasure and Jones, 2008; Lin et al., 2012; Saadati et al., 2010; Van Praag et al., 1999) other studies, in agreement with our findings, have revealed lack of improvement (Titterness et al., 2011; Zagaar et al., 2012a,b). This controversy

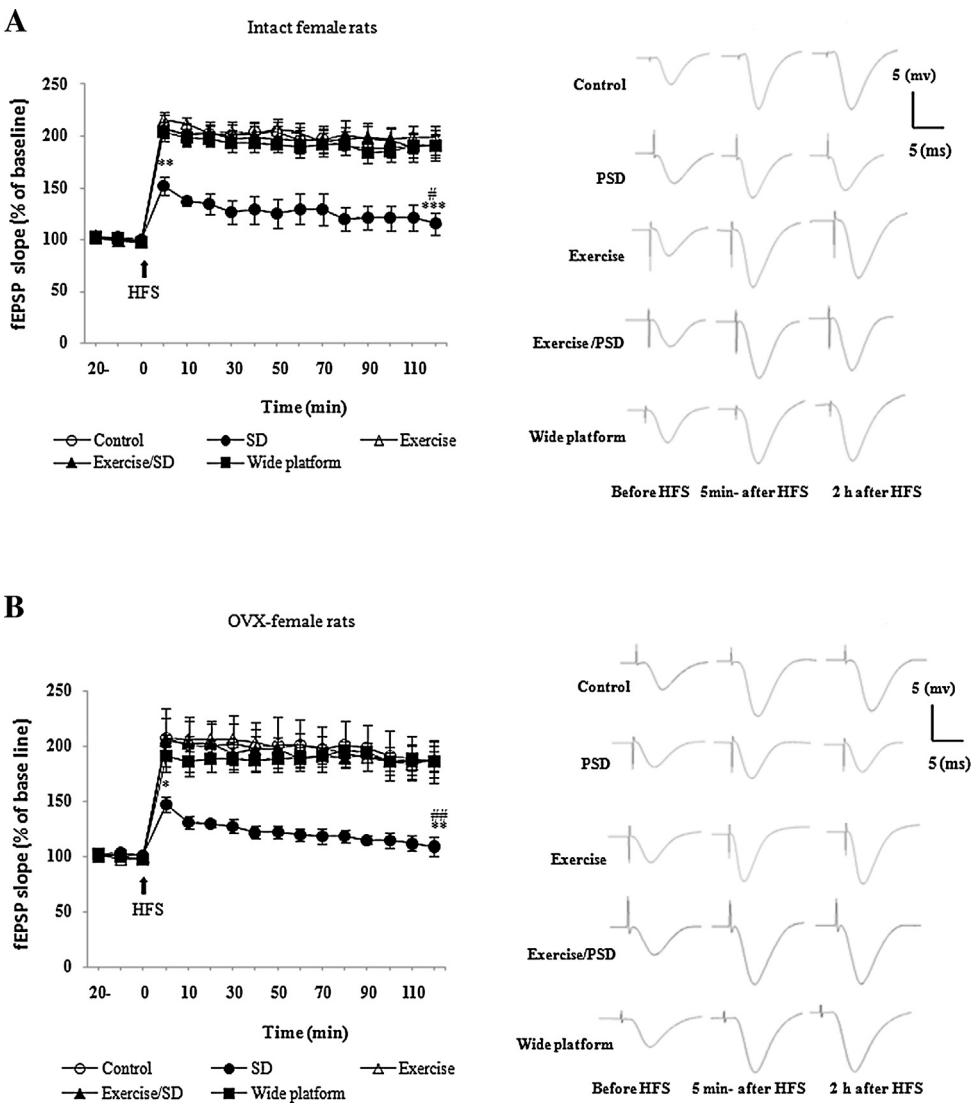

Fig. 3. The effects of SD (sleep deprivation) and exercise on LTP (long term potentiation) induction and maintenance in the CA1 area of the hippocampus in intact (A) and OVX (ovariectomized) (B) female rats. Sleep deprived intact and OVX female rats indicated a significant decrease in the LTP induction in comparison with the other groups. Repeated measures of ANOVA followed by a post hoc test revealed that SD induced a rapid decay of LTP maintenance in the intact and OVX female rats. However, regular exercise prevented the induced deficits of LTP in the CA1 area in the hippocampus. Each point shows the mean ± SEM (7–9 rats/group). Data are plotted as the average percentage change from baseline responses. $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ with respect to other groups. $^{\#}p = 0.02$, $^{\#\#}p = 0.008$ in compared with 5 min after HFS in intact and OVX female rats, respectively. Calibrations, 5 mV/5 ms, were used for all traces before and after induction of LTP.

may be due to the differences in the length, type and intensity of the performed training exercises. Apart from these points, such reverse outcomes might be due to differences in age and strain of the experimented animals.

In the present study, estrogen deprivation over 30 days had no obvious effect on long term potentiation in the CA1 area of the hippocampus. Other studies demonstrated that changes in estrogen levels over 21 days had no significant effect on cell proliferation in the rat hippocampus (Jin et al., 2008; Lagace et al., 2007). Based on the results of these studies, although the detail mechanism is not yet clear, the effects of estrogen deprivation on hippocampal functions may be somewhat transient and hippocampus may become accustomed to the long-term estrogen deprivation.

There were no differences in the input–output curves and PPF ratios among groups, therefore the alternation in LTP induction observed in the groups was not because of fiber excitability and pre-synaptic changes in the CA1 area of the hippocampus.

5. Conclusion

In summary, our findings showed that treadmill running overcame the SD-induced impairments of E-LTP in CA1 area of the hippocampus. These data correspond to the possibility that exercise may suggest protection against SD induced reduction in the learning capability and memory function of the hippocampus in female rats.

Conflict of interest statement

The authors have declared that there are no conflicts of interest.

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