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Enriched environment treatment restores impaired hippocampal synaptic plasticity and cognitive deficits induced by prenatal chronic stress

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Abstract

Prenatal stress can cause long-term effects on cognitive functions in offspring. Hippocampal synaptic plasticity, believed to be the mechanism underlying certain types of learning and memory, and known to be sensitive to behavioral stress, can be changed by prenatal stress. Whether enriched environment treatment (EE) in early postnatal periods can cause a recovery from these deficits is unknown. Experimental animals were Wistar rats. Prenatal stress was evoked by 10 foot shocks (0.8 mA for 1 s, 2–3 min apart) in 30 min per day at gestational day 13–19. After weaning at postnatal day 22, experimental offspring were given the enriched environment treatment through all experiments until tested (older than 52 days age). Electrophysiological and Morris water maze testing was performed at 8 weeks of age. The results showed that prenatal stress impaired long-term potentiation (LTP) but facilitated long-term depression (LTD) in the hippocampal CA1 region in the slices. Furthermore, prenatal stress exacerbated the effects of acute stress on hippocampal LTP and LTD, and also impaired spatial learning and memory in the Morris water maze. However, all these deficits induced by prenatal stress were recovered by enriched environment treatment. This work observes a phenomenon that may contribute to the understanding of clinically important interactions among cognitive deficit, prenatal stress and enriched environment treatment. Enriched environment treatment on early postnatal periods may be one potentially important target for therapeutic interventions in preventing the prenatal stress-induced cognitive disorders.

Keywords: Prenatal stress; Enriched environment treatment; Long-term potentiation; Long-term depression; Learning and memory

1. Introduction

Prenatal stress during human fetal brain development causes profound neurobiological effects on postnatal development, which lead to cognitive deficits and increasing susceptibility to affective disorders in children and adolescents (Wadhwa, 2005; Weinstock, 2001). Animal studies have shown that prenatal stressed offspring display hyperactivity (Louvart, Maccari, & Darnaudery, 2005; Yang, Han, Cao, Li, & Xu, 2006) and a higher behavioral emotionality in stressful conditions such as high levels of anxiety (Lordi, Patin, Protais, Mellier, & Caston, 2000) and depressive-like behavior (Morley-Fletcher et al., 2003a; Secoli & Teixeira, 1998). Studies show that prenatal stress elicits neuroendocrinological changes following acute exposure to variety stress in the adult offspring, such as prolonged elevation in plasma glucocorticoid levels (Koenig et al., 2005; Maccari et al., 2003), increased plasma noradrenaline levels

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(Weinstock, Poltyrev, Schorer-Apelbaum, Men, & McCarty, 1998) as well as increased acetylcholine release in the hippocampus (Day, Koehl, Deroche, Moal, & Maccari, 1998). Moreover, prenatal stress alters pre- and postsynaptic gene expression (Kinnunen, Koenig, & Bilbe, 2003), decreases synaptic density of the hippocampus in offspring (Hayashi et al., 1998). In addition, prenatal stress decreases the number of granule neurons, induces a marked absence of hippocampal neurogenesis (Lemaire, Koehl, Moal, & Abrous, 2000), reduces the density of nitric-oxide producing neurons in the dentate and part of the hippocampus in offspring (Vaid et al., 1997). Furthermore, prenatal stress alters synaptic plasticity responsivity in hippocampal CA1 region and exacerbates the effects of acute stress on synaptic efficacy in young rat offspring (Yang et al., 2006).

Environmental enrichment (EE) is defined as a combination of "complex inanimate objects and social stimulation" (Van Praag, Kempermann, & Gage, 2000). Studies demonstrate that enriched environment treatment counteracts cognitive deficits induced by early life stress in animals (Guilarte, Toscano, McGlothan, & Weaver, 2003; Hellemans, Benge, & Olmstead, 2004), rescues abnormal behaviors such as emotional reactivity, motor skills and spatial learning induced by prenatal stress (Chapillon, Patin, Roy, Vincent, & Caston, 2002). High anxiety-like behavior induced by prenatal stress, exhibit an escape behavior to novelty correlated with high secretion of corticosterone in response to stress, can be reversed by postnatal enriched environment treatment (Koehl et al., 2002; Morley-Fletcher, Rea, Maccari, & Laviola, 2003b). Furthermore, enriched environment treatment in the early postnatal stage counteracts prenatal stress-induced deficits in hippocampal neurogenesis (Lemaire, Lamarque, Moal, Piazza, & Abrous, 2006).

