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Moderate-intensity interval exercise but not high-intensity interval exercise improves the spatial memory of ovariectomized rats

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ABSTRACT

Physical exercise exerts beneficial effects on the spatial learning and memory. High-intensity interval exercise (HIIE) has been proposed as a time-efficient physical exercise regimen. On the other hand, there were evidences that HIIE increased oxidative stress biomarkers and reduced antioxidant capacity, which resulted in oxidative damage. The present study aimed to investigate the effects of high-intensity interval exercise and moderate-intensity interval exercise on oxidative stress biomarkers and oxidative enzymes activity in the hippocampus and the spatial memory of ovariectomized rats. A total of 16 female Sprague Dawley rats aged 12 weeks were randomly assigned into 4 groups, i.e. the sham-operated (SO), ovariectomized without exercise (O), ovariectomized with high-intensity interval exercise (HIIE), and ovariectomized with moderate-intensity interval exercise (MIIE) groups. Rats of the exercise groups (HIIE & MIIE groups) performed 6 sessions of interval exercise per week for 6 weeks. The spatial memory of rats was measured using the Morris water maze procedure. The malondialdehyde (MDA) levels and activity of catalase (Cat) as well as glutathione peroxidase (GPx) in hippocampus were determined using spectrophotometry method. The spatial learning and memory retention of the moderate-intensity interval exercise group was significantly better than that of the high-intensity interval exercise group. The GPx activity of MIIE group was higher than any other groups. The SO group had the lowest hippocampal MDA level and highest Cat activity among groups. Moderate-intensity interval exercise reduces the ovariectomy induced-oxidative stress in the hippocampus and improves spatial learning and memory retention of ovariectomized rats.

ABSTRAK

Latihan fisik memberikan efek menguntungkan pada pembelajaran spasial dan memori. Latihan fisik interval intensitas tinggi (HIIE) telah diusulkan sebagai rejimen latihan fisik yang efisien waktu. Di sisi lain, ditemukan bukti bahwa HIIE meningkatkan *biomarker* stres oksidatif dan mengurangi kapasitas antioksidan, yang mengakibatkan kerusakan oksidatif. Penelitian ini bertujuan untuk menguji efek latihan fisik interval intensitas tinggi dan latihan fisik interval intensitas sedang pada *biomarker* stres oksidatif dan aktivitas enzim oksidatif di hippocampus serta memori spasial tikus yang diovariektomi. Sebanyak 16 tikus Sprague Dawley betina berusia 12 minggu secara acak dibagi menjadi 4 kelompok, yaitu operasi palsu (SO), ovariektomi tanpa latihan fisik (O), ovariektomi dengan latihan fisik interval intensitas tinggi (HIIE), dan kelompok ovariektomi dengan latihan fisik interval intensitas sedang (MIIE). Tikus dari kelompok latihan fisik (kelompok HIIE & MIIE) melakukan 6 sesi latihan interval per minggu selama 6 minggu. Memori

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spasial tikus diukur menggunakan prosedur *Morris water maze*. Kadar malondialdehide (MDA) dan aktivitas katalase (Cat) serta glutation peroksidase (GPx) di hippocampus diukur menggunakan metode spektrofotometri. Pembelajaran dan retensi memori spasial dari kelompok latihan fisik interval intensitas sedang secara signifikan lebih baik daripada kelompok latihan fisik interval intensitas tinggi. Aktivitas GPx kelompok MIIE lebih tinggi daripada kelompok lain. Kelompok SO memiliki tingkat MDA hippocampus terendah dan aktivitas Cat tertinggi di antara kelompok-kelompok. Latihan fisik interval intensitas sedang mengurangi stres oksidatif yang diinduksi ovariektomi dan meningkatkan pembelajaran dan retensi memori spasial pada tikus yang diovariektomi.

