J Physiol Sci (2012) 62:351–357
DOI 10.1007/s12576-012-0211-1

ORIGINAL PAPER

Acupuncture stimulation at HT7 alleviates depression-induced behavioral changes via regulation of the serotonin system in the prefrontal cortex of maternally-separated rat pups

Hyemee Park · Doyoung Yoo · Sunoh Kwon · Tae-Won Yoo · Hi-Joon Park · Dae-Hyun Hahm · Hyejung Lee · Seung-Tae Kim

Received: 11 January 2012 / Accepted: 6 May 2012 / Published online: 25 May 2012

Abstract A possible application of acupuncture in alleviating depression-like behavioral changes and regulating serotonin signaling in the prefrontal cortex (PFC) of maternally-separated rat pups was investigated in this study. On postnatal day 15, rat pups were maternally-separated and received acupuncture stimulation at acupoint HT7 or ST36 once a day for 7 days. On postnatal day 21, the tail suspension test was performed and the PFC was harvested. Tissue levels of serotonin (5-HT) and 5-hydroxyindole-3-acetic acid (5-HIAA) were then measured by high-performance liquid chromatography and expression of serotonin transporter (5-HTT) and brain-derived neurotrophic factor (BDNF) were assessed by western blotting. Levels of 5-HT and 5-HIAA were not significantly changed, but the 5-HIAA/5-HT ratio was significantly increased by maternal separation. The immobility time of maternally-separated rat pups was increased, and increased 5-HTT expression and reduced BDNF level were observed in the PFC. But acupuncture stimulation at HT7 alleviated the behavioral change and regulated the changes of 5-HIAA/5-HT ratio, 5-HTT, and BDNF. In conclusion, acupuncture stimulation at HT7 can relieve maternal separation-induced changes, and we propose that regulation of the 5-HIAA/5-HT ratio and of 5-HTT expression by acupuncture stimulation are important acupuncture-induced benefits in this animal model of depression.

H. Park and D. Yoo equally contributed to this work

H. Park · D. Yoo · T.-W. Yoo · S.-T. Kim (✉)
Division of Meridian and Structural Medicine, School of Korean Medicine, Pusan National University, Mulgeum-eup, Yangsan, Gyeongsangnam-do 626-870, Republic of Korea
e-mail: kimst@pusan.ac.kr

S. Kwon · H.-J. Park · D.-H. Hahm · H. Lee
Acupuncture and Meridian Science Research Center, Kyung Hee University, Seoul 130-701, Republic of Korea

Keywords Acupuncture · HT7 · Depression · Serotonin transporter · Brain-derived neurotrophic factor · Maternal separation

Introduction

Depression is a common disorder that manifests with a variety of symptoms, for example sadness, loss of interest, feelings of worthlessness, insomnia, and thoughts of death [1]. Depression can be induced by a variety of factors. Childhood parental loss is known to be one such factor because early life stress may cause changes in the central nervous system and increase the risk of depressive psychopathology in adult life [2, 3]. Maternal separation (MS), a stressful experience early in life, is therefore regarded as an animal model for studying depression [4].

The molecular mechanisms of this disease are largely elusive, but there is much evidence that imbalances in monoaminergic neurotransmitters are linked to depression [5]. Among the neurotransmitters, serotonin (5-hydroxytryptamine; 5-HT) is known to be of crucial importance in the pathophysiology of depression, and 5-HT signaling in the brain is involved in the symptoms and drug treatment of clinical depression [6]. Serotonin transporter (5-HTT) is a crucial membrane protein that transports 5-HT from synaptic spaces into presynaptic neurons, and transport of 5-HT by this protein terminates the action of serotonin and recycles it in a sodium-dependent manner. Regulation of 5-HT reuptake or metabolism is an important pharmacological target for depression treatment, so this protein is the target of many antidepressant medications [5].

Acupuncture has long been used in East Asia as a therapeutic method for depression, but the mechanism of acupuncture for depression treatment remains elusive.

