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Concomitant increased brain-derived neurotrophic factor and interleukin-6 protein expression with postnatal exercise-associated spatial memory preservation in prenatal-stressed rat offspring

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ABSTRACT: Any perturbation to the neurohormonal-immune system during the fetal developmental period carries over effects later in life. Prenatal stress (PS) induces hippocampal changes in the structure and functions that could lead to cognitive impairment and psychiatric disorders. Increasing evidence indicates that physical exercise could ameliorate cognitive impairment in both young and old rats. We investigated the therapeutic effect of the postnatal voluntary wheel running (VWR) exercise on cognitive impairment that developed from prenatal maternal restraint stress. The restraint stress was carried out during gestation day (GD)14–21 in the pregnant Sprague-Dawley rats. VWR was performed in the rat pups on postnatal day (P)25–40. After that, spatial memory performance was tested with the Morris water maze (MWM) during P36–40. The effect of prenatal stress and the potential effects of the VWR on the levels of hippocampal synaptic proteins, brain-derived neurotrophic factor (BDNF), and interleukin (IL)-6 in the rat offspring were ascertained with Western blot analysis. Stress during the prenatal period induced decreases in synaptic proteins and BDNF, but an increase in IL-6. Postnatal exercise ameliorated the adverse effects of PS on protein expression. The MWM test confirmed the ameliorative effect of VWR on spatial memory performance of the pups. Our findings suggest that postnatal exercise has a high potential to ameliorate the adverse effects of maternal stress and return healthy neuroendocrine-immune system and spatial memory to rat offspring.

KEYWORDS: postnatal exercise, prenatal stress, spatial memory, hippocampus, proinflammatory cytokine

INTRODUCTION

Stress exposure during gestation has a plethora of effects on the fetus. According to the Barker hypothesis, several adult chronic metabolic syndromes are "programmed" during early life. Newborns with lower birth weight have a higher risk of developing coronary heart disease and brain disorders in adulthood [1]. Exposure to higher levels of glucocorticoids (GCs) or prenatal stress induces variation in the intrauterine milieu, which has adverse effects, including impairment of the ability to regulate stress responses and disruption of cognitive processes. The hippocampus is the brain region involved in the modulation of anxiety [2] and is essential in learning and memory [3]. It is of interest that stress induction and repeated corticosterone injections can elevate the level of extracellular glutamate in the rat hippocampus [4]. Prenatal stress exposure induced by repeated maternal restraint during mid- to late pregnancy resulted in a reduction of N-methyl-D-aspartate receptor (NMDAR) subunits [5]. This implies the involvement of prenatal stress in glutamate-induced impairment of learning and memory in the offspring. Glutamate is the major excitatory neurotransmitter in the brain and is essential in two types of synaptic plasticity, long-term potentiation (LTP), and long-term depression (LTD), via the subsequent event of NMDAR. However, overstimulating neurons with glutamate leads to excitotoxicity. Several lines of evidence revealed that prenatal stress decreased the number of the NMDAR subunits, either NR2A or NR2B. NMDAR is anchored on the surface membrane by interacting with postsynaptic density (PSD)-95, which plays a role in synaptic maturation. Prenatal stress turned on the protein degradation system (ubiquitin proteasome system, UPS), which then induced a decrease in PSD-95, NR2A, and NR2B [5]. In addition, the synaptic stabilization of PSD-95 is regulated by a BDNF-tropomyosin receptor kinase (Trk) type B signaling [6]. BDNF plays a key role in the maintenance of hippocampal neurons and synaptic plasticity. An increase in GCs level, which disrupts the BDNF-TrkB signaling cascade, also mediates synaptic plasticity during development [7]. Because the neurohormone system concomitantly regulates the immune response, prenatal stress induces an

increase in proinflammatory cytokines, IL-1β, IL-6, and tumor necrosis factor (TNF)-α in the hippocampus of the offspring [8]. Enhancement of proinflammatory cytokines in the offspring's hippocampus implies an adverse effect on prenatal stress responses.

Voluntary exercise can increase cell proliferation in dentate gyrus and improve object recognition memory in rodents [9]. Exercise is an interesting intervention to reverse prenatal stress-induced impairment of cognitive processes. Physical exercise induces an increase in cortisol, likewise, coping with stressors [10]. However, the therapeutic effect of exercise is obscured. Therefore, we hypothesized that postnatal voluntary wheel running exercise may ameliorate the adverse effects of prenatal stress. Consequently, we aimed to investigate whether exercise influences prenatal stress and alters the expression of synaptic plasticity proteins and learning and memory-related behavior in the rat offspring.