Keywords: ovariectomy - spatial memory - interval exercise – malondialdehyde - catalase

INTRODUCTION

The effects of exercise on health have been extensively investigated, including the prevention of cognitive impairment.[1] Although a substantial amount of evidence of the beneficial effects of exercise on health has been presented, many people are still reluctant to participate in exercise for various reasons, such as "lack of time"[2] or "lack of enjoyment".[3] Recently, high-intensity interval exercise (HIIE) has been proposed as a time-efficient physical exercise regimen that could generate comparable benefits to moderate-intensity continuous physical exercise (MICE).[4,5] HIIE has also been found to increase enjoyment[6] and improve patient adherence to physical activity.[5]

Studies evaluating HIIE and MICE have revealed some advantages of the HIIE over MICE, including the improvement of VO_{2max}[7] the increase of the maximal activities of mitochondrial enzymes,[8] the reduction of lactate accumulation during exercise,[9] and the improvement of metabolic adaptation.[4] Compared to moderate-intensity interval exercise (MIIE), HIIE is better in improving insulin sensitivity of obese adolescent girls,[10] and decreasing body mass, body fat, and waist circumference of healthy obese female adolescents.[11] Despite these many advantages of the HIIE, there were evidences that HIIE increased oxidative stress biomarkers and reduced antioxidant capacity,[12] induced brain mitochondrial dysfunction and decreased BDNF levels in the frontal cortex of mice.[13]

Previous studies have shown that MIIE increased the serum BDNF levels of Parkinson disease patients,[14] and increased the expression of hippocampal BDNF gene of juvenile rats greater than HIIE.[15] The present study intended to compare the effects of HIIE and MIIE on the spatial memory of ovariectomized rats and the association between the spatial memory and oxidative stress biomarkers (MDA) as well as the antioxidant enzymes activity i.e. Cat and GPx.

MATERIALS AND METHODS

Animals and reagents

A total of 16 female Sprague Dawley rats aged 12 weeks, which were initially weighing 150 - 200 g, were used in this study. The rats were obtained from the Animal House of Universitas Gadjah Mada. They were housed in cages under 12-h of natural light-dark cycle. Food and water were given *ad libitum* throughout the experiment. The experimental protocol and animal handling was approved by the Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (ethical number KE/FK/217/EC/2016). After one week of familiarization to the experimental room, the rats were randomly assigned into two main groups, i.e. ovariectomy (12 rats) and sham-operated without exercise (SO; n = 4) groups. Both ovaries of the 12 rats of the first group were removed via a 2–3 cm ventral midline incision on the abdomen under anesthesia (ketamine HCl 60 mg/ kg body weight; PT Guardian Pharmatama, Jakarta, Indonesia). The remaining 4 rats underwent sham surgery. Seven days after ovariectomy, the 12 rats of the first group were divided further into three groups, i.e. ovariectomy without exercise (O; n = 4), ovariectomy with high intensity interval exercise (HIIE; n = 4), and ovariectomy with moderate intensity interval exercise (MIIE; n = 4) groups.

Exercise training protocol

The protocol of exercise was conducted according to the protocol developed by Afzalpour *et al.*[16] with slight modifications. Briefly, the protocol consisted of two periods, i.e. adaptation period and exercise period. The rats of the exercise group were adapted to the exercise protocol and treadmill apparatus (Gama Tread version 2010, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada) for one week. During the adaptation period, the rats had to run on the treadmill with the running speed of 10 m/min, the treadmill slope of 0°, and the duration of exercise of 10 min/day for 6 days. During the exercise period, the rats had to perform 6 sessions of running per week for 6 weeks. The number of intervals and running speeds of training were distinguished between odd and even days. In the odd days, the rats had to run at a high intensity running speed (36 m/min) in the HIIE group and a moderate intensity running speed (18 m/min) in the MIIE group for 30 sec, interspersed with one-minute intervals of running at low intensity running speeds (10 m/min) for recovery phase. The number of intervals started with 2 intervals in the first week up to 6 intervals in the fourth week. In the even days, the rats had to run at the running speeds of 40 m/min for HIIE and 20 m/min for MIIE for 30 sec and interspersed with recovery phase at the same speed (10 m/min) and duration as odd days. The interval increased daily starting at 3 intervals in the first week and settled after reaching 20 intervals by the end of the fourth week. At the beginning and the end of high intensity and moderate intensity interval exercise training procedures, warming-up and cooling-down were performed at 10 m/ min for 5 min. The O and SO groups were only moved to the training room at the same time when the exercise groups performed exercise.