Hippocampal synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD) is believed to be the mechanisms underlying certain types of learning and memory (Bliss & Collingridge, 1993). Evidences suggest that behavior stress impairs spatial learning and memory in the Morris water maze (de Quervain, Roozendaal, & McGaugh, 1998), Consistent with this notion, behavior stress impairs LTP (Foy, Stanton, Levine, & Thompson, 1987; Diamond, Fleshner, Ingersoll, & Rose, 1996; Shors, Seib, Levine, & Thompson, 1989) but facilitates LTD (Kim, Foy, & Thompson, 1996; Xu, Anwyl, & Rowan, 1997) in the hippocampus.

Environmental enrichment treatment has been demonstrated enhancing LTP in the hippocampus and improving spatial learning performance (Duffy, Craddock, Abel, & Nguyen, 2001; Leggio et al., 2005). Our previous study shows that prenatal stress impairs LTP but facilitates LTD of hippocampal CA1 region in slices, as well as impairs spatial learning and memory in young rat offspring (Yang et al., 2006). We now asked the questions whether an enriched environment treatment can counteract those long-term disruptive effects on hippocampal synaptic plasticity and impairment of spatial learning and memory by prenatal stress in adult rat offspring.

2. Materials and methods

2.1. Animals

Pregnant female rats of the Wistar strain (purchased from Animal House Center, Kunming General Hospital, Kunming), weighing 200–250 g, were used in the experiments. All animals had free access to water and standard animal food, with a 12 h light/dark cycle (lights on between 8:00 and 20:00 h) and a thermoregulated environment (20 °C). The animal care and experimental protocol were approved by The Chinese Academy of Sciences.

2.2. Prenatal chronic stress procedure

Prenatal chronic stress protocol was, as previous study (Yang et al., 2006), performed each day from pregnancy day 13 to 19 lasted one week. At pregnancy day 13, pregnant female rats were randomly divided into two groups: control and prenatal stressed group. Prenatal stress was evoked in a Skinner box by 10 foot shocks (0.8 mA for 1 s, 2–3 min apart) in 30 min per day. Pregnant dams assigned to the control group were left undisturbed until delivery. After birth, offspring of each group were fostered by their respectively mothers.

2.3. Enriched environmental conditioning

After weaning at postnatal day 22, half of the prenatal stressed male offspring were housed in the standard cages (PS), and the other half male offspring were housed in the environmental enrichment conditioning (PS/EE). The control male offspring resided in standard cages (Ctrl). Each group was housed under those respectively conditions through all experiments until tested (older than 52 days of age). All experimental offspring were reared in the same room with free access to water and food. Control offspring and PS but none EE treatment offspring were housed in standard cages ($60 \times 40 \times 25$ cm). And the EE treatment offspring were housed in the large cages ($60 \times 50 \times 70$ cm), with one extra level constructed of galvanized wire mesh and connected by ramps of the same material to create two interconnected levels. The EE cages contained wood shavings, a running wheel, a shelter, plastic color toys and small constructions such as chain, swing and tunnels. Throughout the enrichment period (P22–P52), the shelter and running wheel were kept in the cages, while the toys and constructions were changed once a week. Also once a week, the feeding boxes and water bottles were moved to different cage points to encourage foraging and explorative behaviors.

2.4. Offspring acute stress procedure

Offspring acute stress was performed at 8 weeks of age. The procedure was one trains foot shock, i.e., 10 foot shocks (1 mA for 1 s, 30–90 s apart) in 10 min. Promptly after stress, animals were killed under anesthesia for electrophysiological tests.

