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The stress experience dependent long-term depression disassociated with stress effect on spatial memory task

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Abstract

Behavioral stress can either block or facilitate memory and affect the induction of long-term potentiation (LTP) and long-term depression (LTD). However, the relevance of the stress experience-dependent long-term depression (SLTD) to spatial memory task is unknown. Here we have investigated the effects of acute and sub-acute elevated platform (EP) and foot shock (FS) stress on LTD induction in CA1 region of the hippocampus of anesthetized rats and spatial memory in Morris water maze. We found that LTD was facilitated by acute EP stress, but not by sub-acute EP stress that may be due to the fast adaptation of the animals to this naturalistic mild stress. However, FS stress, an inadaptable strong stress, facilitated LTD induction both in acute and sub-acute treatment. In addition, with the same stress protocols, acute EP stress impaired spatial memory but the sub-acute EP stressed animals performed the spatial memory task as well as the controls, may due to the same reason of adaptation. However, acute FS stress slightly impaired learning but sub-acute FS even enhanced memory retrieval. Our results showed that SLTD was disassociated with the effect of stress on memory task but might be related to stress experience-dependent form of aberrant memory.

Keywords: Long-term depression; Stress; Water maze; Synaptic plasticity; Memory; Hippocampus; Stress experience

1. Introduction

Recent development documented that activity-dependent persistent increases in synaptic efficacy, such as long-term potentiation (LTP), is inhibited by behavioral stress or stress levels of corticosterone (Bodnoff et al., 1995; Diamond et al., 1992, 1994; Foy et al., 1987; Gerges et al., 2001; Izaki and Arita, 1996; Kim et al., 1996; Mesches et al., 1999; Pavlides et al., 1996; Reiheld et al., 1984; Shors et al., 1989; Shors and Thompson, 1992) with some exceptions(Bramham et al., 1998). Contrarily, long-term depression (LTD) induction was facilitated by behavioral stress in vivo and vitro (Kim et al., 1996; Xu et al., 1997, 1998b). It is well known that LTP might be the major cellular model of the mechanism underlying learning and memory (Bliss and Collingridge, 1993; Malenka and Nicoll, 1999; Martin et al., 2000). In addition, many forms of experience-dependent plasticity were suggested to involved in chronic pain (Wolpaw and Tennissen, 2001), drug addiction (Mansouri et al., 1999; Pu et al., 2002; Ungless et al., 2001) etc. Thus, stress experience-dependent long-term depression (SLTD) may be also related to stress experience-dependent memory. Activity-dependent LTD that is a sustained decrease in the efficacy of synaptic transmission in hippocampus is all along a controversial focus in the past decades, although growing evidence suggests that hippocampal LTD may play a role in certain types of learning and memory (Abraham and Bear, 1996) such as novelty dependent LTD (Manahan-Vaughan and Braunewell, 1999). However, some evidences indicate remarkably elusive in freely moving animals (Errington et al., 1995), propofol treatment (Wei et al., 2002) and aging (Norris et al., 1996) etc.

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Some sort of stress (such as adaptable and inadaptable stress) is unavoidable in daily life and the experience can be memorized for life-long. Behavioral stress can either block or facilitates memory dependent on different conditions (Diamond et al., 1999; Joels and de Kloet, 1992). The modification of stress on synaptic plasticity and memory may be through the activations of receptors, such as Glucocorticoid receptor (de Quervain et al., 1998; Xu et al., 1998b) and *N*-methyl-D-aspartate (NMDA) receptor (Kim et al., 1996) or intracellular Ca^{2+} levels (Coussens et al., 1997; Kerr et al., 1992). Prolonged stress or stress levels of corticosterone treatment impaired memory (Conrad et al., 1996; McLay et al., 1998; Mizoguchi et al., 2000; Park et al., 2001). However, chronic stress treatment induced other changes of the nervous system such as anxiety/depression (D'Aquila et al., 1994; Mizoguchi et al., 2000), damage of hippocampus structures (Magarinos et al., 1996, 1997; Sousa et al., 2000), that made more complex situations related to memory impairment. However, many reports also indicated that stress enhanced hippocampal dependent memory performance (Bowman et al., 2001; Luine et al., 1996; Luine, 2002) in which some experience-dependent forms of plasticity should be also involved. Since LTP was inhibited under stressful condition, SLTD would be an attractive candidate for stress experience memory or stress induced memory enhancement.