MATERIALS AND METHODS

Animals

Pregnant Sprague-Dawley (S.D.) rats (GD7) weighing 270–280 g and their offspring were used in this experiment. The rats were obtained from the National Experimental Animals Center of Mahidol University, Salaya, Thailand. This experimental procedure was approved by the Institute of Molecular Biosciences Animal Care and Use Committee (MB-ACUC), Mahidol University, Thailand (COA.NO.MB-ACUC 2010/003.1). The rats were housed individually in a single housing condition in a temperature and humidity-controlled environment and maintained on a 12-h light/dark cycle with free access to food and water. Each pregnant female was weighed on GD7–21 before any other manipulation. On GD21, each pregnant female received nesting materials, and the cage was checked twice daily for the appearance of rat pups. The day a rat pup was discovered was designated as P0, and the gestation length was noted. All experiments were conducted in accordance with the Guidelines for Care and Use of Laboratory Animals. Every effort was made to minimize the number of animals used and their suffering. The rat pups from control dams were assigned to the control (C) and the running (R) groups. In contrast, those from restraint stress dams were assigned to the repeated maternal restraint-induced prenatal stress (PS) group and the PS+R group, $n = 8$ for each group, for a total of 32.

Prenatal stress

Prenatal stress was induced by using maternal restraint stress in the pregnant rats. The pregnant rat was put into a small plexiglass cylindrical cage, in which the diameter and length could be adjusted to fit the size of each rat. The restraint stress was performed for 4 h per day at the same time during GD14–21 [11]. The control rats were left undisturbed in their home cages.

Voluntary wheel running exercise

Each rat pup was housed in a cage with a plastic running wheel after weaning on P21–24. The running wheels, 100 cm in circumference, were equipped with a recorder for the timing and rotation of the wheel. Wheel running activity, monitored for average duration (h) and average distance (Km) per 24 h period (per day), was extracted daily and then reset for the new recording at 10 a.m. Pups that ran less than 100 m were excluded. The running performances were recorded during P25–P40.

Morris water maze test

Spatial learning and memory were tested on P36–P40 using MWM. The MWM experiments were performed using a polypropylene circular pool (intentionally painted black, 150 cm diameter) filled with clear water. The water temperature was maintained at approximately 26 ± 1 °C. The pool was divided into four equal quadrants along two axes (North-South and East-West). Each quadrant was given a geometric shape as a hint. A circular platform (15 cm in diameter and 23 cm in height) was submerged under the water by approximately 2 cm and located in the middle of the southwest quadrant. A black curtain surrounded the pool to avoid any other external spatial cues apart from the maze. A digital camera was mounted on the ceiling above the pool. The camera was connected to a tracking program in a recording system within the computer (S-MART: PanLab Co., Barcelona, Spain). After 30 min of acclimation to the room, the rat was put into the water maze facing the tank wall. In our experiment, the MWM started with a visible platform trial on the first day (P36), followed by four days of hidden platform trials from P37–40. The probe trial was performed 1 h after the last session of the hidden platform trial on Day 4.

Visible platform trial

This trial was used to assess the animals' sensorimotor performances and motivation to escape from the water maze. The escape platform was placed in the target quadrant at 2 cm over the water surface to assess their sensorimotor performance and motivation. Animals were allowed to swim for 60 s per training time. If the animals could not find the visible platform within 60 s, they were guided and left on the platform for 20 s. Then, the animals were dried and put in a warm cage. The time spent finding the visible platform (escape latency) was recorded. The animals were trained four times on Day 1, and the average of those trials was used for further statistical calculation.

Hidden platform trail for acquisition test

The animals were trained consecutively for four days after the visible platform trial to investigate the spatial learning and memory, and 60 s probe trial was

performed on the fifth day. The escape platform was submerged 2 cm under the water surface in these trials. The trial lasted a maximum of 60 s. If the rats failed to reach the platform within a given time, it was placed on the platform for 20 s. The water was stirred from one trial to the next to erase the olfactory traces of the previous rat swimming patterns. The rats were placed in the pool with their noses facing directly to the wall in a random quadrant for four trials, and they were towel-dried each time a trial was done. The whole procedure lasted four consecutive days. The time spent finding the platform (escape latency) was analyzed.

