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Impairment of the spatial learning and memory induced by learned helplessness and chronic mild stress

Li Song [a,*], Wang Che [b], Wang Min-wei [a,c], Yukihisa Murakami [d], Kinzo Matsumoto [d,e]

[a] Department of Pharmacology, School of Pharmacy, Shenyang Pharmaceutical University, Shenyang, 110016, China
[b] College of Chemistry and Chemical Engineering, Liaoning Normal University, Dalian, 116029, China
[c] Research Institute of China–Japan Medical and Pharmaceutical Sciences, Shenyang Pharmaceutical University, Shenyang, 110016, China
[d] Department of Medicinal Pharmacology, Institute of Natural Medicine, Japan
[e] COE Program, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194, Japan

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Abstract

Increasing evidences indicate the concurrence and interrelationship of depression and cognitive impairments. The present study was undertaken to investigate the effects of two depressive animal models, learned helplessness (LH) and chronic mild stress (CMS), on the cognitive functions of mice in the Morris water maze task. Our results demonstrated that both LH and CMS significantly decreased the cognitive performance of stressed mice in the water maze task. The escaping latency to the platform was prolonged and the probe test percentage in the platform quadrant was reduced. These two models also increased the plasma corticosterone concentration and decreased the brain derived neurotrophic factor (BDNF) and cAMP-response element-biding protein (CREB) messenger ribonucleic acid (mRNA) levels in hippocampus, which might cause the spatial cognition deficits. Repeated treatment with antidepressant drugs, imipramine (Imi) and fluoxetine (Flu), significantly reduced the plasma corticosterone concentration and enhanced the BDNF and CREB levels. Furthermore, antidepressant treated animals showed an ameliorated cognitive performance compared with the vehicle treated stressed animals. These data suggest that both LH and CMS impair the spatial cognitive function and repeated treatment with antidepressant drugs decreases the prevalence of cognitive impairments induced by these two animal models. Those might in part be attributed to the reduced plasma corticosterone and enhanced hippocampal BDNF and CREB expressions. This study provided a better understanding of molecular mechanisms underlying interactions of depression and cognitive impairments, although animal models used in this study can mimic only some aspects of depression or cognition of human.

Keywords: Depression; Spatial learning and memory; Corticosterone; Brain derived neurotrophic factor; cAMP-response element-binding protein

1. Introduction

Depression is a serious emotional disorder, with estimates of lifetime prevalence as high as 21% of the general population in some developed countries (Gainotti et al., 2001; Wong and Licinio, 2001; Nestler et al., 2002a,b). It is not only life threatening, but also has negative impacts on the ability of learning and memory. Evidences in a variety of studies show a close relationship between depression and spatial cognition deficits in human patients (Kuzis et al., 1997; Dolan, 2002; Ravnkilde et al., 2002; Uekermann et al., 2003). However, the detailed molecular mechanisms underlying the interactions of these two disorders have not been clearly understood. Converging lines of research suggest that the hippocampal complex (HC) plays an important role in the pathophysiology of schizophrenia, bipolar disorder, post-traumatic stress disorder, and major depression (MacQueen et al., 2003; Frodl et al., 2002; Steffens et al., 2000; Mervaala et al., 2000; Sheline et al., 1999). Although postmortem studies show minor cellular death in HC of depressed patients (Lucassen et al., 2001; Muller et al., 2001), animal studies have suggested that factors involved in these pathophysiological changes include elevated glucocorticoid secretion, decreased level of brain derived neurotrophic factor (BDNF) and cAMP-response element-biding protein (CREB) in hippocampus (Duman et al., 2000). All these changes could lead

* Corresponding author. Tel.: +86 24 2399 8824; fax: +86 24 8389 0024.
E-mail address: lisong_spu2005@yahoo.com (L. Song).

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to reduced hippocampal volume and vulnerability to subsequent episodes of depression as a result of decreased neurogenesis, increased remodeling of dendrites, and loss of glial cells (for review see Manji et al., 2001; Nestler et al., 2002a,b; Coyle and Duman, 2003). As HC also has an important role in the process of spatial learning and memory (Von Gunten et al., 2000), the hippocampal volume reductions may be the primary cause for impairment of spatial cognition that coexistent with depression.

Animal models are indispensable in clarifying the pathophysiology that underlies depression, depression–cognition interactions, and in searching for new antidepressants. Several animal models have been established, such as forced swimming test (FST), tail suspension test (TST), learned helplessness (LH) and chronic mild stress (CMS). These models have been used as reliable research tools to screen effective antidepressants and to further research into pathophysiology of depression. However, the value of these animal models in defining the impact of depression producing stressors on spatial learning and memory remains uncertain.