2.5. Preparations of hippocampal slice and electrophysiological test

At 8 weeks of age, animals were killed, and 400-μm-thick hippocampal slices were prepared using standard procedures (Yang et al., 2006). After a minimum recovery period of 1 h, the slices were transferred to a submersion-type recording chamber and were continually perfused with 30–32 °C of an oxygenated artificial CSF solution comprising the following (in mM): 117 NaCl, 4.7 KCl, 2.5 $CaCl_2$, 1.2 $MgCl_2$, 25 $NaHCO_3$, 1.2 NaH_2PO_4, and 11 glucose. Extracellular recordings were performed with Axoclamp-2B amplifier (Axon Instruments, Union City, CA). Stimulating electrodes were made by gluing together a pair of twisted Teflon-coated 90% platinum and 10% iridium wires (50 μm inner diameter, 75 μm outer diameter; World Precision Instruments, Sarasota, FL). Recording electrode was a glass pipette, pulled from borosilicate glass tubing (1.5 mm outer diameter, 0.84 mm inner diameter) (World Precision Instruments, USA) with a Brown Flaming micropipette puller (P-87, Sutter Instruments

Company, USA), filled with 3 M NaCl (2–3 MΩ resistance). Postsynaptic responses were induced in CA1 stratum radiatum by stimulation of Schaffer collateral–commissural afferents. Test fEPSP was evoked at a frequency of 0.033 Hz and at a stimulation intensity adjusted to give a fEPSP amplitude of 50% maximum response. LTD was induced by low-frequency stimulation (LFS, 900 pulses, 1 Hz) and LTP was induced by high-frequency stimulation (HFS, 10 trains of stimulus with 20 pulses at 200 Hz, with 2 s inter-train intervals), with the same stimulation intensity used for baseline recordings.

2.6. Morris water maze test

Morris water maze is a model widely used for studying learning and memory in rats (Morris, Anderson, Lynch, & Baudry, 1986). It was consisted of a circular pool (250 cm diameter, 60 cm deep at the side) filled with water at 25 ± 1 °C to a depth of 20 cm, covering the surface with floating black resin beads. Yellow curtains were drawn around the pool (50 cm from the pool periphery) and contained distinctive visual marks as cues, which allowed rats to learn associate the location of the hidden platform to visual cues. The water maze was divided into four imaginary quadrants. A submerged Perspex platform (13 cm × 13 cm) (2 cm below water surface) was placed in the middle of one quadrant for all training trials. The training and testing procedures were similar as those described previously (Yang et al., 2006). Tests were performed at 8 weeks of age. Before training day, a 120 s free swim trial was run in which the platform was removed. Training consisted of 6 trials per day with inter-trial intervals of 20–40 min for consecutive 4 days and the retrieval test of memory was examined on day 5. The hidden platform was fixed during training day and removed during testing day. Starting positions were randomly rotated in different quadrants and the animals always faced the wall when were placed into the maze. Animals were allowed to swim until found the hidden platform and stayed there for 30 s before picked up. The animals that had failed to find the hidden platform in 120 s were guided to it. Swimming paths for trainings and retrieval tests were monitored by using an automatic tracking system.

2.7. Data analysis

LTD or LTP was measured 30–40 min after LFS or HFS and reported as mean ± S.E.M. of baseline fEPSPs amplitude (n is the number of slices or the rats in behavior studies). Student's paired t-test or ANOVA (SPSS 10.0) was used to analysis the results of electrophysiological and behavior studies. The significance level was set at $p < .05$.

3. Results

3.1. Enriched environment treatment recovered synaptic plasticity changes induced by prenatal stress

We examined the effects of prenatal stress and enriched environment treatment on LTP and LTD in hippocampal CA1 region in slices. There was no significant difference in basal synaptic transmission among groups, because the input/output curves had no significant difference among groups. The results showed that prenatal stress significantly impaired hippocampal LTP, but enriched environment treatment recovered these changes to control levels (Ctrl: $n = 7$, 1.30 ± 0.026; PS: $n = 9$, 1.16 ± 0.027; PS/EE: $n = 7$, 1.34 ± 0.031; $F_{(2,20)} = 20.472$, $p < .01$. Ctrl vs PS/EE $p > .05$; Ctrl vs PS $p < .01$; PS/EE vs PS $p < .01$) (Fig. 1a). Conversely, prenatal stress significantly facilitated hippocampal LTD but enriched environment treatment recovered these changes to control levels (Ctrl: $n = 8$, 0.89 ± 0.052; PS: $n = 7$, 0.75 ± 0.028; PS/EE: $n = 8$, 0.88 ± 0.055; $F_{(2,20)} = 10.762$, $p < .01$. Ctrl vs PS/EE $p > .05$; Ctrl vs PS $p < .01$; PS/EE vs PS $p < .01$) (Fig. 1b).