Probe trial for the retention test

On the last day, 1 h after the last hidden platform trial was completed, the platform was removed from the pool for the retention test of the probe trial. The rats were given 60 s to search the arena. The time and distance the rat spent searching in the former platform quadrant versus the other three quadrants were recorded and measured for each rat.

Tissue preparation and Western blot analysis

The whole hippocampal tissues were removed from the rats at P40. Protein samples were prepared following the previous study [12]. The protein bands were then transferred to polyvinylidene difluoride (PVDF) membrane (Amersham Biosciences, Little Chalfont, UK). The membranes were incubated in a blocking buffer for 1 h at room temperature. After that, the membranes were incubated overnight at 4 °C with the following primary antibodies: a mouse monoclonal anti-NR2A (sc515148), a mouse monoclonal anti-NR2B (sc365597), a mouse monoclonal anti-PSD-95 (sc32290), and a mouse monoclonal anti-IL-6 (sc57315) (Santa Cruz Biotechnology, Dallas, TX, USA), a rabbit monoclonal anti-BDNF (ab108319) (Abcam, Cambridge, UK), and a mouse polyclonal anti-β-actin (AB3563) (Chemicon International, Temecula, CA, USA). The membranes were incubated with the appropriate HRP-conjugated secondary antibodies for 1 h at room temperature. The signals were visualized using an ECL reagent (Amersham Biosciences), and the immunoreactive bands were exposed using the Azure c400 Chemiluminescent Western Blot Imaging System™ (Azure Biosystems, Inc., Dublin, CA, USA). The immunoblot band densities were quantified using a densitometer with ImageJ software. The thickness of β-actin neutralized the density of each band density thickness as the internal control.

Data and statistical analysis

The results were expressed as mean ± SEM. The multiple t-test was performed to compare the VWR distance and duration data from R and PS+R groups. The statistical significance of the differences among the means of the four groups was evaluated using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparisons test. For assessment of the MWM, the data were evaluated using one-way ANOVA with repeated measures followed by Tukey's multiple comparisons test. The probability level of $p \leqslant 0.05$ was considered a statistically significant difference between the two sets of data. The data were statistically analyzed using GraphPad Prism software.

RESULTS

PS-induced increases in VWR distance and duration

The rats in R and PS+R groups were allowed to freely perform VWR. The distance and duration of running performances were recorded from P25 through P40. The sets of data from R and PS+R animals were statistically compared with multiple t-tests (Table S1). The VWR distance was significantly higher in the PS+R group than that of the R group on all test days. However, the VWR duration was significantly longer for the PS+R group than for the R group only on P25, 30, 34, 37, and 40.

The effect of PS on the expression of neuroplasticity-regulated proteins

PS has a long-term impact on the regulating proteins of the neuroplasticity process in the hippocampus. PS induced a dramatic decrease in the levels of BDNF (Fig. 1A), NR2A (Fig. 1B), and NR2B (Fig. 1C) in the hippocampus, compared with C group [BDNF: $F(3,16) = 33.7$, $p < 0.01$; NR2A: $F(3,16) = 6.31$, $p < 0.05$; NR2B: $F(3,16) = 31.9$, $p < 0.001$]. Changes in NMDAR expression, in turn, regulated its scaffolding protein, resulting in a decrease in PSD-95 (Fig. 2) in the PS group, compared with C group [$F(3,16) = 146$, $p < 0.01$].

The ameliorative effect of VWR on maternal restraint stress-induced downregulation of synaptic proteins

The effect of VWR on the expression level of BDNF and NMDAR was determined by Western blot analysis. The physical exercise during P25–40 significantly increased the expression level of BDNF (Fig. 1A) in the R group [$F(3,16) = 33.7$, $p < 0.001$], compared with the C group, but not NR2A (Fig. 1B) or NR2B (Fig. 1C) in the R group [NR2A: $p = 0.997$; NR2B: $p = 0.419$], compared with C group. Compared with the PS group alone, VWR induced a dramatic increase in BDNF (Fig. 1A), NR2A (Fig. 1B) and NR2B (Fig. 1C) [BDNF: $F(3,16) = 33.7$, $p < 0.001$; NR2A: $F(3,16) = 6.31$, $p < 0.05$; NR2B: $F(3,16) = 31.9$, $p < 0.001$]. Meanwhile, there was no significant difference [BDNF: $p = 0.149$; NR2A: $p = 0.885$; NR2B: $p = 0.401$], when compared with the C group.