In this study, we directly examined the influences of two animal models, LH and CMS, on the spatial learning and memory performance using the Morris water maze task, and investigated the therapeutic effects of two antidepressants, imipramine (Imi) and fluoxetine (Flu). Concurrently, plasma corticosterone level, the BDNF mRNA and the CREB mRNA expressions in hippocampus of the stressed mice were also investigated in order to explore further mechanisms involved in the impairments of spatial learning and memory induced by LH and CMS.

2. Materials and methods

2.1. Animals

Male ICR mice weighting 30–35 g (aged 7 weeks) were housed in groups under standard conditions (12 h light/dark cycle; lights on from 0730 to 1930; 22±2 °C ambient temperature; 55±10% relative humidity; food and water ad libitum). All animals were randomized into 6 groups with 12 mice per group in each test. The experiments procedures involving animals and their care were conducted in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals and with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

2.2. Measurement of body weight gain and food consumption

Separate groups of mice (12/group) were housed 2 per cage and gave water and mouse chow ad libitum. After 2 weeks of repeated administrations to mice with drugs, saline or without any injection, body weight was measured every eighth day. Food was monitored for spillage, which was negligible. Daily intake was determined by an averaging of 7 days total.

2.3. LH paradigm

The LH procedure, a model of stress and coping behavior, is widely accepted as an animal model of depression (Nestler et al., 2002a,b). Although this model only mimics certain aspects of depression of humankind, it satisfies criteria for face and predictive validity.

LH model were performed and the escape behavior was assessed by a previously described method for rats (Itoh et al., 2004). In this paradigm, an animal is initially exposed to uncontrollable (inescapable) stress. When the animal is later placed in a situation in which shock is controllable (escapable), the animal not only fails to acquire the escape responses, but also often makes no efforts to escape the shock at all. In the present study, the exposures to inescapable footshocks were started at 0800 in the morning. Each mouse was placed in a Plexiglas chamber and exposed to 60 inescapable electric footshocks (intensity 0.6 mA, duration 15 s) at variable intervals of 20–90 s (mean=45 s) once a day for 3 days (days 1–3). Non-stressed mice were placed in identical chambers for 60 min without receiving footshocks. The escape performances of the mice were tested in the shuttle-box at 1, 8 and 15 days after the third day of exposure to inescapable footshocks (days 4, 11 and 18, respectively). The animals were individually placed in the shuttle-box, allowed to habituate to the environment for 3 min and then subjected to a 30 trials testing session. The intertrial interval was 8–22 s (mean=15 s). In each trial, a tone signal (80 dB) was first presented for a maximum of 3 s with a light signal. If no avoidance response occurred during the 3-s period, an electric shock (0.6 mA) was delivered to the mice through grid floor for a maximum of 3 s with the tone and light signal. The mice could escape the shock by moving to the other side of the box (escape response); the signals and the shock terminated on the response. If no escape response occurred, the shock and signals terminated automatically. A non-crossing response during the shock delivery was referred to as an escape failure. On day 12, the spatial learning and memory performance of animals were determined by the Morris water maze task.

2.4. CMS procedure

The CMS model of depression is accepted as a valuable method for evaluating antidepressant effects in animals. In this model, animals subject to various stressors such as unpredictable order, stimulating conditions in the natural environment, show many behavioral, biochemical and physiological impairments, which parallel the symptoms of depression in human. In the present study, the CMS procedure described by Willner et al. (1987) and Moreau et al. (1992) for rats was applied for the mice. The CMS procedure consisted of a variety of unpredictable mild stressors including repeated periods of 45° cage tilt, two 2-h periods of separated housing, one overnight period of limited access to food (12-h separation of mouse chow from direct touching of mice by glass clapboard with holes of 3 mm diameter, and without any reduction in the actual daily food ration), one period of continuous overnight illumination, and one overnight period in a soiled cage (50 ml of water/l of sawdust bedding). Animals were also placed on a reversed light/dark cycle from Friday evening to Monday morning. These stressors were scheduled over a one-week period and

repeated throughout the 5-week experiment. In contrast to previous procedures in rats, nociceptive stressors were excluded, and only environment and social disturbances were applied (Pardon et al., 2000). The non-stressed control animals were housed in normal conditions without any influences. After 4 weeks of CMS procedure, the spatial learning and memory of the stressed animals were determined by the Morris water maze task.