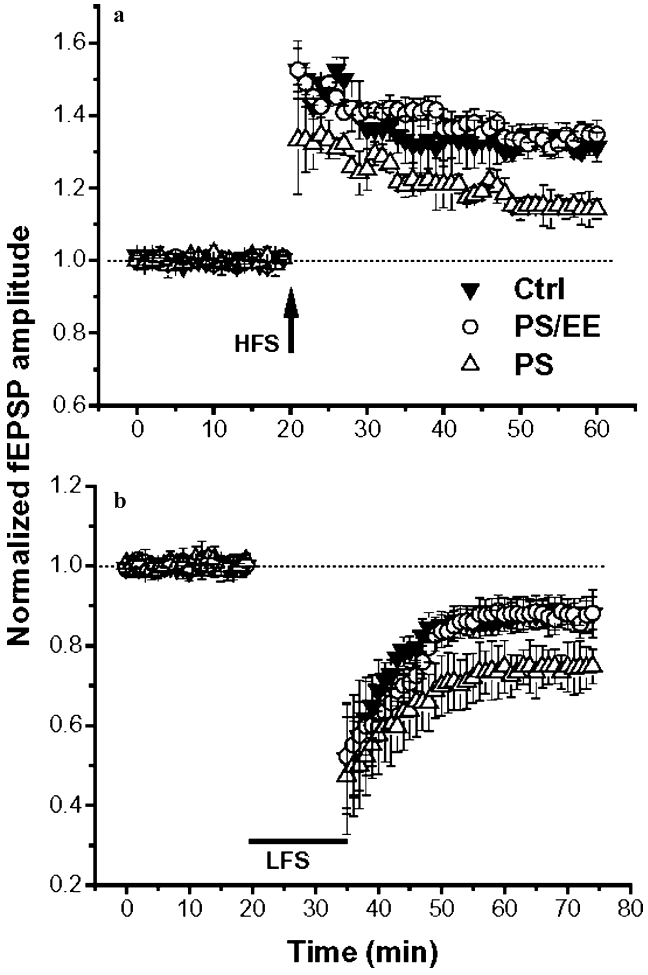

Fig. 1. Enriched environment treatment counteracted prenatal stress impaired LTP and facilitated LTD in the hippocampal CA1 region in slices of the adult rat offspring. (a) Prenatal stress (PS) impaired LTP by high-frequency stimulation (HFS, arrow, 200 Hz) compared with control (Ctrl), but these changes were reversed in enriched environment treated offspring (PS/EE). (b) Prenatal stress enabled low-frequency stimulation (LFS, bar, 1 Hz) to induce a robust LTD (PS) compared with control (Ctrl) and these impacts disappeared in enriched environment treated offspring (PS/EE).

3.2. Enriched environment treatment counteracted the altered synaptic plasticity reactivity to acute stress by prenatal stress

Previous study demonstrates that prenatal stress alters the response to acute stress in rat offspring (Louvart et al., 2005). Then, we further examined LTP and LTD in adult rat offspring that were exposed to foot shock immediately before slices preparation. We found that acute stress (Str) further suppressed LTP in prenatal stressed offspring compared with that of control offspring when both groups exposed to the same acute stress, but enriched environment treatment counteracted the exacerbated impairment of acute stress on LTP by prenatal stress (Ctrl/Str: $n = 8$, 1.13 ± 0.054; PS/Str: $n = 9$, 1.04 ± 0.046; PS/Str/EE: $n = 8$, 1.12 ± 0.05; $F_{(2,22)} = 9.838$,