Morris water Maze task

The Morris water maze (MWM) test was conducted based on the protocol described elsewhere.[17] The test consisted of two phases, i.e. escape acquisition and memory persistence phases, and an additional visible platform test. The test apparatus consisted of a white-painted circular pool with a diameter of 150 cm and a height of 40 cm. The pool was filled with fresh cow milk to hide the platform, up to the depth of 18 cm. A circular white platform was placed 2 cm below the surface of the water. The temperature of the water was around 25°C. To record the movement of animals in the pool, a video camera was installed above the center of the pool, and linked to a personal computer. Several geometric pictures with different colors were attached to the white curtain wall around the pool. The pool was divided into four equally imaginary quadrants. The circumference wall of the pool was marked with 8 equally spaced starting points.

Six days before the exercise training finished, the MWM test began. In order to familiarize with the test room, the rats were moved to the room twenty-four hours before the trials. On the day of testing, the platform was positioned in the center of a randomly chosen quadrant for each rat. One starting point was randomly chosen for each trial. The test began when any randomly selected rat was placed at this starting point with its head facing toward the inner side of the circumference wall of the pool, and then allowed to swim and find the hidden platform as a way to escape.

Escape acquisition test. Each rat was given four trials each day for 4 consecutive days with 60 sec inter-trial interval. The rat was allowed to swim for a maximum of

60 sec to find the hidden platform at each trial. The time (‘escape latency’) for the rat to find the platform was recorded. Once the rat reached the platform, it was left there for 20 sec. If the rat failed to find the platform within 1 min, the rat was given a latency score of 60 sec and placed on top of the platform for 20 sec.

Memory persistence test. To examine the animal ability in retaining the spatial memory about the location of the platform, the rats underwent memory persistence test, 24 h after the escape acquisition test. Each rat was allowed to swim in the pool without a platform for 60 sec. The latency of each rat to swim in the quadrant where the platform was previously placed during the escape acquisition test was recorded. The percentage of time expended in the correct quadrant to a total of 60 sec was calculated.

Visible platform test. In the same day with and after the memory persistence test, the rats were given a visual test to examine their sensory and motor functions. Before the test began, a starting point was randomly selected for each rat. The platform was located in a different place from where the platform was previously positioned during the escape acquisition and memory persistence tests. The platform was made visible with a flag was attached on the platform up to 2 cm high from the surface of the water. The test consisted of three trials which lasted for a maximum of 60 sec per trial. The latency was recorded for each test. If a rat failed to find the platform within 60 sec, the latency was recorded as 60 sec. The data on latency were then used for further statistical analysis.

Hippocampal tissue collection

The rats were euthanized under anesthesia (ketamine HCl 100 mg/ kg body weight; PT Guardian Pharmatama, Jakarta, Indonesia) approximately 24 h after the last exercise training. The hippocampi of the rats were removed from their skulls and subsequently were extracted from the forebrains of the rats in iced phosphate buffered saline (PBS). The extracted hippocampus was homogenized in 10% PBS. The homogenates were then centrifuged at 14.000 rpm for 5 min at 4°C, and the supernatants of the homogenates were used for the examination of the activity of Cat and GPx, as well as the level of MDA using spectrophotometry method.

Statistical analysis

The data from the acquisition phase of the spatial memory test were analyzed using two-way repeated measures analysis of variance (Anova). The memory persistence tests data, level of MDA and the activity of antioxidant enzymes (Cat and GPx) were analyzed using one-way Anova. The post hoc least significant difference (LSD) test was performed when appropriate. The Pearson correlation tests were conducted to assess the correlation between the spatial memory persistence test data with the hippocampal MDA level as well as the activity of Cat and GPx enzymes. The statistical analyses were performed using either SPSS (version 19) or Sigmastat (version 4.0) software. All data were presented as the means ± standard error of the mean (SEM) and the significance levels were set at $p < 0.05$.

RESULTS

The sensory-motor functions of rats

Visible platform test. All groups performed equally well on the three trials of the visible platform test (FIGURE 1). The escape latencies data of the first trial in visible platform test were not homogenous. The Kruskal-Wallis analysis of these data did not show any significant difference between groups ($p = 0.414$). One-way Anova of the escape latencies of the second and third trials of the visible platform test did not show any significant difference between groups ($p = 0.297$ and $p = 0.269$, respectively). Overall, there was no significant difference in the sensory-motor functions between all groups of rats.