2.5. Plasma corticosterone level

Separate groups of animals were used for the measurement of plasma corticosterone level of LH and CMS treated mice. The animals were sacrificed 2 h after the escape test of LH paradigm or sacrificed weekly after 3 weeks of CMS. The blood samples were collected and kept on ice and then centrifuged immediately at 2000 ×*g* at 4 °C for 15 min. The obtained plasma was kept at −80 °C until analysis. Corticosterone levels were measured using commercially available radioimmunoassay (RIA) kits (ICN Biomedicals, Costa Mesa, CA, USA).

2.6. Reverse transcription polymerase chain reaction (RT-PCR) of BDNF and CREB

Separate groups of animals (12/group) were also used for measurement of BDNF and CREB levels in hippocampus of LH and CMS mice. Twenty-four hours after the escape test at day 11 in LH paradigm or after 4 weeks stress in CMS, the animals were sacrificed. Then, the brains were sectioned and frozen on dry ice before storage in a −80 °C freezer. RT-PCR and quantification of BDNF mRNA or CREB mRNA were performed as previously described (Lee et al., 2004; Tiraboschi et al., 2004). Total RNA was extracted according to the TRIzol protocol (Invitrogen, San Diego, CA, USA). A 5 μg portion of total RNA and 1.5 μg oligo-dT primer were incubated at 70 °C for 10 min and gradually cooled to room temperature. Each RT mixture, containing 25 U of M-MLV reverse transcriptase (Promega, Madison, WI, USA), 10 μl 5× Reaction buffer, 0.5 mM dNTP, and nuclease-free distilled water, were added to a final volume of 50 μl. The samples were incubated at 37 °C for 90 min followed by denaturation at 95 °C for 10 min. Each PCR (20 μl) contained 2 μl of RT product, 1 U of Taq DNA polymerase (Promega, Madison, WI, USA), 2 μl 10×PCR buffer plus $MgCl_2$, 0.2 mM dNTP, and 0.5 μM gene-specific primers (BDNF: forward 5′ - GAC AAG GCA ACT TGG CCT AC - 3′, reverse 5′ - CCT GTC ACA CAC GCT CAG CTC - 3′, product size: 356 bp; CREB: forward 5′ - TAC CCA GGG AGG AGC AAT AC - 3′, reverse 5′ - GAG GCA GCT TGA ACA ACA AC - 3′, product size: 183 bp; GAPDH: forward 5′ - ACA TTG TTG CCA TCA ACG AC - 3′, reverse 5′ - ACG CCA GTA GAC TCC ACG AC - 3′, product size: 216 bp). Amplified reaction was performed with a thermocycler for a single 3-min initial denaturation at 94 °C followed by 33 cycles (BDNF), 45 cycles (CREB) or 26 cycles (GAPDH) under the conditions: 94 °C (20 s), 55 °C (20 s), and 72 °C (20 s) and final extension at 72 °C for 4 min. The PCR products were separated on 1.5% agarose gels containing ethidium bromide and quantified by densitometry. The BDNF or CREB PCR product was normalized to that of the GAPDH PCR product in each sample.

2.7. Morris water maze (MWM) task

The MWM task was performed from day 11 in LH paradigm or day 28 in CMS. One day before the start of training, the mice were given a pre-training session in which they were allowed to swim freely in a water tank (70 cm diameter, with a 15 cm water depth) for 60 s without an escape platform (Morris, 1994; Murakami et al., 2005). The tank was placed in a dimly lit, soundproof test room with various visual cues. In the training block, the tank was filled to a depth of 15 cm with water maintained at 25±1 °C. A transparent platform (5 cm diameter) was put 1 cm below the surface of the water. The tank was divided into four quadrants with the platform in a fixed position in one quadrant. Daily training consisted of four trials in which the mouse was placed in the water from four random starting positions (N, E, S, W) and the latency of escaping onto the platform was recorded. This was conducted for 5 consecutive days. A maximum of 60 s was allowed during which the mouse had to find the platform and climb onto it. On the sixth day of the MWM, each mouse was subjected to a probe test where no platform present. The time of swimming in the former platform quadrant and the total time of swimming in all four quadrants were recorded for 60 s. The percentage of swimming in the quadrant of the former platform was calculated as a measurement of spatial memory. The MWM sessions were recorded with a video camera for offline analyzing.