Among acupoints, acupoint HT7 has been used as a therapeutic acupoint in clinical studies of depression [7, 8], and acupuncture stimulation at HT7 can modulate the hypothalamic–pituitary–adrenal system [9] and increase neuropeptide Y expression [10] in maternally-separated rats. These results indicate that acupuncture stimulation at HT7 could improve MS-induced behavioral changes and regulate depression-related substances, but it is still unknown whether acupuncture stimulation can affect serotonin signaling.

It is known that a variety of brain structures are involved in depression. Among these, the prefrontal cortex (PFC) is one of the major targets for depression treatment because it is linked to cognitive behavior, personality expression, and social behavior [11] and is known to be important in the development and treatment of depression [12]. Nevertheless, there has been little research on changes of depression-related substances in the PFC as a result of acupuncture, and most acupuncture research for depression has been focused on changes in other brain regions, for example the hippocampus [10], amygdala [13], and hypothalamus [9]. In this study, to evaluate the potency of acupuncture stimulation as an antidepressant, we investigated whether acupuncture stimulation of HT7 can regulate levels of 5-HT, 5-hydroxyindole-3-acetic acid (5-HIAA), 5-HTT, and brain-derived neurotrophic factor (BDNF) in the PFC of maternally-separated rat pups.

Materials and methods

Animals

This study was approved by Pusan National University Institutional Animal Care and Use Committee, and care of the animals and the experimental procedures were conducted in strict accordance with the guidelines of the NIH and Korean Academy of Medical Sciences. Adult pregnant Sprague–Dawley rats (Orient Bio, Korea) were housed individually in Plexiglas cages and checked daily until delivery. Dams were kept on a 12 h light/dark cycle (lights on at 0700 hours) and maintained at constant temperature (22 ± 2 °C), humidity (45–60 %) with food and water ad libitum. The day of delivery was designated postnatal day (PND) 0.

Grouping and maternal separation procedure

Rat pups generally open their eyelids within PND 14–17 [14]. On PND 15, after we confirmed that all of the litters had opened their eyelids, they were randomly assigned to one of four groups, with twelve pups in each group: the normal group (NOR), the maternally separated control group (MS), the maternally separated group with acupuncture stimulation at Shenmen (HT7) acupoint (MS + HT7), and the maternally separated group with acupuncture stimulation at Zusanli (ST36) acupoint (MS + ST36). The pups in the normal group were housed with their mothers under standard conditions and those in the remaining groups were transferred from their home cages to individual cages (one pup per cage) and maintained individually to be sacrificed. On the basis of previous studies [9, 10], the MS period selected was 7 days.

Acupuncture treatment

The rats in the MS + HT7 and MS + ST36 groups were lightly immobilized, and stainless acupuncture needles (0.16 mm in diameter) were inserted to a depth of 3 mm at their HT7 (MS + HT7 group) or ST36 (MS + ST36 group) acupoint, turned at two revolutions per second for 15 s, and removed immediately afterward. They underwent this procedure from left to right acupoint in sequence (treatment lasting 30 s). This treatment continued at 24-h intervals for 7 consecutive days at a fixed time. HT7 is located at the end of the transverse crease of the ulnar wrist of the forepaw, which has been used to treat mental disorders in Oriental medicine and had significant effects on depression-like behavior and depression-induced brain changes in maternally-separated rat pups [9, 10]. ST36, regarded as an important acupoints for relieving gastrointestinal ailments [15], is near the knee joint of the hind limb, 2 mm lateral to the anterior tubercle of the tibia. The rats in the NOR and MS groups were also lightly immobilized for 30 s without acupuncture and then returned to their cages [10].

Open field test (OFT)

On PND 20, locomotor activity was measured, at 30 min after the acupuncture stimulation, in a dark room equipped with a video camera above the center of the floor. The animals were individually placed in the center of a rectangular container (60 × 60 × 30 cm) made of black polyethylene and their behavior was recorded over a chosen period. The distance they traveled was monitored by use of a computerized video-tracking system using S-MART software (PanLab, Barcelona, Spain) for 20 min. The floor surface of each chamber was thoroughly cleaned with 70 % ethanol between tests.