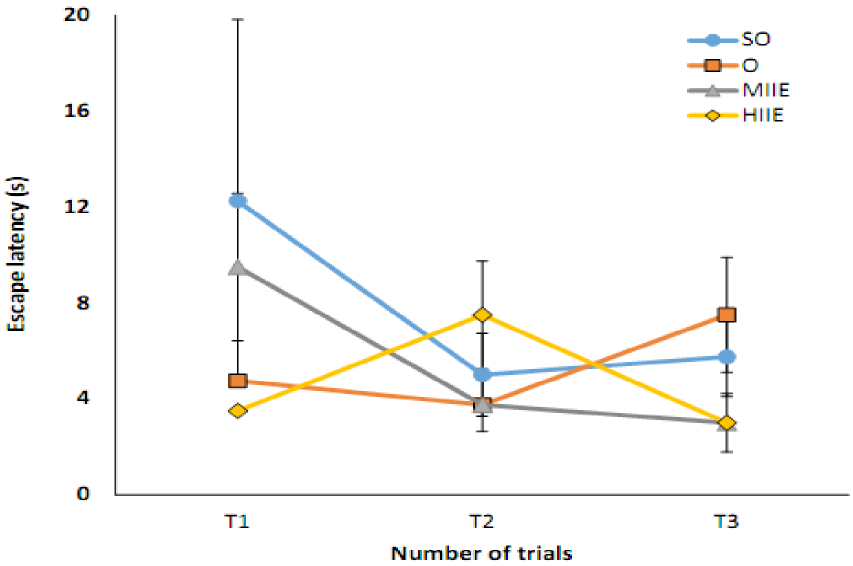

FIGURE 1. Means ± SEM of escape latency (s) of sham-operated (SO) group, ovariectomized (O) group, moderate-intensity interval exercise (MIIE) group and high-intensity interval exercise (HIIE) group rats during sensory-motor test of the Morris water maze procedure; T, trial. Result of Kruskal-Wallis of T1 wasp > 0.05, Results of one-way Anova of T2 and T3 were p > 0.05

The effects of exercise on the spatial memory

Escape acquisition test. The data of the escape acquisition test are shown in FIGURE 2. The two-way repeated measures Anova of these data showed significant main effects of groups (df = 3, 180; F = 3.996; p = 0.035) and day/trial (df =15, 180; F = 10.773; p = <0.001), but not groups x day/trial interaction. The post-hoc LSD test (complete data not presented) showed that the escape latency of the MIIE group was significantly shorter than the other three groups.

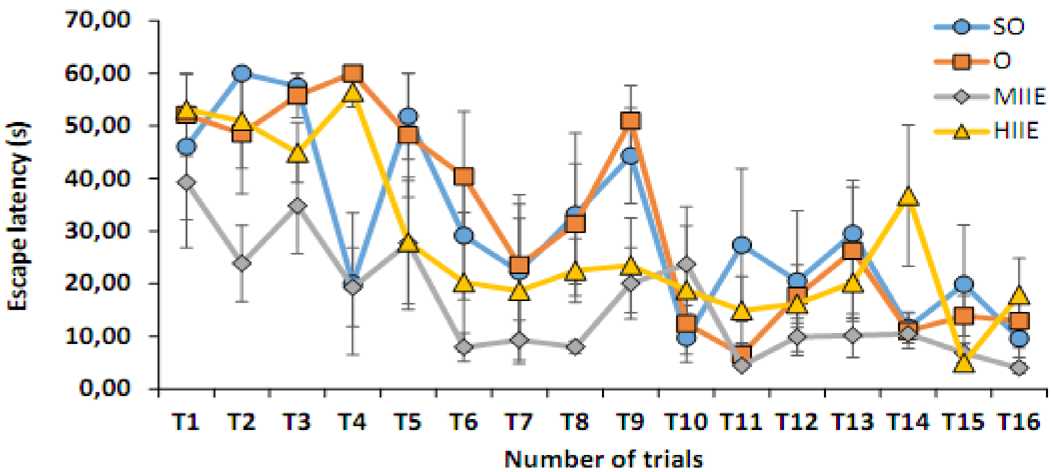

FIGURE 2. Means ± SEM of the $\log_{10}$ of the escape latency (s) of the sham-operated (SO) group, moderate-intensity interval exercise (MIIE) group and high-intensity interval exercise (HIIE) group rats during 4 consecutive escape acquisition test days of the Morris water maze procedure; T, trial. Results of two-way Anova repeated measures. Groups; df = 3, 180; F = 3.996; p = 0.035. Day/trial; df= 15, 180; F = 10.773; p = <0.001. Groups x day/trial interaction; df = 45, 180; F = 1.301; p = 0.117. Anova, analysis of variance; df, degree of freedom; F, F value; p, p value

Memory persistence test. The memory persistence ability was analyzed from the data of percentage **of** time spent in the target quadrant of the probe test (FIGURE 3). One-way Anova of these data showed that there was a significant main effect of groups ($p = 0.005$). The post-hoc LSD test of these data (complete data not presented) revealed that the percentage of time expended in the correct quadrant of the MIIE group was significantly shorter than that of the O ($p = 0.023$) and HIIE ($p = 0.027$) groups but not significantly different from the SO group ($p = 0.232$).