2.8. Drugs administration

Flu (10 mg/kg), Imi (5 mg/kg) (Sigma, St. Louis, MO, USA) or vehicle solutions were intraperitoneally administered with a volume of 10 ml/kg repeatedly. The repeated treatment was performed twice daily. For the LH animals, the treatment of antidepressants was from day 4 to day 18 and 60 min before escaping test. For the CMS animals, the administration of antidepressants was from day 22 to day 35. The dose levels of these drugs in this present study were determined as referred to previous studies (Itoh et al., 2004; Shirayama et al., 2002). Doses of 5 mg/kg of Imi and 10 mg/kg of Flu were chosen because at such dose level Imi and Flu have been reported to show antidepressant action in previous work (Itoh et al., 2004; Shirayama et al., 2002). Chronic administration with excess dose of Imi (10 to 20 mg/kg) or Flu (20 to 40 mg/kg) had some adverse effects in our present research, including a reduction of food intake and body weight loss. These effects will influence the measurement of behavioral and cognitive performance of mice. Therefore, the dose of Imi and Flu in this present study was only set at 5 and 10 mg/kg, respectively.

2.9. Statistical analysis

All results were expressed as the mean±S.E.M. values. The statistical analyses were carried out using the SIGMA-STAT system (Version 3.1) for Microsoft Windows. Statistical significance between groups of three or more was analyzed by two-way analysis of variance (ANOVA) or one-way ANOVA among the groups followed by Dunnett's test. A

Student's *t*-test was used for the analysis of significant differences between the two groups. All tests were two-tailed. The *P* values of less than 0.05 were considered to be statistically significant.

3. Results

3.1. Chronic Imi and flu administrations on body weight and food consumption

14 consecutive days of Imi (10~20 mg/kg) or Flu (20~40 mg/kg) administration to mice led to a significant reduction ($P<0.05$) of body weight relative to the mice receiving the vehicle injections (Fig. 1). In contrast to the high dose of drugs, repeated injections with lower dose of Imi (5 mg/kg) or Flu (10 mg/kg) made no changes in the body weight and appetite of mice. The repeated injections of saline made no influence on the food intake and body weight gain compared with the control animals without any injections.

3.2. LH behavior

In this study, compared to the non-stressed animals, LH mice showed a significantly larger number of escape failures when tested at 4, 11 and 18 days after the inescapable footshocks. The enhanced number of escape failure indicated that the stressed animals failed to acquire the escape responses during the 30 trials testing session. The behavioral deficits prolonged for at least 14 days and were ameliorated by treatment of antidepressant drugs. Repeated administration of Imi (5 mg/kg, ip) or Flu (10 mg/kg, ip) for 7 days reduced the number of escape failure in LH mice. However, neither Imi nor Flu could completely ameliorate the escape behavior to a level similar to that of the non-stressed control group (Fig. 2).

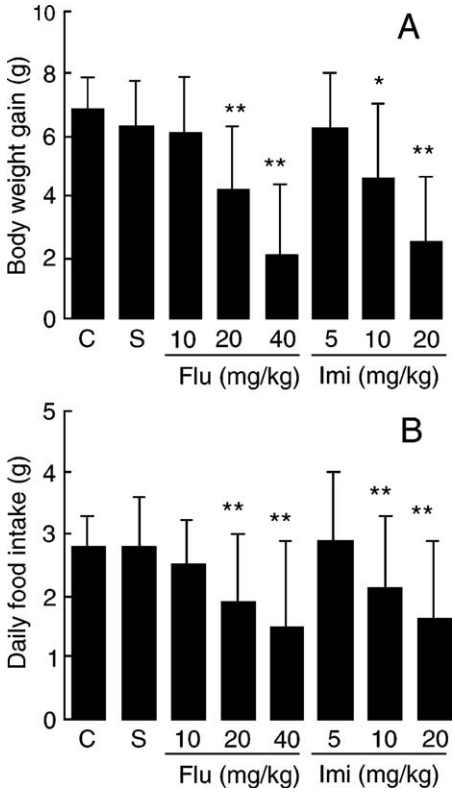

Fig. 1. Effects of Imi or Flu on body weight and food consumption. Values are expressed as the mean of body weight gain (A) and food consumption (B)±S.E.M. ($n=12$ per group). C means control group without any injection of drugs or saline. S means group treated with saline. $^{*}P<0.05$, $^{**}P<0.01$ versus saline injection group (Dunnett's test).