Thus, it is important to test whether SLTD is related to memory enhancement or stress experience memory. In our designs, we tested the relationship between LTD induction and spatial memory under acute or sub-acute elevated platform (EP) (a mild adaptable stress) and foot shock (FS) (a strong inadaptable stress) stress.

2. Materials and methods

Male Wistar rats (3–4 weeks old) were used. Animals were group-housed with free access to water and food in the Animal House Center of Kunming General Hospital having a 12-h light:12-h dark cycle and thermoregulation control.

2.1. Electrophysiology and surgery

Experiments were carried out under pentobarbitone sodium (50–60 mg/kg, i.p.) anesthesia and core temperature was maintained at 37 ± 0.5 °C. Recordings of field excitatory postsynaptic potential (EPSP) were made from the CA1 stratum radiatum of the hippocampus in response to ipsilateral stimulation of the Schaffer collateral/commissural pathway using techniques similar to those described(Xu et al., 1998b). Electrode implantation sites were identified by using stereotaxic coordinates. Two stainless steel screws (1.5 mm diameter) were inserted into the skull through a drill hole without piercing the dura. One served as a ground electrode (7 mm posterior to bregma and 5 mm left of the midline), the other served as the reference electrode (8 mm anterior to bregma and 1 mm left of the midline). Recording and stimulating electrodes were made by gluing together a pair of twisted Teflon-coated 90% platinum/10% iridium wires (50 μm inner diameter, 75 μm outer diameter). The recording electrode was inserted 3.5 mm posterior to bregma and 2.5 mm right of the midline and the stimulating electrode was inserted 4.2 mm posterior to bregma and 3.5 mm right of the midline. The optimal depth of the wire electrodes in the stratum radiatum of the CA1 area of the dorsal hippocampus was determined by using electrophysiological criteria and was verified by post mortem examination. In all experiments test EPSPs were evoked by stimulating with a square wave constant current pulse of 0.2 ms duration, at a frequency of 0.033 Hz and at a stimulation intensity adjusted to given an EPSP amplitude of 40–50% of maximum. There was no different on the stimulus required to evoke a 40–50% of maximum EPSP in acute and sub-acute stress animals. After 40 min stable baseline recording, a low frequency stimulating (LFS) consisted of 900 pulses at 3 Hz was delivered to the Schaffer collaterals/commissural pathway to induce LTD.

2.2. Behavioral and stress protocol

Water maze 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 that severed as distal cues. Before training, a 180 s free swim trial was run in which the platform was removed. For the training, a submerged (1.5 cm below the surface of the water, invisible for the animal) Perspex platform (13 cm × 13 cm) was placed in the center of a quadrant fixedly to make animal to learn the location of the platform that could be used to escape from the water. The training was given six trials with six different starting positions that were equally distributed around the perimeter of the maze. Thirty minutes after the end of the sixth trials, a probe trial was given which consisted of a 180 s free swim period without the Perspex platform. Swimming paths for training session and probe trial were monitored using an automatic tracking system. This computerized tracking system was used to record the swimming trace, calculate the escape latency (latency to find the platform) and distance traveled to reach the platform in four different quadrants for each trial.

For the EP stress groups, animals were placed on an elevated platform which was 10 × 10 cm and about 1.6

m high in the middle of a bright room for 30 min every time. Acute EP animals were immediately anesthetized for electrophysiological study or placed in water maze for behavioral study. Sub-acute EP animals had been experienced twice EP per day with inter stress interval 6 h for 5 days before electrophysiological and behavioral study. For the FS animals, one set of electric shock was consisted of three electric stimuli with 0.8 mA constant current for 1 and 5 s inter stimulus interval. Acute FS animals were experienced one set of electric shock before electrophysiological and behavioral study and sub-acute FS animals were experienced 10 sets of electric shock in 5 days before the experiments. Stresses were applied at 09:00 and 15:00 h to these animals individually. The time schedule after acute or final stress was closely matched when probe trail in behavior test and LFS in LTD induction was given.

Significance level was set at $P < 0.05$. Data were expressed as mean ± S.E.M.% of baseline EPSP amplitude in the electrophysiology section. In water maze experiments, data were showed as the mean time ± S.E.M. spent in finding the platform or the time spent in the platform quadrant and opposite quadrant. Statistical comparisons were made using Student's *t*-test or repeat measure of ANOVA.