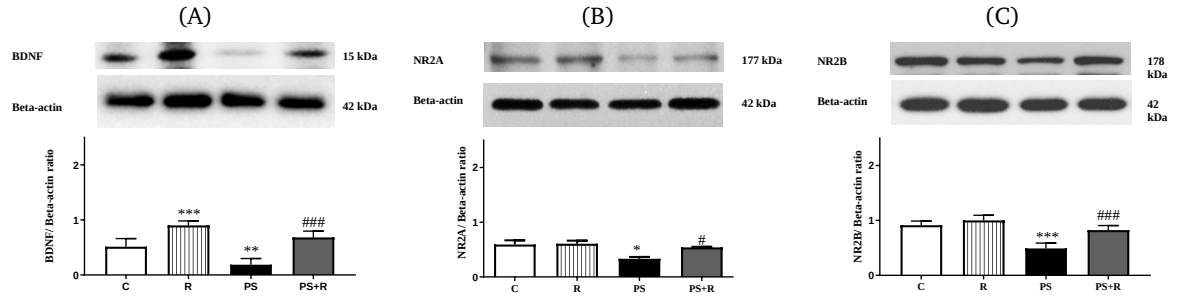

Fig. 1 Effects of PS on the expression of neuroplasticity-regulated proteins. (A) Upper panel: representative expression of BDNF; lower panel: relative levels of BDNF protein normalized to total β-actin. (B) Upper panel: representative expression of NR2A; lower panel: relative levels of NR2A protein normalized to total β-actin. (C) Upper panel: representative expression of NR2B; lower panel: relative levels of NR2B protein normalized to total β-actin. Data are expressed as mean ± SEM. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ compared with the C group; $^{\#}$ $p < 0.05$, $^{\#\#}$ $p < 0.01$, and $^{\#\#\#}$ $p < 0.001$ compared with the PS group.

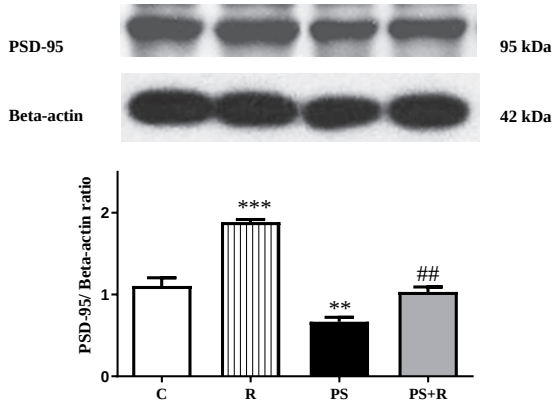

Fig. 2 Voluntary wheel running exercise ameliorating maternal restraint stress-induced downregulation of PSD-95 expression. Upper panel: representative expression of PSD-95; lower panel: relative levels of PSD-95 protein normalized to total β-actin. Data are expressed as mean ± SEM. ** $p < 0.01$ and *** $p < 0.001$ compared with the C group; $^{\#\#}$ $p < 0.01$ compared with the PS group.

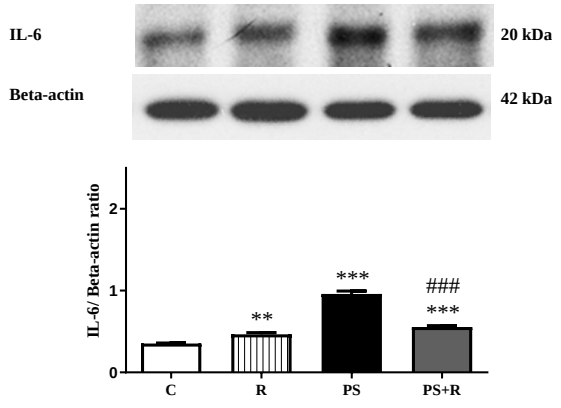

Fig. 3 Voluntary wheel running exercise ameliorating maternal restraint stress-induced downregulation of the expression of IL-6. Upper panel: representative expression of IL-6; lower panel: relative levels of IL-6 protein normalized to total β-actin. Data are expressed as mean ± SEM of three independent experiments. ** $p < 0.01$ and *** $p < 0.001$ compared with the C group; $^{\#\#\#}$ $p < 0.001$ compared with the PS group.