Tail suspension test (TST)

On PND 21, TST was performed 30 min after the last acupuncture stimulation. The rats were suspended 50 cm above the floor of the chamber by adhesive tape placed

approximately 1 cm from the tip of the tail according to the methods of Steru [16]. The total duration of immobility induced by tail suspension was measured, for 6 min, by use of BSTST2CA computerized TST equipment with BSTST2LOG software (Bioseb, Boulogne, France).

Analysis of tissue levels of 5-HT and 5-HIAA

After TST, animals were immediately sacrificed by cervical dislocation and their prefrontal cortices were extracted, weighed, and stored at −80 °C until analysis.

Concentrations of 5-HT and 5-hydroxyindole-3-acetic acid (5-HIAA) were quantified by high-performance liquid chromatography (HPLC). HPLC equipment consisted of model 1525 binary pump and 717plus autosampler (Waters, Milford, USA) using Coulochem® III (ESA, Chelmsford, USA) electrochemical detector with a 5011A analytical cell with an oxidation potential of +320 mV. The column was a 4-μm, 3.9 × 150 mm, Nova-Pack® column (Waters), and the column temperature was ambient.

The mobile phase (pH 3.2) was made up of 150 mM NaH_2PO_4, 50 μM ethylenediaminetetraacetic acid, 1.85 mM 1-octanesulfonic acid, and 100 μL/L triethylamine (Sigma, St Louis, MO, USA) in methanol–acetonitrile–water 4:6:90 (*v*/*v*) (Mallinckrodt Baker, Phillipsburg, USA) and the flow rate was 0.8 mL/min.

Each tissue ($n = 6$ per each group) was homogenized in 0.3 M perchloric acid solution. Upon complete homogenization, the samples were centrifuged at 27,000×*g* for 30 min at 4 °C. After homogenization, the supernatant was extracted and loaded into a Costar Spin-X® tube (0.22 μM Nylon Part, Corning Incorporated) filter and centrifuged at 12,000×*g* for 5 min at 4 °C. The filtered brain samples were injected into the system at an injection volume of 20 μL.

The chromatograms were integrated and quantified by use of Smart Chrome ver.2.02 (Kya Tech, Tokyo, Japan), and the amount of each compound was determined by comparison with the peak area of standards run in each assay. A standard curve was generated from concentrated standard samples and samples were not analyzed unless a linear standard curve with R^2 greater than 0.995 was achieved.

Western blotting

Expression of 5-HTT and BDNF was determined by western blotting. The collected prefrontal cortex tissues ($n = 6$ in each group) were homogenized on ice and lysed in RIPA buffer. After homogenization, the tissues were centrifuged at 12,000×*g* for 20 min at 4 °C. Equal amounts of protein (30 μg) from each sample were separated on SDS–polyacrylamide gels (12 % SDS-PAGE) and transferred to nitrocellulose membranes. After being blocked with 5 % nonfat dry milk in Tris-buffered saline (TBS, pH 7.6), the membranes were incubated overnight at 4 °C with anti-5-HTT (Abcam, Cambridge, UK) or BDNF (Santa Cruz Biotechnology, Santa Cruz, CA, USA) antibodies that were diluted 1:1000 in blocking solution. The secondary antibody was horseradish peroxidase-conjugated anti-rabbit antibody (1:2000; Pierce, Rockford, IL, USA). Band detection was performed by use of the Enhanced Chemiluminescence (ECL) detection kit (Pierce). These blots then were re-probed with mouse monoclonal anti-β-actin antibody (1:1000; Santa Cruz). The band intensity of the detected proteins was measured by densitometry.

Statistical analysis

Experimental results are expressed as mean ± SEM. Statistical analysis was performed by analysis of variance (ANOVA). Significance was determined by use of the Neuman–Keuls post-hoc test. In all analyses, differences were considered statistically significant at $P < 0.05$.

Results

Effect of acupuncture on locomotor activity in the OFT

The locomotor activity of the NOR group was 2137.14 ± 92.94 cm, but there was no significant difference from that of the MS group (2094.65 ± 134.30 cm). Acupuncture stimulation at HT7 (2257.26 ± 114.60 cm) and ST36 (2209.30 ± 84.34 cm) also had no significant effect on their activity (Fig. 1).