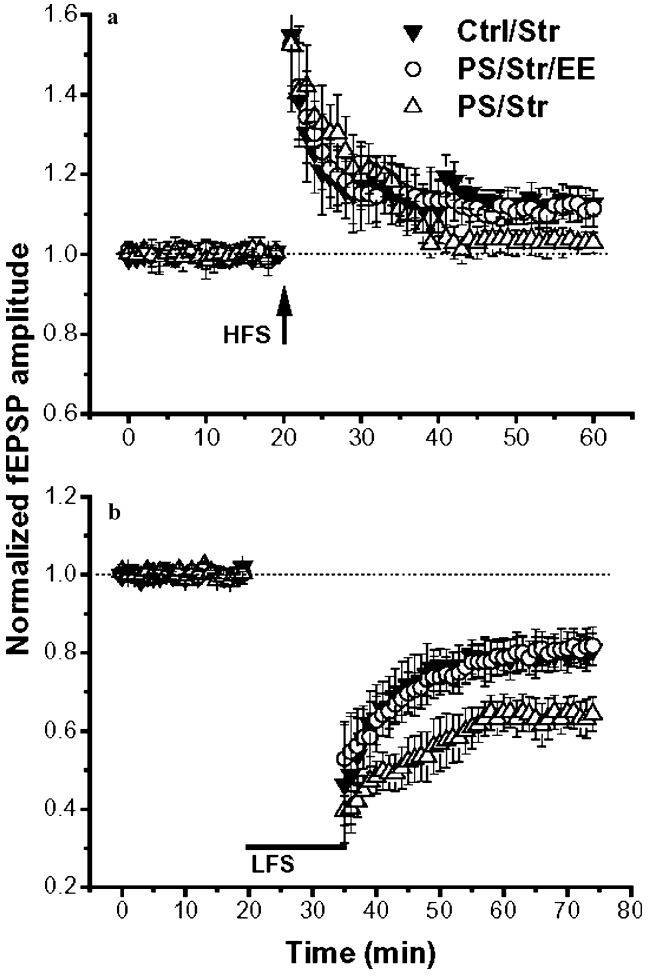

Fig. 2. Enriched environment treatment prevented prenatal stress exacerbated the effects of acute stress on LTP and LTD in hippocampal CA1 region in adult rat offspring. (a) Prenatal stress enabled acute stress to further suppress LTP (PS/Str) compared with that of control offspring exposed to the same acute stress (Ctrl/Str), but these changes were restored in enriched environment treated offspring (PS/Str/EE). (b) Prenatal stress enabled acute stress to further facilitate LTD (PS/Str) compared with that of control offspring exposed to the same acute stress (Ctrl/Str) and these deficits were counteracted in enriched environment treated offspring (PS/Str/EE).

$p<.01$. Ctrl/Str vs PS/Str/EE, $p>.05$; Ctrl/Str vs PS/Str, $p<.01$; PS/Str/EE vs PS/Str, $p<.01$) (Fig. 2a). Conversely, acute stress further facilitated LTD in prenatal stressed offspring compared with that of control offspring exposed to the same acute stress, but enriched environment treatment counteracted prenatal stress promoted facilitation of acute stress on LTD (Ctrl/Str: $n=8$, 0.79 ± 0.044; PS/Str: $n=7$, 0.65 ± 0.045; PS/Str/EE: $n=8$, 0.81 ± 0.052; $F_{(2,22)}=8.444$, $p<.01$. Ctrl/Str vs PS/Str/EE, $p>.05$; Ctrl/Str vs PS/Str, $p<.01$; PS/Str/EE vs PS/Str, $p<.01$) (Fig. 2b).