The ameliorative effect of VWR on maternal restraint stress-induced downregulation of NMDAR scaffolding protein, PSD-95

NMDAR is anchored on the surface membrane by PSD-95, the major postsynaptic density protein; the anchoring contributes to the protein complex associated with the postsynaptic membrane. The effect of VWR on PS-induced vulnerability of NMDAR is shown in Fig. 2. There is a significant increase in the level of PSD-95 in the R group [$F(3,16) = 59.9$, $p < 0.001$] compared with the C group and in the PS+R group [$F(3,16) = 59.9$, $p < 0.01$] compared with the PS group.

VWR-mediated amelioration of maternal restraint stress-induced upregulation of IL-6, a proinflammatory cytokine

Stress during neurodevelopment causes an alteration of the inflammatory cytokine, increasing its expression. The effects of PS on hippocampal IL-6 expression levels in rat offspring are presented in Fig. 3. PS induced a significant increase in the expression of IL-6 [$F(3,16) = 146$, $p < 0.001$] compared with the C group. The distinct roles in the efficacy of exercise have been shown by the significant increase in the level of IL-6 in the R group [$F(3,16) = 146$, $p < 0.01$] compared

with the C group. Meanwhile, a significant decrease in the IL-6 expression in the PS+R group was observed [$F(3,16) = 146$, $p < 0.001$] as compared with the PS group. Unexpectedly, the expression of IL-6 significantly increased in the PS+R group compared with the C group [$F(3,16)$, $p = 33.7$, $p < 0.001$].

The ameliorative effect of VWR on maternal restraint stress-induced spatial memory impairment

The ameliorative effect of VWR on spatial memory was ascertained by the MWM test, in which rats learned to move to a visible platform, then a hidden platform, and the probe trial. Firstly, we investigated the effect of prenatal stress on the latency time to find the hidden platform (escape latency) over five days of training. Our data showed significantly decreased mean escape latency for C, R, and PS+R groups on Day 5 [C: $F(4,28) = 5.58$, $p < 0.05$; R: $F(1.93,13.50) = 29.4$, $p < 0.001$; PS+R: $F(1.62,11.3) = 2.49$, $p < 0.05$] compared with Day 1 (Fig. 4A,B). Interestingly, our data showed that PS impaired spatial memory formation, as reflected by a significant increase in the escape latency [$F(3,12) = 61.8$, $p < 0.001$] as compared with the C group (Fig. 4B). Later on, VWR showed improved spatial memory, with a significant decrease in the escape latency of the R group [$F(3,12) = 61.8$, $p < 0.05$] compared with the C group, and a significant decrease in the escape latency of the PS+R group [$F(3,12) = 61.8$, $p < 0.001$] compared with the PS group (Fig. 4B). In addition, animals in R and PS+R groups spent significantly more time in the target quadrant than those in the C and PS groups, respectively [$F(2.07,14.5) = 74.2$, $p < 0.001$] (Fig. 4C).

DISCUSSION

The perturbation of stress during pregnancy has long-term effects on the offspring, distorting cognitive processes and causing neuropsychiatric disorders [13]. The stress hormone cortisol has been shown to induce the dismantling of NMDAR scaffolding proteins via NMDAR downstream signaling [5]. Here, our study shows decreases in NR2A, NR2B, and PSD-95 in PS rat models. NMDAR-PSD-95 interactions are bidirectional: NMDAR activation induces phosphorylation of PSD-95 at Ser-561 by microtubule affinity-regulating kinase (MARK)/partitioning-defective 1 (Par1) family of kinases [14], thereby strengthening its association with Spine-Associated RapGAP (SPAR) [15] protein and stabilizing the postsynaptic architecture. Conversely, PSD-95 regulates NMDAR clustering through PDZ-mediated binding to NR2A/NR2B subunits [16, 17]. Degradation of SPAR by the UPS destabilizes PSD-95 and reduces surface NMDAR expression [15, 17]. This suggests a bidirectional effect between NMDAR activity and PSD-95: an increased level of PSD-95 induces higher stability of NMDARs at the synaptic site, which in turn enhances learning and memory [15, 18, 19]. The PSD-95-enriched dendritic spine head indicates the maturation of synapses [19]. Both recruitment of PSD-95 on the dendritic spine and maintenance of neurons in the hippocampus were positively mediated by BDNF [20]. Furthermore, BDNF refines the postsynaptic activity of NMDAR [21]. Exercise has previously been shown to be an effective therapeutic intervention that improves memory function and hippocampal neurogenesis in young and adult rodents [22]. Moreover, postnatal exercise has been shown to reverse the adverse effects of neonatal stress by enhancing both spatial and recognition memory in rat pups [23]. In this experiment, postnatal VWR was performed throughout P25-P40. The semi-quantification of the protein expression level shows that exercise reversed both NR2A and NR2B downregulation (as a result of PS) back to their basal levels. In addition, exercise was able to reverse the effects of PS on spatial learning memory impairment. The shorter mean escape latency on Day 5 compared with Day 1 in the PS+R group indicates that exercise restored the animals' learning ability, which had been abolished in the PS group. Moreover, the PS+R group showed significantly more time spent in the target quadrant than that of the PS group. Physical exercise enhances the expression of BDNF, promoting hippocampal neurogenesis and memory function [9]. Postnatal exercise has been reported to alleviate hippocampal neuron apoptosis [24] and attenuate psychiatric problems and cognitive impairment related to enhancing hippocampal neurogenesis in prenatal stress rats [23]. Corresponding to our results, the elevations of BDNF and PSD-95 levels in the pup hippocampus have been induced by exercise, as shown in both the R and PS+R groups.