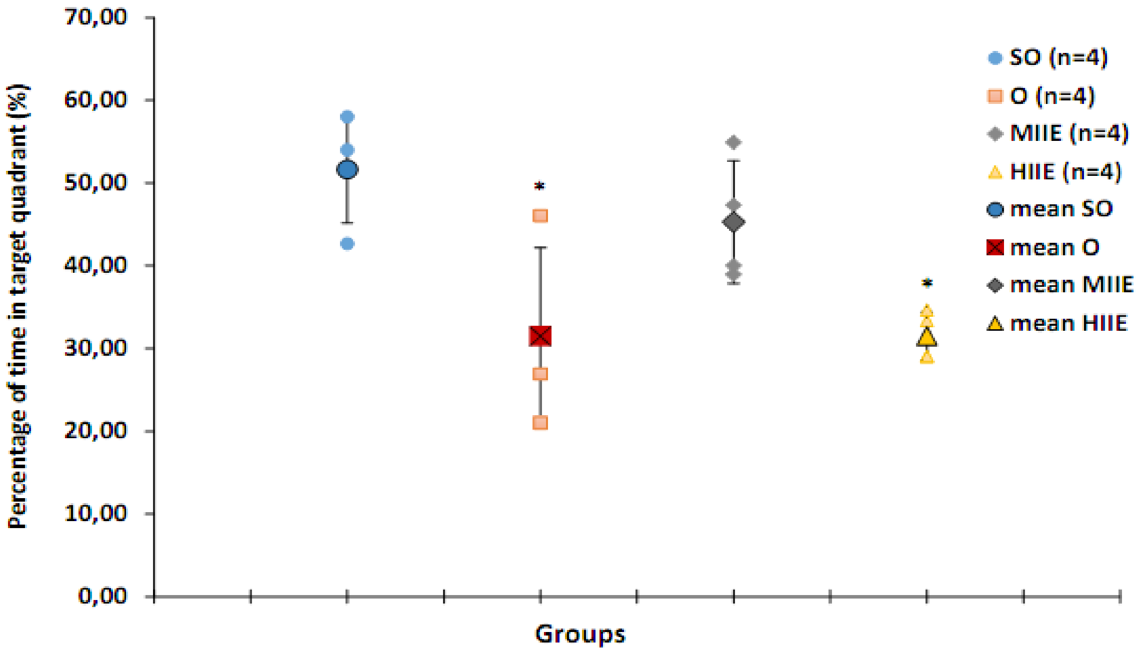

FIGURE 3. Means ± SEM of the escape latency (s) in memory persistence test of the Morris water maze test; SO, sham-operated group, O, ovariectomized group, MIIE, moderate-intensity interval exercise group, HIIE, high-intensity interval exercise group. *, $p < 0.05$ compared to SO group

The effects of exercise on the hippocampal MDA level

FIGURE 4 presents the data of hippocampal MDA concentration of all groups of rats. One way Anova of these data showed a significant main effect of groups ($p < 0.001$). The post-hoc LSD test of the data revealed that the mean level of hippocampal MDA of the SO group (1.49 ± 0.065 nmol/g tissue weight) was significantly lower than that of the O (6.16 ± 0.241 nmol/g tissue weight), MIIE (3.90 ± 0.229 nmol/g tissue weight), and HIIE (2.46 ± 0.144 nmol/g tissue weight) groups ($p<0.05$). The mean of hippocampal MDA level of the HIIE group was significantly lower than that of the O and MIIE groups ($p<0.05$).