3. Results

Animals were anesthetized by pentobarbitone sodium (50 mg/kg, i.p.) immediately after the acute/final behavioral stress. Previous study showed that the effect of stress on synaptic plasticity was prolonged by anesthesia (Xu et al., 1998b) and even in vitro (Kim et al., 1996). Consistent with previous results (Xu et al., 1998b), low frequency stimulation failed to induce LTD of the field EPSP amplitude in the CA1 area of controls ($n = 5$, 101.1 ± 3.3% of baseline 60 min after low frequency stimulation, $P > 0.05$ compared with baseline; Fig. 1A). As expected, LTD was induced by low frequency stimulation (≈ 90 min after stress) in the animals that had been stressed before anesthesia ($n = 10$, 86.3 ± 2.6% of baseline 60 min later, $P < 0.01$ compared with baseline; Fig. 1B). However, in the sub-acute EP animals, low frequency stimulation (≈ 2 h after the final stress) failed to induce LTD ($n = 15$, 100.9 ± 2.1% of baseline 60 min later, $P > 0.05$ compared with baseline; Fig. 1C), may due to the fast acclimatization to the naturalistic mild EP stress.

Chronic behavioral stress impacts the synaptic plasticity and hippocampal dependent memory and the fine structure of hippocampus (Magarinos et al., 1996, 1997; Sousa et al., 2000). However, the effect of short period of behavioral stress on synaptic plasticity was showed different here, and would be different on the hippocampal dependent memory.

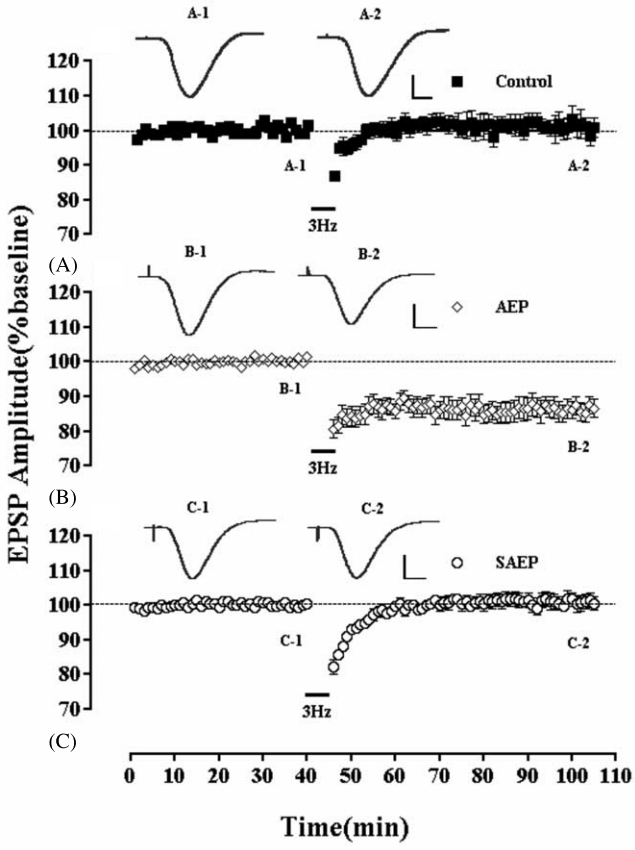

Fig. 1. Low frequency stimulation failed to induce LTD in the animals received sub-acute EP stress, may due to the fast acclimatization to the naturalistic mild EP stress. (A) Low frequency stimulation (3 Hz, bar) failed to induce LTD in nonstressed controls ($n = 5$, 101.1 ± 3.3% of baseline 60 min after LFS, $P > 0.05$ compared with baseline). (B) Acute EP stress (AEP) facilitated LTD induction by LFS (3 Hz, bar) ($n = 10$, 86.3 ± 2.6% of baseline 60 min later, $P < 0.01$ compared with baseline). (C) Low frequency stimulation (3 Hz, bar) failed to induce LTD in the animals received sub-acute EP stress (SAEP) ($n = 15$, 100.9 ± 2.1% of baseline 60 min after LFS, $P > 0.05$ compared with baseline). (Insets) Representative traces of field potentials at the times indicated by the numbers on the graph. Horizontal bar = 5 ms. Vertical bar = 1 mV.