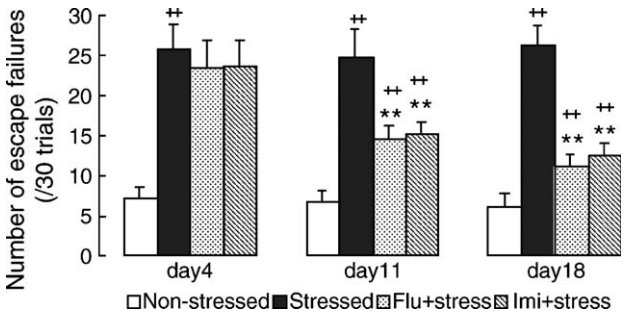

Fig. 2. Effect of Imi or Flu on the number of escape failures in LH mice. Values are expressed as the mean number of escape failures±S.E.M. during 30-trial escape test ($n=12$ per group). $^{**}P<0.01$ versus stressed group (Dunnett's test). $^{+}P<0.05$, $^{++}P<0.01$ versus non-stressed group (Student's *t*-test).

3.3. Plasma corticosterone level

As shown in Fig. 3, the plasma corticosterone level of the LH or CMS mice was significantly higher than those of the non-stressed mice. This elevation persisted for at least 14 days indicating that the stressed animals might show an impaired feedback regulation in the hypothalamic–pituitary–adrenal (HPA) axis after the exposure to inescapable footshocks (Fig. 3A) or CMS procedure (Fig. 3B). Seven days' repeated

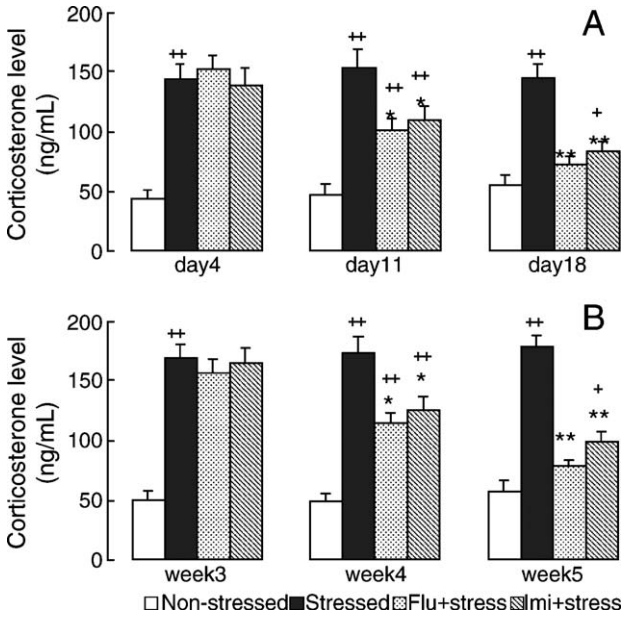

Fig. 3. Effect of Imi or Flu on the enhanced corticosterone levels in CMS (A) or LH (B). Values are expressed as the mean±S.E.M. ($n=12$ per group). $^{*}P<0.05$, $^{**}P<0.01$ versus stressed group (Dunnett's test). $^{+}P<0.05$, $^{++}P<0.01$ versus non-stressed group (Student's *t*-test).

treatment with Flu (10 mg/kg) or Imi (5 mg/kg) significantly decreased the elevated corticosterone level.

3.4. BDNF mRNA and CREB mRNA levels in hippocampus

The decreased BDNF and CREB expression might indicate both stress and cognitive impairment levels. Our results demonstrated that the levels of mRNA for BDNF and CREB in the hippocampus of the vehicle-treated mice had been exposed to LH or CMS were significantly lower than that of the non-stressed mice (Fig. 4). This result coincided with the data from plasma corticosterone level test as that during the MWM task and indicated the mice without antidepressant treatment were still suffering from biological deficits. Compared to the vehicle group, Imi or Flu significantly increased the levels of BDNF (Fig. 3A) and CREB mRNA (Fig. 3B) in the hippocampus after LH and CMS.