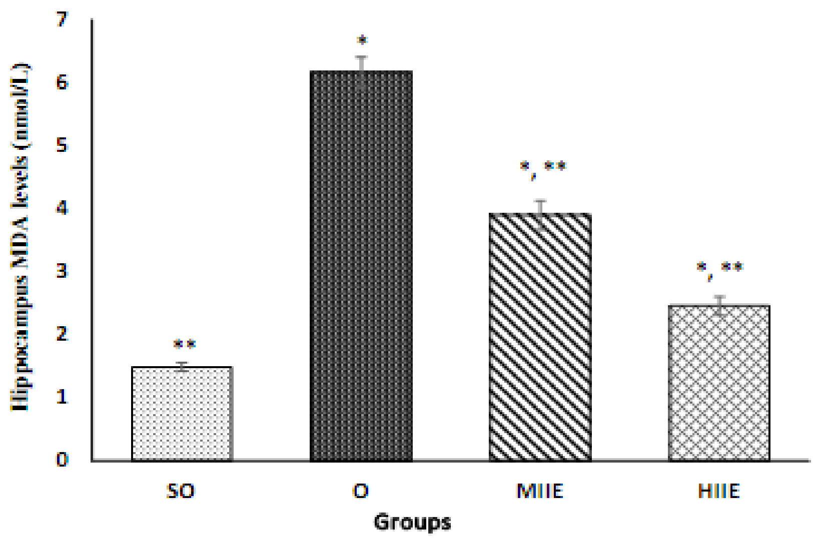

FIGURE 4. Means ± SEM of the levels of malondialdehyde (MDA) in the hippocampus of the sham-operated (SO) group, ovariectomized (O) group, moderate-intensity interval exercise (MIIE) group and high-intensity interval exercise (HIIE) group rats. *, $p < 0.05$ compared to the SO group.

The effects of exercise on activity of antioxidant enzymes in hippocampus

FIGURE 5 presents the data of the activity of GPx in hippocampus of all rats. One way Anova of these data revealed a significant main effect of groups ($p < 0.001$). The post-hoc LSD test of the data demonstrated that the GPx activity in the hippocampus of the O group (33.38 ± 1.456 IU/mL) was significantly lower than that of the SO (56.72 ± 2.388 IU/mL), MIIE (61.54 ± 2.978 IU/mL), and HIIE (54.98 ± 2.051 IU/mL) groups.

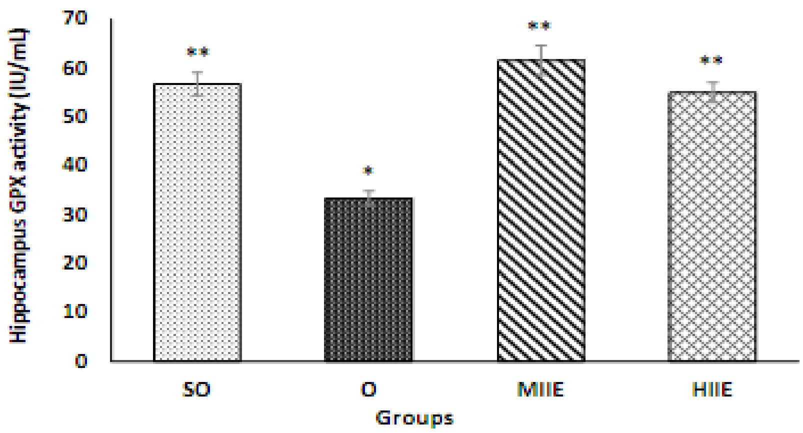

FIGURE 5. Means ± SEM of the activity of glutathione peroxidase (GPx) in the hippocampus of the sham-operated (SO) group, ovariectomized (O) group, moderate-intensity interval exercise (MIIE) group and high-intensity interval exercise (HIIE) group rats. *, $p < 0.05$ compared to the SO group

FIGURE 6 shows the data of the activity of Cat in hippocampus of all groups of rats. One way Anova procedure of these data showed a significant main effect of groups ($p < 0.001$). The post-hoc LSD test of the data showed that the Cat activity in the hippocampus of the SO group (6.40 ± 0.034 IU/mL) was significantly higher than that of the O (1.46 ± 0.037 IU/mL), MIIE (2.13 ± 0.035 IU/mL), and HIIE (5.60 ± 0.016 IU/mL) groups.