3.3. Enriched environment treatment rescued the learning and memory impairment caused by prenatal stress

Then, we compared the effects of prenatal stress and enriched environment treatment on spatial learning and memory in the Morris water maze. We found that prenatal stress impaired the spatial learning task, as indicated by longer latencies to escape onto a hidden platform during training day 3–4 (3rd day: Ctrl $n=11$, 30.29 ± 7.16 s; PS $n=10$, 43.77 ± 4.4 s, $F_{(2,28)}=21.230$, $p<.01$, Ctrl vs PS. 4th day: Ctrl 25.93 ± 6.0 s, PS 37.76 ± 5.3 s, $F_{(2,28)}=12.794$, $p<.01$, Ctrl vs PS) (Fig. 3a), but enriched environment treatment rescued prenatal stress induced the changes to control levels (3rd day: PS/EE $n=10$, 28.7 ± 5.1 s; Ctrl vs PS/EE $p>.05$; PS/EE vs PS $p<.01$. 4th day: PS/EE 23.87 ± 6.16 s; Ctrl vs PS/EE, $p>.05$; PS/EE vs PS, $p<.01$) (Fig. 3a). Meanwhile, the prenatal stressed offspring showed higher thigmotaxis in water maze especially on the first 2 training days (1st day: Ctrl $39.75\pm6.34\%$, PS $61.52\pm4.91\%$, $F_{(2,28)}=16.887$, $p<.01$,Ctrl vs PS. 2nd day: Ctrl $25.74\pm5.04\%$, PS $48.25\pm4.15\%$, $F_{(2,28)}=7.851$, $p<.01$,Ctrl vs PS) (Fig. 3b), but enriched environment treatment rescued prenatal stress induced the changes to control levels (1st day: PS/EE $43.28\pm5.04\%$; Ctrl vs PS/EE, $p>.05$; PS/EE vs PS, $p<.01$. 2nd day: PS/EE $29.64\pm4.91\%$; Ctrl vs PS/EE $p>.05$; PS/EE vs PS $p<.01$) (Fig. 3b).

Twenty-four hours after the training, retention tests revealed that prenatal stress impaired the retrieval of spatial memory, as indicated by longer latencies in the first time to cross the location where the platform had been placed but enriched environment treatment restored these changes to control levels (Ctrl 15.32 ± 5.59 s, PS 31.78 ± 5.39 s, PS/EE 16.83 ± 5.24 s; $F_{(2,28)}=6.286$, $p<.01$. Ctrl vs PS/EE, $p>.05$; Ctrl vs PS, $p<.01$; PS/EE vs PS, $p<.01$) (Fig. 3c). And prenatal stressed offspring displayed fewer crossing times in the platform location but enriched environment treatment restored these changes to control levels (Ctrl 5.08 ± 0.58, PS 3.2 ± 0.53, PS/EE 5.2 ± 0.42; $F_{(2,28)}=4.594$, $p<.05$. Ctrl vs PS/EE $p>.05$; Ctrl vs PS $p<.05$; PS/EE vs PS $p<.05$) (Fig. 3d).

Our recent report has shown that EE experience on postnatal days 22–52 has no effect on spatial learning and memory in control rats (Cui et al., 2006). In this study, the effects of prenatal stress and/or EE experience on spatial learning and memory were not due to the changes in motor activity because the swim speed was not different among groups ($F_{(2,28)}=0.508$, $p>.05$).

4. Discussion

Stressors presented during the late prenatal and early postnatal periods can have long-term effects on offspring's behavior, because those are the sensitive periods when the formation of brain circuitry associating with early development happens. In this report, we demonstrated that chronic prenatal stress impaired LTP and facilitated LTD in the hippocampus of offspring. Furthermore, prenatal stress altered synaptic plasticity reactivity to acute stress and impaired learning and memory in adult offspring. Conversely, in early postnatal periods, enriched environment treatment counteracted these abnormal alterations induced by prenatal stress.