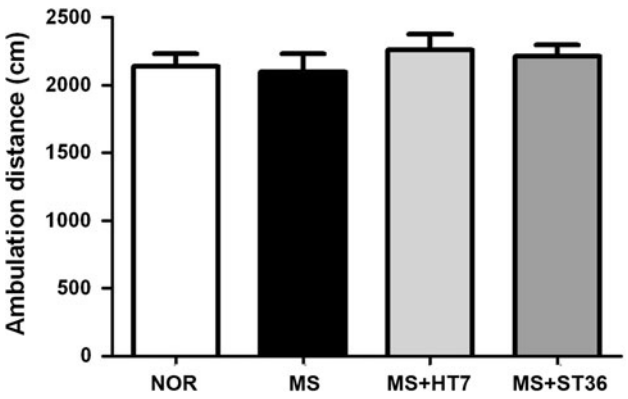

Fig. 1 Ambulation distances of rat pups in the open field test. There were no significant differences among the groups. *NOR* normal group, *MS* maternally separated control group, *MS + HT7* maternally separated group with acupuncture stimulation at HT7 acupoint, *MS + ST36* maternally separated group with acupuncture stimulation at ST36

Effect of acupuncture on immobility time in the TST

The immobility time of the mice in the MS group (87.75 ± 13.09 s) was significantly higher than that of mice in the NOR group (44.80 ± 7.25 s, $P < 0.05$). However, that in the MS + HT7 group (31.20 ± 5.61 s) was significantly less than that in the MS group ($P < 0.05$) and not significantly different from that in the NOR group, whereas that in the MS + ST36 group (58.00 ± 17.31 s) was not significantly different from that in the MS group (Fig. 2).

Effect of acupuncture on 5-HT and 5-HIAA levels in the PFC

The effects of acupuncture stimulation on levels of 5-HT and 5-HIAA and the 5-HIAA/5-HT ratio in the PFC of maternally separated rats are shown in Table 1. No significant differences were found in 5-HT or 5-HIAA, but 5-HIAA/5-HT ratio was increased significantly in the MS group (0.97 ± 0.05, $P < 0.05$ vs. NOR group) compared with that in the NOR group (0.77 ± 0.06). Acupuncture stimulation at HT7 significantly suppressed the 5-HIAA/5-HT ratio (0.80 ± 0.05, $P < 0.05$ vs. MS group) and the ratio was not different significantly from that in NOR group, but acupuncture stimulation at ST36 did not significantly change the ratio (0.87 ± 0.04).

Effect of acupuncture on expressions of serotonin transporter protein

Maternal separation induced a significant increase in 5-HTT expression (139.80 ± 7.86 %, $P < 0.05$ vs. NOR group) in the PFC, but acupuncture stimulation at HT7 suppressed it significantly (78.01 ± 9.25 %, $P < 0.01$ vs. MS group) and it was not significantly different from that in the NOR group. Acupuncture stimulation at ST36 did not significantly affect its expression (112.42 ± 14.96 %, Fig. 3).

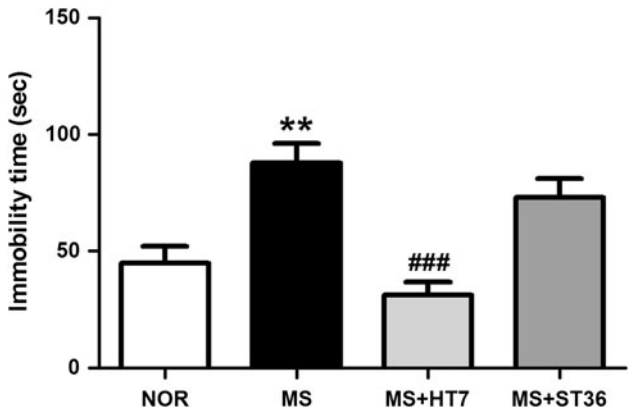

Fig. 2 Immobility times of rat pups in the open field test. *NOR* normal group, *MS* maternally separated control group, *MS + HT7* maternally separated group with acupuncture stimulation at HT7 acupoint, *MS + ST36* maternally separated group with acupuncture stimulation at ST36. $^{**}P < 0.01$ versus NOR group, and $^{###}P < 0.001$ versus MS group