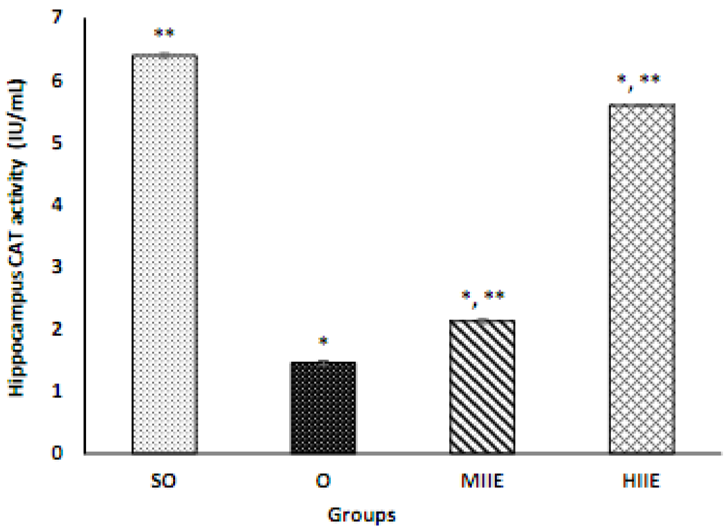

FIGURE 6. Means ± SEM of the activity of catalase (Cat) in the hippocampus of the sham-operated (SO) group, ovariectomized (O) group, moderate-intensity interval exercise (MIIE) group and high-intensity interval exercise (HIIE) group rats. *, $p < 0.05$ compared to the SO group. **, $p < 0.05$ compared to the O group.

Correlation

The Pearson correlation test revealed a significantly ($p = 0.019$) positive correlation ($r = 0.576$) of the percentages of time spent in the target quadrant during the memory persistence test with the activity of GPx enzyme in hippocampus. On the other hand, the hippocampal MDA levels had a significantly ($p = 0.047$) negative correlation ($r = -0.502$) with the percentages of time expended in the correct quadrant of the memory persistence test. There was no significant correlation ($p > 0.05$) between the percentages of time expended in the correct quadrant with the activity of catalase. The regression analysis could not be conducted because the data do not fulfill the requirements for the analysis.

DISCUSSION

The present study found that the spatial learning of the MIIE group was significantly better than the O, SO, and HIIE groups. The escape latency of trials 1- 4 of the fourth day of all groups was significantly shorter than that of the first day. Although all groups of rats demonstrated a similar trend of final escape latencies (trials 13 - 16 in the fourth day), the latency curve of the MIIE group already declined since trial 6. This may indicate that the MIIE group learned the spatial information faster than any other groups. The spatial memory retention of the MIIE group was not different from the SO group. However, it was significantly better than the O and HIIE groups. Therefore, moderate-intensity interval exercise may inhibit the spatial memory decline induced by ovariectomy.

There was a significantly positive correlation between the hippocampal GPx activity and the percentage of time in the target quadrant in the memory persistence test. In contrast, there was a significantly negative correlation between the percentage time in the target quadrant in the memory persistence test with the hippocampal MDA level. This may suggest that the spatial memory retention of ovariectomized rats was affected by the activity of antioxidant enzyme (GPx) and the level of oxidant (MDA) in the hippocampus.

The hippocampal MDA level of the O group was higher than that of the SO group. This suggests that ovariectomy induces oxidative stress. The hippocampal MDA level of the MIIE group was lower than the O group but still higher than that of the SO and HIIE groups. In addition, the MDA level of the HIIE group was lower than that of the O and MIIE groups, but still higher than that of the SO group.

The hippocampal GPx activity of the O group was lower than that of the SO group ($p < 0.01$). This indicates that ovariectomy suppresses the GPx activity. The hippocampal GPx activity of the MIIE and HIIE groups was not significantly different from the SO group. The GPx/MDA ratio of the HIIE group was higher (1: 26) than that of the MIIE group (1:15). It appears that HIIE-induced oxidative stress triggered the increase of GPx response that rapidly counteracted the increase of the MDA level of the ovariectomized rats.

Despite the fact that the hippocampal MDA level of the HIIE group was the lowest among all groups and the GPx/MDA ratio of the HIIE group was higher than the MIIE group, the spatial learning and memory persistence of the HIIE group was not as good as the MIIE group. It seems that a sufficient hippocampal MDA level, such as that in the MIIE group, is required to maintain an adequate response of the antioxidant and oxidative damage repair systems against oxidative stress to yield an optimum improvement of the spatial learning and memory functions of the hippocampus.