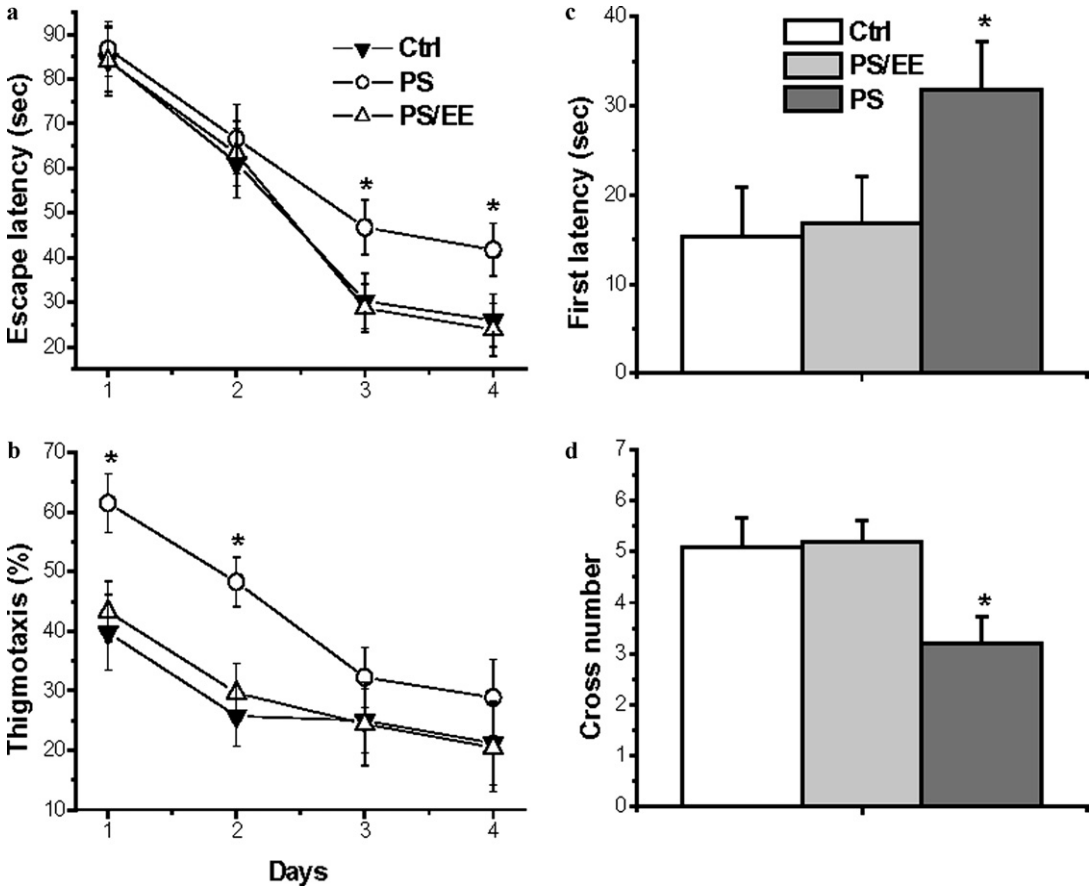

Fig. 3. Enriched environment treatment restored the deficit of spatial learning and memory induced by prenatal stress in the Morris water maze of adult rat offspring. (a) Prenatal stress caused the offspring (PS) to show longer escape latencies than those of control (Ctrl) in escape onto a hidden platform on training day 3–4, but these changes were reversed in enriched environment treated offspring (PS/EE). (b) Prenatal stress caused the offspring (PS) to show higher thigmotaxis than those of control (Ctrl) in the water maze on training day 1–2, but these changes were reversed in enriched environment treated offspring (PS/EE). (c) Prenatal stressed offspring (PS) showed a longer latency in the first time of crossing the location of platform compared with control (Ctrl), but these changes were restored to control levels in enriched environment treated offspring (PS/EE). (d) Prenatal stressed offspring (PS) crossed the location of platform fewer times than control (Ctrl), but enriched environment treatment (PS/EE) reversed these changes to control levels. ($^{*}p < 0.05$). Error bars represent SEM.

Stressful stimuli during pregnancy induce complex effects that influence the development of offspring. Animal studies have shown that prenatal stressed offspring display hyperactivity (Louvart et al., 2005; Yang et al., 2006), and exhibit the high levels of anxiety (Lordi et al., 2000) and depressive-like alterations (Morley-Fletcher et al., 2003a; Secoli & Teixeira, 1998). In offspring, prenatal stress also alters pre- and postsynaptic gene expression (Kinnunen et al., 2003), decreases synaptic density in the hippocampus (Hayashi et al., 1998), reduces the number of granule neurons and hippocampal neurogenesis (Lemaire et al., 2000), and decreases the density of nitric-oxide producing neurons in the dentate and part of the hippocampus (Vaid et al., 1997). Moreover, prenatal stress enhances synaptic plasticity responsiveness in hippocampus CA1 region and exacerbates effects of acute stress on synaptic efficacy of young offspring (Yang et al., 2006). Human studies show that prenatal stress causes profound neurobiological effects on postnatal development, which lead to cognitive deficits and increasing susceptibility to affective disorders in children and adolescents (Weinstock, 2001; Wadhwa, 2005). Consistent with these studies, our results demonstrated that prenatal stress impaired LTP but facilitated LTD in hippocampal CA1 region in slices of offspring. Furthermore, prenatal stress exacerbated the effects of acute stress on the hippocampal LTP and LTD and impaired spatial learning and memory in the Morris water maze in the adult offspring.