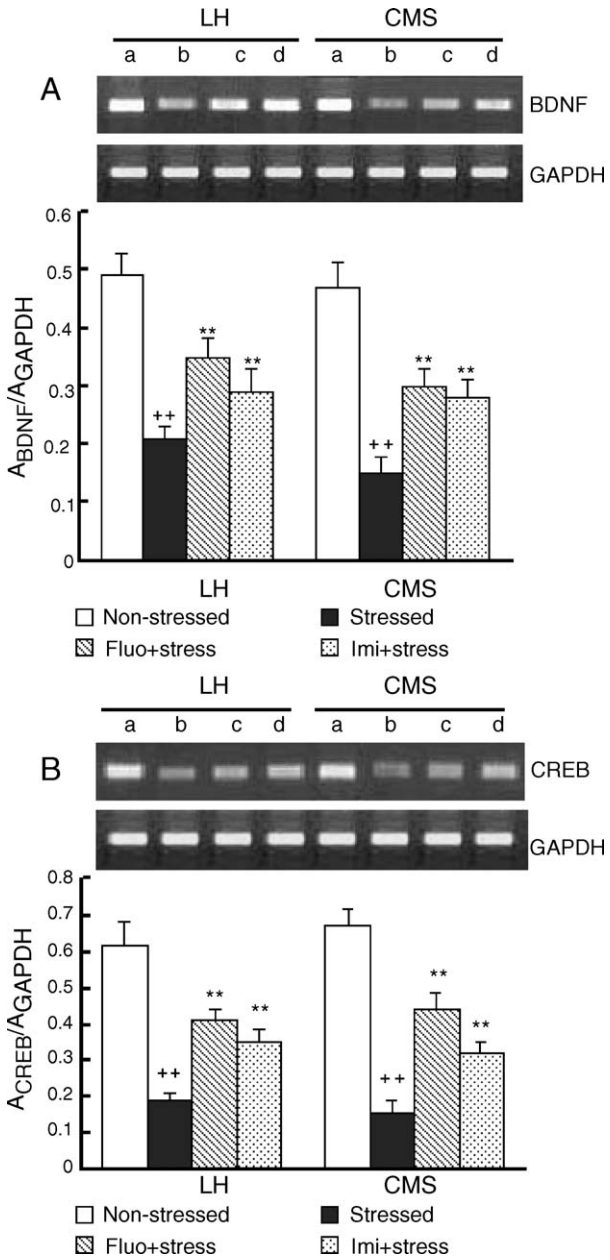

Fig. 4. Effects of Flu and Imi on decreased expression of BDNF mRNA and CREB mRNA induced by LH or CMS. Panel A and B shows representative experiments of BDNF mRNA and CREB mRNA levels in stressed animals (a), non-stressed control animals (b), and the Imi (c) or Flu (d) treated animals. The results were calculated as the intensity of the lane of each transcript over the intensity of the corresponding GAPDH band and expressed as the mean ± S.E.M. (n = 12 per group). $^{+}P< 0.05$, $^{++}P< 0.01$ versus control group (non-stressed animals). $^{**}P<0.01$ and $^{*}P<0.05$ versus stressed group.

3.5. Impairment of spatial cognitive performance

In order to investigate the influence of LH and CMS on the spatial cognition performance, the MWM task was performed. As shown in Fig. 5, the latency to escape to the platform in all groups of mice decreased following the training sessions, indicating that all groups showed some degrees of learning. However, the speed and the extent of the learning were significantly different. Statistical analysis revealed that spatial learning of the stressed mice after LH and CMS was significantly slower than those in the control group. The mice subjected to LH or CMS required a longer time to locate the hidden platform than the non-stressed control mice during the learning trials (Fig. 5A, B), although both the LH paradigm and CMS procedure did not affect the swimming ability of the mice in the pre-training trials of the water maze. The average swimming speeds in the pre-training were comparable for all the groups in the water maze task (LH: non-stressed controls, 13 ± 0.5 cm/s; stressed, 12 ± 0.6 cm/s; Flu, 12 ± 0.7 cm/s; Imi, 12 ± 0.8 cm/s. CMS: non-stressed controls, 14 ± 0.4 cm/s; stressed, 12 ± 0.6 cm/s; Flu, 12 ± 0.4 cm/s; Imi, 11 ± 0.6 cm/s; $P>0.05$, Dunnett's test).

The results of probe test indicated that the stressed mice showed an impaired cognitive performance compared with control animals. Repeated administration of Imi and Flu ameliorated these deficits as shown by the decreased escaping time and the increased probe test percentage. Furthermore, fluoxetine or imipramine treatment showed no effects on the spatial learning and memory in the non-stressed control animals (Fig. 5C, D, E).

4. Discussion

The prime objective of this study was to investigate whether LH and CMS, used to make animal model of depression, would significantly impair learning and memory performance in mice. Concurrently, BDNF and CREB levels were also determined. In this study, we clearly demonstrated that both LH and CMS indeed had a dramatic influence on subsequent spatial cognitive performance. Furthermore, the up-regulation of plasma corticosterone concentration and down-regulation of the hippocampal BDNF or CREB levels were coincident with the impairment of spatial learning and memory. Repeated administration of Imi and Flu significantly could ameliorate the cognitive deficits induced by either LH or CMS. The effects might in part be attributed to the up-regulation of BDNF or CREB levels in the hippocampus and the decrease of elevated plasma corticosterone concentration.