Several lines of evidence reported that neurodevelopmental and neurodegenerative disorders demonstrated an abnormal increase in the levels of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α, in the postmortem brain [25, 26]. Prolonged stress is an insult to the brain, which in turn interferes with immune balance [8]. Stress during pregnancy devastates both maternal immunity and fetal development. Here, our data elucidated an elevation of IL-6 expression in the PS group. Stress exposure during pregnancy enhances the maternal serum proinflammatory cytokines IL-6 and TNF-α in humans [27]. An elevated maternal serum IL-6 subsequently induces an increase in placental proinflammatory cytokines with downstream effects on fetal development and enhances IL-6 in the offspring [28, 29]. IL-6 can be released by both glial cells and neurons, which respond to injury and inflammatory processes. Consequently, we hypothesized that physical activity increased BDNF but decreased IL-6. We conducted the postnatal VWR as an intervention to reverse the adverse effects of maternal stress. Although our results show a reduction of IL-6 levels in the PS+R

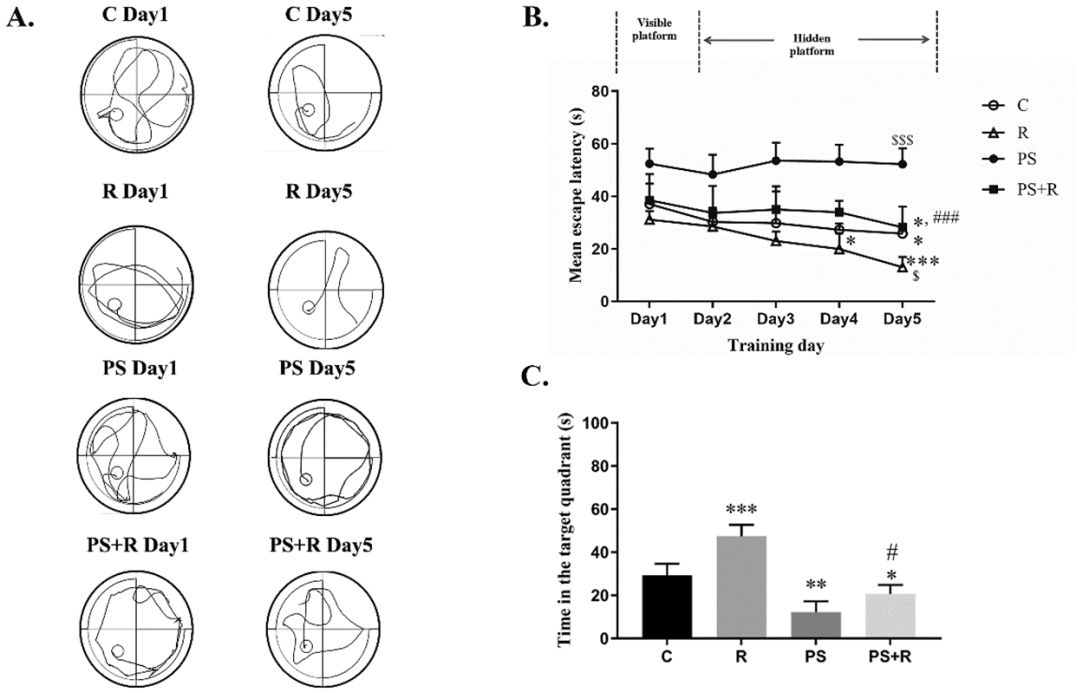

Fig. 4 The ameliorative effect of the wheel running exercise on spatial learning memory performance. (A) A representative sample of swim traces on Day 1 and Day 5. (B) Mean escape latency during the acquisition phase. Day 1 represents the visible platform trial, whereas Days 2–5 represent the hidden platform trials. Data are expressed as mean ± SEM. * $p < 0.05$ and *** $p < 0.001$ compared with Day 1; $^{\$}$ $p < 0.05$ and $^{\$\$\$}$ $p < 0.001$ compared with the C group; $^{\#\#\#}$ $p < 0.001$ compared with the PS group. (C) The time spent in the target quadrant during the probe trial. The behavioral test was performed in the morning of P36–P40. Data are expressed as mean ± SEM. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ compared with the C group; $^{\#}$ $p < 0.05$ compared with the PS group.

group compared to the PS group, it is still higher than that of the control group. The results show an increase in the level of IL-6 in the R group compared with the control group. A recent study highlighted that physical activity stimulates the release of myokines, including IL-6, which mobilize energy substrates during exercise [30]. Because IL-6 can cross the blood-brain barrier [31], it also mediates muscle-brain communication. Exercise-induced IL-6 has been shown to activate cAMP-response-element binding (CREB) signaling [32], which, in turn, enhances BDNF-TrkB pathways that regulate NMDAR trafficking and synaptic protein expression such as PSD-95 and synapsin-1. This mechanism provides a plausible link between exercise and the synaptic restoration observed in our study. Additionally, previous work has reported that strenuous exercise increases CSF IL-6 in rodents [33]. Although our freely accessible wheel-running model may not fully reflect strenuous exercise, the observed elevation in hippocampal IL-6 