We have examined the spatial learning performance in acute and sub-acute EP stressed animals. A probe trail was given after the animals received six trials training in Morris water maze task (≈ 90 min after the acute/final behavioral stress). Acute EP stress impaired memory retrieval in probe trail ($n = 14$, $P < 0.05$, compared with the controls; Fig. 2B) without affecting learning performance ($P > 0.05$, Fig. 2A). However, sub-acute EP stress did not show any difference in learning and memory retrieval compared with controls ($n = 14$, $P > 0.05$; Fig. 2A, B), may due to the same reason of adaptation as in synaptic plasticity studies.

The time required in electrophysiological and behavioral study was accurately matched. These results suggested that the effect of acute/sub-acute stress on LTD induction was correlated with the impairment of

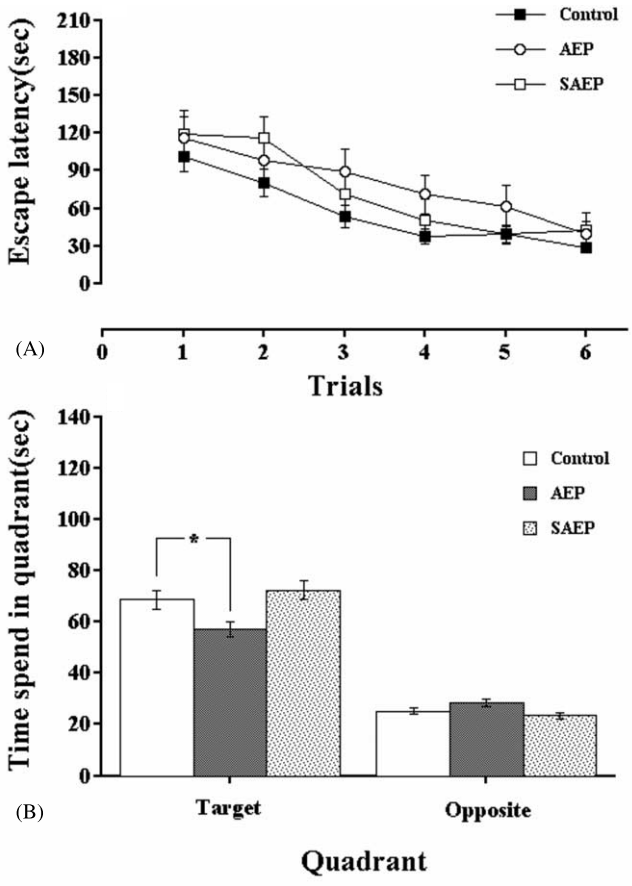

Fig. 2. Memory retrieval was impaired in acute EP stressed but not in sub-acute EP stressed animals that might due to the acclimatization to the naturalistic mild EP stress. (A) Acute EP stress ($n = 14$) or sub-acute EP stress ($n = 14$) did not affect the animals performing the spatial learning task compared with controls ($n = 22$; $P > 0.05$). (B) However, Acute EP stressed animals (AEP) spent significantly less time in the target quadrant than in the opposite quadrant compared with controls (*$P < 0.05$). The animals received sub-acute EP stress (SAEP) performed the probe trial as well as the controls did.