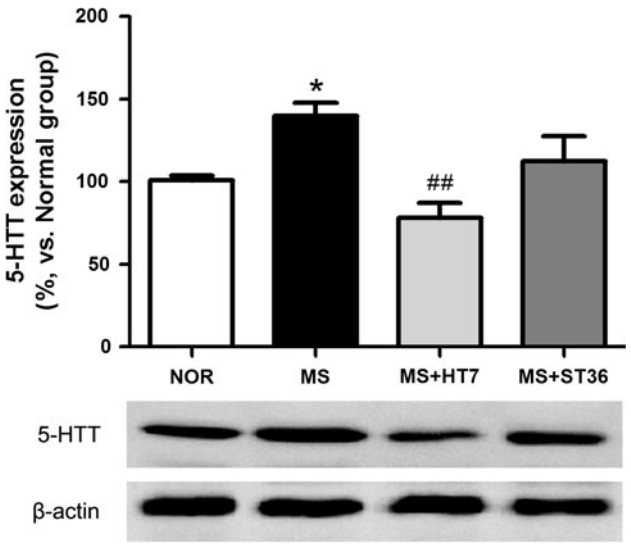

Fig. 3 Expression of serotonin transporter (5-HTT) in the prefrontal cortex of rat pups. *NOR* normal group, *MS* maternally separated control group, *MS + HT7* maternally separated group with acupuncture stimulation at HT7 acupoint, *MS + ST36* maternally separated group with acupuncture stimulation at ST36. $^{*}P < 0.05$ versus NOR group, and $^{##}P < 0.01$ versus MS group

Table 1 Levels of serotonin (5-hydroxytryptamine; 5-HT) and 5-hydroxyindole-3-acetic acid (5-HIAA) in the prefrontal cortex of maternally-separated rat pups

Monoamine or metabolite	NOR	MS	MS + HT7	MS + ST36
5-HT	107.70 ± 5.63	98.26 ± 3.90	112.80 ± 4.39	103.80 ± 3.24
5-HIAA	82.46 ± 5.28	95.03 ± 3.14	90.20 ± 6.19	90.36 ± 4.02
5-HIAA/5-HT	0.77 ± 0.06	0.97 ± 0.05*	0.80 ± 0.05$^{\#}$	0.87 ± 0.04

There were no significant differences among the groups. The units of 5-HT and 5-HIAA were ng/g tissue

* $P < 0.05$ versus NOR group, and $^{\#}$ $P < 0.05$ versus MS group

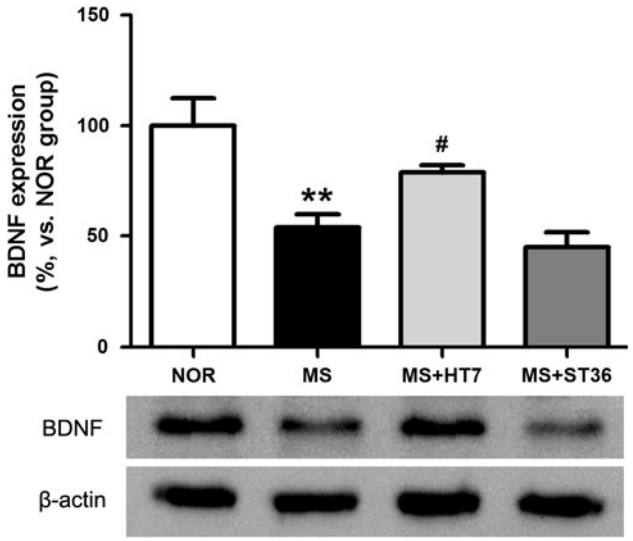

Fig. 4 Expression of brain-derived neurotrophic factor (BDNF) in the prefrontal cortex of rat pups. *NOR* normal group, *MS* maternally separated control group, *MS + HT7* maternally separated group with acupuncture stimulation at HT7 acupoint, *MS + ST36* maternally separated group with acupuncture stimulation at ST36. $^{**}P < 0.01$ versus NOR group, and $^{\#}P < 0.05$ versus MS group