suggests that even moderate activity can modulate cytokine signaling relevant to synaptic plasticity. Also, the data show that the PS+R group has significantly greater running distance than the R group. The pleiotropic roles of IL-6 have been generated in the current study by playing roles of either pro- or anti-inflammatory cytokines. The distinct roles of IL-6 expression have been equivocal, whereas the IL-6 receptor complex and subsequent signaling might be the key regulators governing the switch in IL-6 function. The anti-inflammatory property of IL-6 is mediated by the so-called classic signaling through binding to the transmembrane complex of mIL-6R and glycoprotein (GP)130. Meanwhile, the binding of IL-6 to soluble IL-6R (sIL-6R) or trans-signaling is crucial for pro-inflammatory response. The IL-6/sIL-6R is selectively inhibited by sGP130 [34]. The number of sIL-6R and sGP130 are regulated by a disintegrin and metalloprotease (ADAM) family, which involves cellular processes, including inflammatory states. ADAM is shortly upregulated and followed by gradually declining in function over time, responsible for the insults [35]. Treadmill exercise improved cognitive functions and upregulated ADAM10 in the hippocampus of AD mouse model [36]. Increases in

plasma IL-6 concentration, sGP130 and sIL-6 during acute exercise stress [37] may imply an increase in ADAM activating-mediated shedding of the receptor from the surface membrane. Besides, the effect of sustained neuronal activation, including exercise, elevates a sympathetic tone to mobilize and use energy stored in the body. The expression of norepinephrine in repeated exercise induces a dramatic increase in cerebral IL-6 [38]. Owing to the most abundant level of IL-6 expression in astrocytes and microglia, the increase in IL-6 protein levels observed in our study is potentially of glial cell origin. This study is the first evidence to show a direct and isolated effect of physical exercise on hippocampal IL-6 protein expression, concomitantly associated with an increase in BDNF protein expression. IL-6 was shown to impair neurogenesis and reduce BDNF expression, which is thought to be involved in a pathophysiological process underlying several neurological disorders [39]. The process contradicts our findings that both IL-6 and BDNF protein levels increased due to exercise. A possible explanation is that physical exercise stimulates factors that are upstream in the signaling cascade and therefore are able to increase the expression levels of both molecules. The potential targets include norepinephrine, which is heavily secreted during exercise, and glutamate, which is important for neural plasticity within the hippocampus. Both norepinephrine and glutamate have been reported to regulate the expression of IL-6 and BDNF, albeit not all from glial cell origin [40]. Whether concomitant upregulation of IL-6 and BDNF is mediated via exercise-induced increases in norepinephrine or glutamate signaling remains an open and important question.