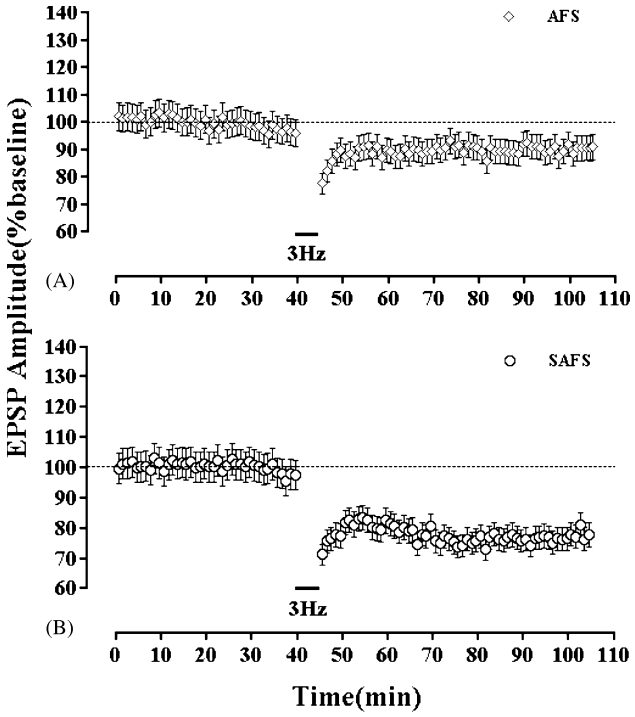

Fig. 3. Low frequency stimulation induced LTD in the animals received sub-acute FS stress. (A) Acute FS stress (AFS) facilitated LTD induction by LFS (3 Hz, bar) ($n = 5$, $90.3 \pm 0.5\%$ of baseline 60 min after LFS, $P < 0.05$ compared baseline). (B) Low frequency stimulation (3 Hz, bar) induced LTD in the animals received sub-acute FS stress (SAFS) ($n = 5$, $78.1 \pm 0.6\%$ of baseline 60 min after LFS, $P < 0.05$ compared with baseline). The magnitude of LTD was greater in the sub-acute FS stress than in the acute treatment ($P < 0.05$).

memory retrieval. However, careful design with acute/sub-acute FS stress showed much different on LTD and memory retrieval.

Both acute and sub-acute FS stress facilitated LTD induction by low frequency stimulation (≈ 90 min after acute/sub-acute stress) ($n = 5$, $90.3 \pm 0.5\%$ and $78.1 \pm 0.6\%$ of baseline 60 min later, $P < 0.05$, compared with baseline; Fig. 3A, B). The magnitude of LTD was larger in the sub-acute FS stress than in the acute treatment ($P < 0.05$). In addition, with the same behavioral protocol as that in the acute/sub-acute EP stress, acute FS slightly impaired spatial learning without affecting memory retrieval ($n = 21$, $P < 0.05$ compared with controls; Fig. 4A, B). However, the animals with sub-acute FS stress performed the learning task as good as the controls but did the memory retrieval task better than the controls ($n = 17$, $P < 0.05$ compared with the controls; Fig. 4A, B). With the same experimental protocol, different stress (mild, EP stress and strong, FS stress) induced different correlation between LTD and learning/memory.

4. Discussion

Our findings demonstrated that mild stress (EP) facilitated LTD was correlated with the impairment of memory retrieval (Figs. 1 and 2). Contrarily, strong stress (FS) facilitated LTD was correlated to the enhancement of memory retrieval (Figs. 3 and 4), under the same experimental protocol. May due to the acclimatization of the animals to EP stress, that sub-acute EP did not affect synaptic plasticity and memory is reasonable. The results of acute EP, acute FS and sub-acute FS in behavioral results and synaptic plasticity might due to the consequences of the interaction between stressful events and behavioral trainings.

Persistent changes in synaptic efficacy, such as LTP are believed to underlie certain types of memory(Bliss and Collingridge, 1993; Martin et al., 2000). However, many forms of experience-dependent synaptic plasticity were found (Pu et al., 2002; Ungless et al., 2001; Wolpaw and Tennissen, 2001). Thus, stress experience