Effect of acupuncture on expression of BDNF protein

As shown in Fig. 4, the level of BDNF was significantly reduced in the MS (54.06 ± 5.87 %, $P < 0.01$) and MS + ST36 (44.98 ± 6.73 %, $P < 0.001$) groups compared with that in the NOR group, but acupuncture stimulation at HT7 (78.95 ± 3.06 %, $P < 0.05$) significantly increased the BDNF level. That in the MS + HT7 group was not different significantly from that in the NOR group.

Discussion

These results reveal that acupuncture stimulation at acupoint HT7 can improve MS-induced behavioral changes, normalize 5-HIAA/5-HT ratio, and alleviate the 5-HTT increase and BDNF reduction in the PFC of maternally separated rat pups.

To evaluate the effect of acupuncture treatment on depression, we measured the immobility time of the rats in the TST and ambulation distance in the OFT. The TST has become one of the most widely used models for assessing antidepressant-like activity. The test is based on the fact that animals subjected to short-term, inescapable stress of being suspended by their tail will develop an immobile posture [17]. In the TST, the immobility time was remarkably increased in the MS group, thus early MS induces depressive-like behavior. However, the MS + HT7 group had a significant reduced immobility time compared with the MS group and the MS + ST36 group. This result indicated that acupuncture stimulation at HT7 had an anti-depressive effect.

Ambulation distances in the OFT in this study were not significantly different among the groups, which was different from that in the previous study. In the previous study, rat pups were maternally-separated on PND 14, and the ambulation distances in the MS and MS + HT7 groups were significantly different from each other on PND 21 [10]. But we found there was some possibility that some undiscovered factor besides MS might intervene in the result of the study. After MS on PND 14, maternally-separated rats lost body weight for 2 days [10], which might indicate they experienced unintended 2-day starvation. Therefore we separated rat pups from their mothers on PND 15, a day later than in the previous study, to minimize the starvation in this study, and found there was no significant difference in the distances of the maternally-separated groups. This result suggests that the significant change of the body weight in the previous study might be because of unintended starvation, however more rigorous studies are needed to confirm this.

Depression-like behavior is related to neurobiological responses in the brain, and the PFC is important in the development and treatment of depression [12]. Although many factors are related to depressive behavior, the 5-HT system has been strongly implicated in the effects of early-life stress on behavior [18] and chronic stress in attempts to produce animal models of depression give rise to increased 5-HT turnover in brain regions [19]. To observe the relationship between depression-like behavior and 5-HT in the PFC, levels of 5-HT and 5-HIAA in the PFC were evaluated by HPLC, and neither MS nor acupuncture stimulation significantly changed levels of 5-HT and its metabolite. Other reports evaluating these levels also showed that MS within 2 weeks did not change in the PFC [20, 21]. But 5-HIAA/5-HT ratio was significantly increased by maternal separation, and acupuncture stimulation at HT7 regulated the change of 5-HIAA/5-HT ratio in this study. These results suggest that MS could not significantly change levels of 5-HT and 5-HIAA at this time but did induce the disturbance of 5-HT/5-HIAA turnover in the PFC, and acupuncture stimulation at HT7 could suppress the disturbance.

In the 5-HT system implicated in the behavioral change, 5-HTT is of crucial importance in 5-HT neurotransmission because it regulates reuptake of 5-HT from the synaptic cleft after release and terminates the actions of the biogenic amines by clearing them from the extracellular space. So it is the primary site of action for many antidepressant drugs [18, 22]. Previous studies have suggested that 5-HTT expression is involved in the transition between early life

stress and mental disease behavior [23, 24]. In this study, expression of 5-HTT protein was significantly increased in the PFC of the MS group, which may indicate depressive behavior because of excessive reuptake of 5-HT. But acupuncture stimulation at HT7, but not at ST36, significantly suppressed the increase of 5-HTT by MS. These results indicate that the abnormal increase of 5-HTT is a major factor in the MS-induced behavioral change and that acupuncture stimulation at HT7 could improve the depressive behavior by suppressing 5-HTT expression.