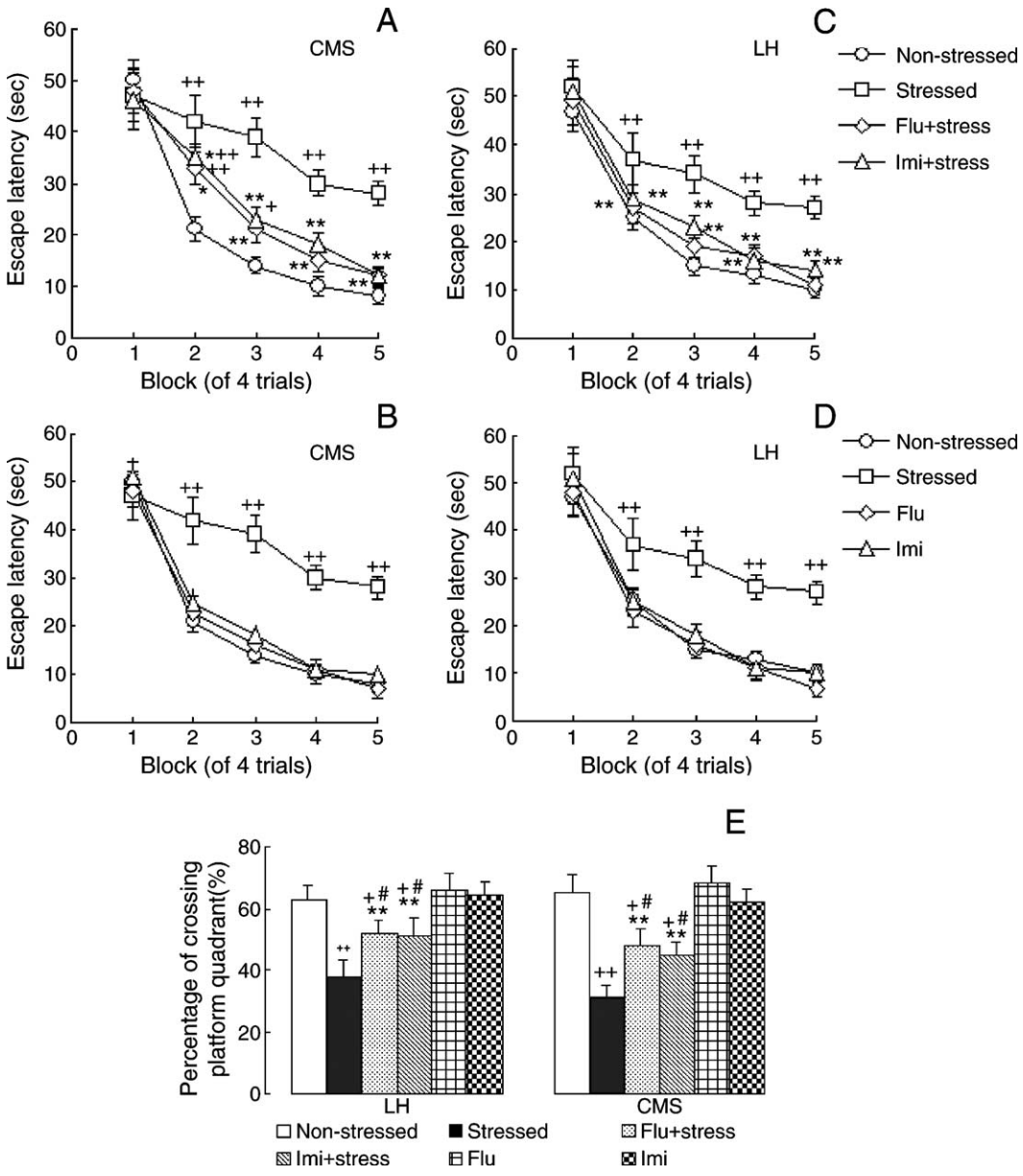

Fig. 5. Effects of Flu and Imi on the Morris water maze performance in mice exposed to LH or CMS. The trial test was performed with four trials/block/day for 5 days. (A–D) Time course of the change in the latency of escaping to the platform in the pool. Each point represents the mean of the latency with the S.E.M. (E) The percentage of swimming time in the platform quadrant was recorded at the probe trial for 1 min after the platform was removed on the sixth day of the test. Each column represents the mean percentage of crossing platform quadrant with S.E.M. ($n=12$ per group). $^{+}P<0.05$, $^{++}P<0.01$ versus non-stressed control group. $^{*}P<0.05$, $^{**}P<0.01$ versus stressed group. $^{\#}P<0.05$, $^{\#\#}P<0.01$ versus Flu or Imi group.