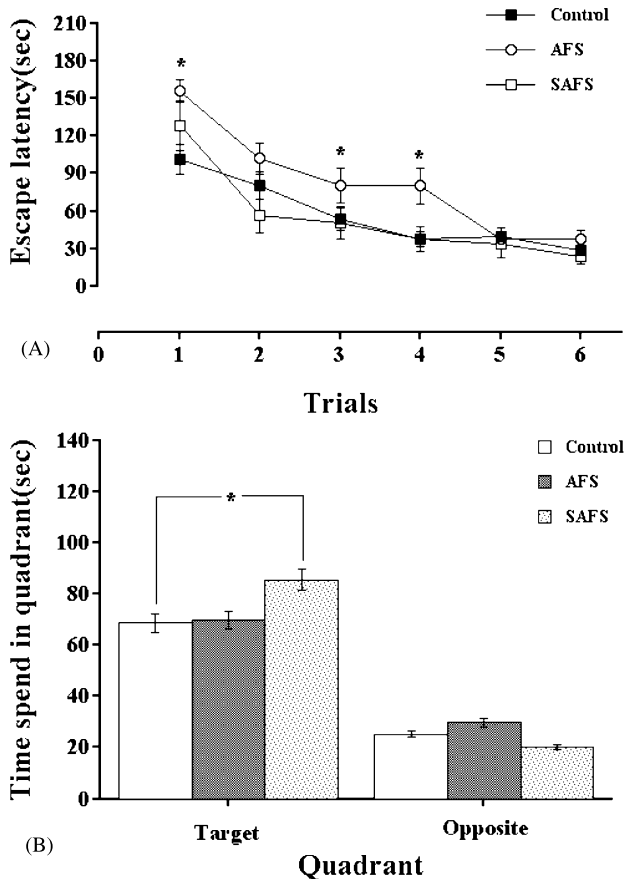

Fig. 4. Memory retrieval was enhanced in the animals received sub-acute FS stress. (A) Acute FS stress (AFS) ($n = 21$) slightly impaired the performance of spatial learning task ($^*P < 0.05$) without affecting the memory retrieval compared with controls ($n = 22$; controls is the same as in Fig. 2; $P > 0.05$). (B) Sub-acute FS ($n = 17$) stressed animals spent significantly more time in the target quadrant than in the opposite quadrant compared with controls ($^*P < 0.05$).

might also induce changes of synaptic plasticity to underlie this form of memory.

Sub-acute stress protocol has its advantage to study the effect of stress on synaptic plasticity and learning/memory. Because chronic stress will induce stress related diseases and changes such as anxiety, depression and post-traumatic stress disorder (PTSD) (D'Aquila et al., 1994; Sachinvala et al., 2000) or damage of the fine structure of hippocampus (Magarinos et al., 1996, 1997; Sousa et al., 2000), or suppression of LTP induction and input-output relationship in the hippocampal trisynaptic circuit (Ma et al., 2000; Pavlides et al., 2002), which causes cognition impairments (Sachinvala et al., 2000).

The present findings also showed that synaptic plasticity was very sensitive to the changes by acclimatization to stress. LFS failed to induce LTD in the sub-acute EP stressed animals (Fig. 1C) even though the animals showed signs of behavioral stress during the final stress treatment (e.g. defecating, urinating).

Behavioral stress releases adrenal hormones and a wide variety of neurotransmitters that is known to interfere with learning and memory and the induction of LTP and LTD (Diamond et al., 1994; Shors et al., 1989). It was well documented that the opposing action of the two receptors (mineralocorticoid receptor and the glucocorticoid receptor) might count for the inverted U-shape relation between corticosterone level and LTP (Diamond et al., 1992). When glucocorticoid receptors are activated by corticosterone, LTP is suppressed and the threshold for LTD induction is altered (de Kloet et al., 1999; Kim and Yoon, 1998). This metaplasticity provides a possible explanation why behavioral stress can either block or facilitates memory dependent on different conditions and the adaptation of sub-acute EP stress and SLTD in present finding. Other explanation cannot be ruled out since memory can also be either impaired or enhanced by stress dependent on when stress is given, in the context or out of the context (Garcia et al., 1998; Kim et al., 1996; Shors and Servatius, 1997) and out of the context stress protocol was used in present experiments.

Exploration of novel environment could induce LTD expression or enhanced LTD magnitude (Manahan-Vaughan and Braunewell, 1999) or induced LTP reversal (Xu et al., 1998a) that might relate to theta rhythm in hippocampus, involving in memory processing. Actually, theta rhythm changes in hippocampus induced by stress was documented (Balleine and Curthoys, 1991; Simonov and Rusalova, 1980; Yamamoto, 1998). Thus, additional explanation is possible that stress experience, like other forms of plasticity (Manahan-Vaughan and Braunewell, 1999; Mansouri et al., 1999; Pu et al., 2002; Ungless et al., 2001; Wolpaw and Tennissen, 2001; Xu et al., 1998a), could induce plasticity in hippocampus such as the enhanced magnitude of SLTD and memory retrieval in sub-acute FS in our results or stress experience-dependent LTP inhibition in which LTP was selectively inhibited at the acquisition stage of avoidance learning (Izaki and Arita, 1996). Acute stress or sub-acute stress may trigger the processes underlying stress form of memory such as SLTD that interacts with the memory (e.g. LTP/or LTD) in behavioral task and then results in that sub-acute EP stress does not impair spatial memory and even enhances spatial memory retrieval by sub-acute FS stress.

In all, our findings showed that stress experience dependent LTD was disassociated with the stress effect on spatial memory task but might be associated with stress experience form of memory.

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