Brain-derived neurotrophic factor is the central neurotrophic factor related to critical CNS function, and it is important in the control of mood, emotion, and cognition [25]. According to previous animal studies, BDNF expression is altered by stressors including immobilization stress, foot shock, social defeat, and early maternal deprivation, and MS-induced stress reduces BDNF expression or its activity in the PFC, hippocampus, amygdala, and striatum [26–28]. Thus we investigated whether BDNF expression in the PFC is altered by MS or acupuncture stimulation; we observed that MS was responsible for a significant reduction in BDNF levels, as in previous studies, and that acupuncture stimulation at HT7 prevented the reduction. Antidepressants, for example monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRI), and tricyclic agents, can prevent the reduction of BDNF [29, 30], and chronic SSRI treatment increased BDNF protein levels by increasing 5-HT neurotransmission in adult rats [31]. In this study, acupuncture stimulation suppressed the 5-HTT expression, which had the effect of increasing 5-HT neurotransmission as an SSRI treatment. Therefore, the increase of BDNF by acupuncture stimulation may be related to the increase of 5-HT neurotransmission via 5-HTT suppression.

In conclusion, this study showed that acupuncture stimulation at HT7 can improve MS-induced behavioral changes and regulate the MS-induced changes of 5-HIAA/5-HT ratio, 5-HTT, and BDNF in the PFC of rat pups. Although it remains elusive which is more crucial in improving the behavior between reduction of 5-HTT expression and restoration of 5-HIAA/5-HT ratio by the acupuncture stimulation, it is obvious that acupuncture stimulation at HT7 alleviated the MS-induced impairment of the 5-HT system in this study. On the basis of our results and previous studies, we propose that regulation of 5-HT system by acupuncture stimulation is important in the acupuncture-induced benefits in the animal model of depression.

Acknowledgments This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (nos 2010-0021190 and 2005-0049404).

References

1. Mill J, Petronis A (2007) Molecular studies of major depressive disorder: the epigenetic perspective. Mol Psychiatry 12:799–814
2. Kendler KS, Sheth K, Gardner CO, Prescott CA (2002) Childhood parental loss and risk for first-onset of major depression and alcohol dependence: the time-decay of risk and sex differences. Psychol Med 32:1187–1194
3. Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB (1999) The role of corticotropin-releasing factor in depression and anxiety disorders. J Endocrinol 160:1–12
4. Francis DD, Meaney MJ (1999) Maternal care and the development of stress responses. Curr Opin Neurobiol 9:128–134
5. Haenisch B, Bonisch H (2011) Depression and antidepressants: insights from knockout of dopamine, serotonin or noradrenaline re-uptake transporters. Pharmacol Ther 129:352–368
6. Sharp T, Cowen PJ (2011) 5-HT and depression: is the glass half-full? Curr Opin Pharmacol 11:45–51
7. Roschke J, Wolf C, Muller MJ, Wagner P, Mann K, Grozinger M, Bech S (2000) The benefit from whole body acupuncture in major depression. J Affect Disord 57:73–81
8. Xiujuan Y, Xiang L, Hecun L, Jia Y (1994) Comparative study of electro-acupuncture and maprolitine in treating depression. J Tradition Chin Med 14:14–18
9. Park HJ, Chae Y, Kim JW, Lee H, Chung JH (2011) Effect of acupuncture on hypothalamic–pituitary–adrenal system in maternal separation rats. Cell Mol Neurobiol 31:1123–1127
10. Lim S, Ryu YH, Kim ST, Hong MS, Park HJ (2003) Acupuncture increases neuropeptide Y expression in hippocampus of maternally-separated rats. Neurosci Lett 343:49–52
11. Yang Y, Raine A (2009) Prefrontal structural and functional brain imaging findings in antisocial, violent, and psychopathic individuals: a meta-analysis. Psychiatry Res 174:81–88
12. Koenigs M, Grafman J (2009) The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. Behav Brain Res 201:239–243
13. Park HJ, Chae Y, Jang J, Shim I, Lee H, Lim S (2005) The effect of acupuncture on anxiety and neuropeptide Y expression in the basolateral amygdala of maternally separated rats. Neurosci Lett 377:179–184
14. Suckow MA, Weisbroth SH, Franklin C (2006) The laboratory rat. Elsevier Academic Press, Burlington
15. Skjeie H, Skonnord T, Fetveit A, Brekke M (2011) A pilot study of ST36 acupuncture for infantile colic. Acupunct Med 29:103–107
16. Steru L, Chermat R, Thierry B, Simon P (1985) The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology 85:367–370
17. Cryan JF, Mombereau C, Vassout A (2005) The tail suspension test as a model for assessing antidepressant activity: review of pharmacological and genetic studies in mice. Neurosci Biobehav Rev 29:571–625
18. Fuller RW, Wong DT, Robertson DW (1991) Fluoxetine, a selective inhibitor of serotonin uptake. Med Res Rev 11:17–34
19. Blanchard DC, Cholvanich P, Blanchard RJ, Clow DW, Hammer RP Jr, Rowlett JK, Bardo MT (1991) Serotonin, but not dopamine, metabolites are increased in selected brain regions of subordinate male rats in a colony environment. Brain Res 568:61–66
20. Oreland S, Raudkivi K, Oreland L, Harro J, Arborelius L, Nylander I (2011) Ethanol-induced effects on the dopamine and serotonin systems in adult Wistar rats are dependent on early-life experiences. Brain Res 1405:57–68
21. Niwa M, Matsumoto Y, Mouri A, Ozaki N, Nabeshima T (2011) Vulnerability in early life to changes in the rearing environment plays a crucial role in the aetiopathology of psychiatric disorders. Int J Neuropsychopharmacol 14:459–477