It has been shown that ovariectomy triggers oxidative stress, including lipid peroxidation.[18] MDA was an aldehyde compound produced by lipid peroxidation.[19] It has been found in the current study that the SO group had the lowest hippocampal MDA level, which was followed by the HIIE group. Probably the capability of the HIIE to decrease the MDA level in the hippocampus of ovariectomized rats was better than the MIIE group, although the decline of the MDA level did not reach the level of the SO group. The present study also revealed an inverse correlation between the MDA level in the hippocampus and the spatial memory persistency test performance. This result corroborate other studies showing that the parenteral administration of MDA decreased the ability of learning and spatial memory of rats,[20] and the decrease of spatial memory function was parallel with the hippocampal MDA level in the STZ-induced diabetes mellitus type 2 in mice.[21]

Exercise-induced mild oxidative stress seems to be able to reduce oxidative damage by upregulating antioxidant enzymes e.g. GPx and Cat.[22] GPx is known as an enzyme that catalyze the reduction of H_2O_2 or organic hydroperoxides to water or alcohols, respectively, using reduced glutathione (GSH) as the reductant.[23] Decreased GPx activity was found in tissues suffering from oxidative stress.[24] In this study, the lowest and highest GPx activities were observed in the O and SO groups, respectively. The GPx activity of both HIIE and MIIE groups was not significantly different from the SO group. This indicates that both HIIE and MIIE regimens have a similar ability to increase the GPx activity of ovariectomized rats.

Another antioxidant enzyme that was affected by oxidative stress was catalase. Cat is an antioxidant enzyme that catalyzes the conversion of H_2O_2 into water and oxygen.[25] Thus catalase is effective in reducing H_2O_2 levels.[26] In this study, the lowest and highest Cat activities were observed in the O and SO groups, respectively. The catalase activity of the HIIE group was higher than the MIIE group, but still lower than that of the SO group. This suggests that HIIE has a better ability to increase the Cat activity of ovariectomized rats than MIIE. The increase of the Cat activity of the HIIE group was possibly induced by the increase of H_2O_2 level after exercise, which was higher in the HIIE group than the MIIE group.[27]

The correlation analysis revealed that the spatial memory persistence of the rats was positively correlated with the GPx but not with the Cat activity in the hippocampus. The reasons of this pattern of correlation are probably that GPx is more potent than catalase[28] in that GPx affinity against H_2O_2 is higher than catalase[26] and that GPx not only breaks down H_2O_2 but also breaks down lipid peroxide (LOOH).[26]

Physical exercise modulates oxidative stress which in turn stimulates an adaptation as homeostatic responses. An increase in the free radical level initiates an adaptive response of the antioxidant and oxidative damage repair systems which may lead to the increase in the activity of suitable antioxidant enzymes.[29] The beneficial effects of repeated physical exercise obtained from the adaptation process serve as an answer to the oxidative stress. The adaptive effects of regular exercise are systemic and specific, depending on the characteristics of exercise and target organ.[30] The adaptation process may also result in a failure which is primarily due to inappropriate/very light stimuli, or incomplete recovery.[29,31] In the present study, the MIIE and HIIE was comparable in terms of their capability to increase the GPx activity of the ovariectomized rats. However, the MIIE seems to be greater in improving learning and spatial memory function of ovariectomized rats than the HIIE.

The beneficial effects of physical exercise depend on the adaptive responses of genes expression.[30] Physical exercise gives rise to the increase in the hippocampal growth factors, for instance brain-derived neurotropic factor (BDNF),[32] insulin-like growth factor-1 (IGF-1)[33] and vascular endothelial growth factor (VEGF).[34] The positive effects of exercise on the hippocampal function is thought to occur through hippocampal neurogenesis stimulation by BDNF,[33] IGF-1[33] and VEGF.[35] The underlying mechanisms of hippocampal-dependent spatial learning and memory improvement in the present study, however, are beyond the scope of the present study since it is primarily designed only to compare the effects of MIIE and HIIE on the spatial memory of ovariectomized rats

CONCLUSION

In conclusion, our study found that moderate-intensity physical exercise prevented the ovariectomy-induced spatial memory retention deficits of the Sprague Dawley rats. Physical exercise may exert these beneficial effects on the hippocampus via its modulation on the hippocampal GPx activity. The detailed mechanism of these effects, however, remains unclear at present, and therefore requires further investigations

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