The concurrence and interrelationship of depression and cognitive impairment in humans are striking features of these two disorders. Several possible interactions may exist between depression and dementia, for instance increasing cognitive impairments may induce depression, and dementia may also occur as a symptom of depression (Kuzis et al., 1997; Payne et al., 1998; Zubenko, 2000; Zubenko et al., 2003). More importantly, depression and dementia may share similar neuropathological factors such as CREB and BDNF (Heun et al., 2003; Zubenko et al., 1990). Lines of evidences have suggested that impaired cognition is an element of depression and that antidepressant therapy may improve the cognitive function (Fann et al., 2001; Nowakowska et al., 2001; Harmer et al., 2002; Meneses, 2002; Yau et al., 2002). However, most of these studies were performed in human or aged animal models. The detailed molecular mechanisms underlying adult animal models of depression used to investigate the interaction of depression and cognitive deficits still remain uncertain. Our results provided direct evidence that LH and CMS, two animal models of depression, significantly impaired spatial learning and memory. These deficits occurred as the consequence of damaged corticosterone, BDNF and CREB regulation, which have a crucial role in the development of both spatial cognition and depression (Duman et al., 2000).

An emerging hypothesis suggests that depression has a close association with neuroplasticity and cellular adaptation

(Duman et al., 2000), which may be due to the downstream events beyond the receptors at the level of intracellular signaling molecules (Nestler et al., 2002a,b). Recent basic and clinical studies provide evidence for a neurotrophic hypothesis of depression and antidepressant action. According to this hypothesis, the decreased expression of BDNF or CREB could contribute to the atrophy of hippocampus in response to stress in the depressed patients, and the up-regulation of BDNF and CREB could contribute to the action of antidepressant treatment (Duman et al., 1997, 2000). Our results provide further support for this hypothesis and demonstrate that treatment of antidepressants ameliorate the changes of behavior and hippocampus BDNF and CREB levels induced by LH and CMS.

Furthermore, BDNF is implicated in synaptic plasticity such as long-term potentiation (LTP) (Barde et al., 1982; Leibrock et al., 1989; Patterson et al., 1992; Figurov et al., 1996). LTP in the hippocampus is an activity-dependent modification of synaptic strength and considered as a potential cellular mechanism underlying learning and memory (Bliss and Collingridge, 1993). Mizuno et al. (2000) and Yamada et al. (2002) also demonstrated that BDNF mRNA in the hippocampus increased after a radial maze training, and the treatment with an antisense BDNF oligonucleotide led to impairment of not only the acquisition but also the maintenance and/or the recall of spatial memory. In our study, LH and CMS significantly damaged the cognitive performance of the mice in the MWM task, while repeated antidepressant treatment ameliorated these impairments. All these behavior changes appeared in parallel with the alteration of the hippocampal BDNF and CREB levels.

Except BDNF and CREB, glucocorticoid level was another factor that impacts not only on cognition but also on emotion. Both acute and chronic physical or psychological stressors can provoke the secretion of glucocorticoid (McEwen and Sapolsky, 1995). Brief periods of stress potentiate memory formation, whereas more severe or prolonged stress has damaging effects upon broad aspects of cognition (McEwen and Sapolsky, 1995). It has been suggested that the effects of stress, in particular of elevated glucocorticoid, on memory are mediated through their influences on hippocampus. Numerous studies have consistently demonstrated that stress or stress elevated corticosterone levels inhibit the induction of excitatory plasticity (LTP) and promote the induction of inhibitory plasticity (long-term depression, LTD) in the hippocampus (Foy et al., 1987; Diamond et al., 1992; Pavlides et al., 1993; Xu et al., 1998; Akirav and Richter-Levin, 1999; Maroun and Richter-Levin, 2003). In addition to affecting synaptic plasticity and memory, stress and corticosterone have been shown to alter hippocampal dendritic morphology and inhibit neurogenesis in the adult brain, which could also have an impact on memory-related functioning (Kim and Diamond, 2002). The present study demonstrates that after LH paradigm or CMS procedure, the plasma corticosterone concentration is elevated and the mice with higher corticosterone level show a poor water maze performance. These results can be ameliorated by chronic administration of antidepressants.

In conclusion, the present results suggest that both LH and CMS procedure impair the spatial cognitive function in the Morris water maze task. Repeated treatments with antidepressants decrease the prevalence of cognitive impairment. This may, in part, be a consequence of reduced plasma corticosterone levels and enhanced expression of BDNF and CREB expressions in hippocampus of the stressed mice.

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