22. Hoffman BJ, Hansson SR, Mezey E, Palkovits M (1998) Localization and dynamic regulation of biogenic amine transporters in the mammalian central nervous system. Front Neuroendocrinol 19:187–231
23. Kinnally EL, Tarara ER, Mason WA, Mendoza SP, Abel K, Lyons LA, Capitanio JP (2010) Serotonin transporter expression is predicted by early life stress and is associated with disinhibited behavior in infant rhesus macaques. Genes Brain Behav 9:45–52
24. Pluess M, Velders FP, Belsky J, van Ijzendoorn MH, Bakermans-Kranenburg MJ, Jaddoe VW, Hofman A, Arp PP, Verhulst FC, Tiemeier H (2011) Serotonin transporter polymorphism moderates effects of prenatal maternal anxiety on infant negative emotionality. Biol Psychiatry 69:520–525
25. Ernfors P, Wetmore C, Olson L, Persson H (1990) Identification of cells in rat brain and peripheral tissues expressing mRNA for members of the nerve growth factor family. Neuron 5:511–526
26. Roceri M, Hendriks W, Racagni G, Ellenbroek BA, Riva MA (2002) Early maternal deprivation reduces the expression of BDNF and NMDA receptor subunits in rat hippocampus. Mol Psychiatry 7:609–616
27. Lippmann M, Bress A, Nemeroff CB, Plotsky PM, Monteggia LM (2007) Long-term behavioural and molecular alterations associated with maternal separation in rats. Eur J Neurosci 25:3091–3098
28. Taliaz D, Loya A, Gersner R, Haramati S, Chen A, Zangen A (2011) Resilience to chronic stress is mediated by hippocampal brain-derived neurotrophic factor. J Neurosci 31:4475–4483
29. Coppell AL, Pei Q, Zetterstrom TS (2003) Bi-phasic change in BDNF gene expression following antidepressant drug treatment. Neuropharmacology 44:903–910
30. Balu DT, Hoshaw BA, Malberg JE, Rosenzweig-Lipson S, Schechter LE, Lucki I (2008) Differential regulation of central BDNF protein levels by antidepressant and non-antidepressant drug treatments. Brain Res 1211:37–43
31. Gardier AM (2009) Mutant mouse models and antidepressant drug research: focus on serotonin and brain-derived neurotrophic factor. Behav Pharmacol 20:18–32