Running distances recorded in our experiment might be one of the important confounding factors contributing to the observed results, as the animals in the PS+R group ran significantly greater distances than those in the R group. However, the effect of prenatal stress on hippocampal BDNF, NR2A, NR2B, PSD-95, and IL-6 protein levels is more pronounced than that of exercise. Even though PS+R animals ran significantly greater distances than R animals, their protein levels do not fully compensate for prenatal stress. A similar observation can also be made regarding the behavioral results. These results suggest that even though exercise might be effective at attenuating adverse effects from prenatal stress, prevention of prenatal maternal stress would be a better approach for generating better cognitive ability in the offspring.

CONCLUSION

Overall, our results support the notion that stress during late gestation has a long-term effect on the offspring's later life. The offspring hippocampus is a target brain region vulnerable to maternal stress hormones. PS induces dramatic decreases in BDNF and NMDAR, which decrease PSD-95. The neurohormonal-immune system has a solid, determining relationship with the structure and function of the offspring hippocampus. We have shown the ameliorative effects of postnatal VWR on reversing the damaging effects of maternal stress on the offspring, concurrently supporting the importance of preventing prenatal maternal stress and its detrimental effects on cognitive functions in the offspring. The distinctive roles of IL-6 in response to PS- and postnatal exercise-induced stress hormones have been demonstrated in this study. The duration and intensity of exercise may switch the role of IL-6, and subsequent signaling is beneficial to the offspring. Interestingly, postnatal VWR promotes a more helpful role for IL-6 to protect the hippocampus of the rat offspring. The impact of sustained neuronal activations may further our understanding of the role that postnatal exercise plays in regulating IL-6 and ADAM-mediated shedding receptors plays in learning and memory.

Appendix A. Supplementary data

Supplementary data associated with this article can be found at https://dx.doi.org/10.2306/scienceasia1513-1874.2026.017.

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Appendix A. Supplementary data

Table S1 The VWR distance and duration of the R and PS+R groups.

Age	Distance (Km)			Duration (h)		
	R	PS+R	*p*-value	R	PS+R	*p*-value
P25	6.06 ± 1.58	19.28 ± 3.95	0.011*	1.86 ± 0.21	3.34 ± 0.61	0.044*
P26	5.66 ± 1.12	15.11 ± 2.36	0.005**	1.92 ± 0.30	2.57 ± 0.60	0.347
P27	4.63 ± 1.20	12.54 ± 2.16	0.010*	1.53 ± 0.29	2.00 ± 0.47	0.417
P28	5.87 ± 1.36	17.34 ± 4.70	0.041*	1.74 ± 0.20	2.49 ± 0.43	0.143
P29	6.51 ± 1.74	26.24 ± 10.61	0.046*	1.79 ± 0.21	3.08 ± 0.56	0.055
P30	4.61 ± 1.25	25.71 ± 7.24	0.017*	1.26 ± 0.38	3.19 ± 0.57	0.018*
P31	5.43 ± 1.26	22.54 ± 6.63	0.030*	1.48 ± 0.35	2.88 ± 0.57	0.062
P32	4.51 ± 0.82	19.28 ± 3.79	0.003**	1.32 ± 0.28	2.99 ± 0.86	0.095
P33	4.42 ± 1.49	24.43 ± 3.81	<0.001***	1.17 ± 0.51	3.21 ± 0.78	0.054
P34	3.32 ± 0.40	20.94 ± 2.44	<0.001***	0.83 ± 0.24	2.93 ± 0.61	0.010*
P35	5.47 ± 1.03	21.92 ± 4.81	0.007**	1.61 ± 0.40	2.80 ± 0.49	0.089
P36	5.27 ± 0.77	18.35 ± 4.44	0.016*	1.35 ± 0.25	2.43 ± 0.69	0.173
P37	4.43 ± 0.79	25.85 ± 7.12	0.014*	1.08 ± 0.27	3.64 ± 1.10	0.047*
P38	5.27 ± 0.96	29.15 ± 9.98	0.039*	1.28 ± 0.28	3.42 ± 1.11	0.092
P39	7.80 ± 1.91	21.83 ± 4.02	0.010*	2.17 ± 0.45	2.81 ± 0.53	0.377
P40	5.25 ± 0.85	23.93 ± 5.15	0.011*	1.49 ± 0.21	3.30 ± 0.84	0.044*

Data are expressed as mean ± SEM. Multiple *t*-tests were performed to compare the data from the R and PS+R groups with * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.