Many studies demonstrate that enriched environment treatment can counteract cognitive deficits induced by early life stress in animals (Guilarte et al., 2003; Hellemans et al., 2004), rescue abnormal behaviors such as emotional reactivity, motor skills and spatial learning induced by prenatal stress (Chapillon et al., 2002). High anxiety-like behavior induced by prenatal stress, such as escape behavior to novelty with high secretion of corticosterone in response to stress, can be reversed by postnatal enriched environment treatment (Koehl et al., 2002; Morley-Fletcher et al., 2003b). Furthermore, prenatal stress reduces hippocampal cell proliferation all throughout life and the survival rate of newborn cells. The number of immature neurons and differentiated new neurons are also reduced in young and old

prenatal stressed rats. However, all of above mentioned deleterious effects can be counteracted by enriched housing conditioning (Lemaire et al., 2006). Consistent with these studies, our results showed that enriched environment treatment recovered impairments caused by prenatal stress. These impairments include synaptic plasticity alterations of hippocampal CA1, exacerbated effects of acute stress on the hippocampal LTP and LTD, and impaired spatial learning and memory in the Morris water maze in adult offspring.

The mechanisms underling the changes of LTP and LTD from prenatal stress in the hippocampus in adult offspring remain to be determined. One possibility might be the neuroendocrine changes caused by prenatal stress, such as the prolonged elevation in plasma glucocorticoid (Maccari et al., 2003) and noradrenalin levels (Weinstock et al., 1998), and increased acetylcholine release in the hippocampus (Day et al., 1998), because these changes can either impair LTP or facilitate LTD in the hippocampus. Furthermore, prenatal stress alters hippocampal pre- and postsynaptic gene expression, such as decreased postsynaptic density complexes (Hayashi et al., 1998) and reduced vesicle exocytosis machinery including NMDA receptor NR1 and NR2A subunits, densin-180, guanylate kinase-associated protein, synaptosome-associated protein and vesicle-associated membrane protein 2 (Kinnunen et al., 2003). All these alterations might contribute to the induction of hippocampal LTP and LTD and the impairment of spatial learning and memory. Recent reports demonstrate that NR2A- and NR2B-containing NMDA receptor govern the direction of hippocampal synaptic plasticity (Liu et al., 2004) and the behavior stress-facilitated hippocampal LTD can be prevented by the NR2B-containing NMDA receptor antagonist (Yang, Huang, & Hsu, 2005). Therefore, it is possible that prenatal stress may cause long-term effects on the expression or function of NR2A- and NR2B-containing NMDA receptors in the hippocampus, leading to the impaired LTP and facilitated LTD in adult offspring.

Conversely, enriched environment treatment counteracts prenatal stress-induced deficits in hippocampal neurogenesis (Lemaire et al., 2006), cell proliferation, and synaptic protein expression (Koo et al., 2003), increase the expression of nerve growth factors and neurotransmitter receptors (Duffy et al., 2001; Leggio et al., 2005; Rampon et al., 2000). Moreover, enriched environment treatment reverses the effects of prenatal stress on HPA axis reactivity in rats (Morley-Fletcher et al., 2003b). All these effects of enriched environment treatment in early postnatal period may reverse the hippocampal plasticity deficits and therefore restore prenatal stress impaired spatial learning and memory in adult offspring.

In conclusion, this work observed a phenomenon that might contribute to the understanding of clinically important interactions among cognitive deficit, prenatal stress and enriched environment treatment. Enriched environment treatment on early postnatal periods might be an important therapeutic intervention in preventing the prenatal stress-induced cognitive disorders.

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