Available online at www.sciencedirect.com
ScienceDirect
Pharmacology, Biochemistry and Behavior 87 (2007) 41–47
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Antidepressant-like effects of *Albizzia julibrissin* in mice: Involvement of the 5-HT_{1A} receptor system

Ji-Hyun Kim [a], Sun Yeou Kim [b], Seok-Yong Lee [a], Choon-Gon Jang [a,*]

[a] *Department of Pharmacology, College of Pharmacy, Sungkyunkwan University, Suwon 440-746, Republic of Korea*
[b] *Department of Medical Science, Graduate School of East–West Medical Science, Kyung Hee University, Youngin 446-701, Republic of Korea*

Received 17 May 2006; received in revised form 10 March 2007; accepted 30 March 2007
Available online 6 April 2007

Abstract

The present study was undertaken to investigate the antidepressant-like effects of the methylene chloride fraction of *Albizzia julibrissin* (MCAJ) using a tail suspension test in mice. MCAJ was orally administered at 50, 100, or 200 mg/kg to mice, 1 h before the tail suspension test. Acute treatment with MCAJ at 200 mg/kg significantly reduced the immobility time compared with the control group, and thus showed an antidepressant-like effect. This effect was comparable to that of imipramine at 10 mg/kg. This antidepressant-like effect was reversed by treatment with WAY-100635 (a 5-HT_{1A} receptor antagonist) or pindolol (a 5-$HT_{1A/1B}$ receptor antagonist). However, the antidepressant effect of MCAJ was not effected by treatment with GR55562 (a 5-HT_{1B} receptor antagonist) or ketanserin (a 5-HT_{2A} receptor antagonist). Therefore, our findings suggest that MCAJ exerts its antidepressant-like effect via the 5-HT_{1A} receptor system.

Keywords: *Albizzia julibrissin*; Tail suspension; Depression; Mice; 5-HT receptor

1. Introduction

Albizzia julibrissin Durazz (Leguminosae), commonly named mimosa or silk trees, are widely distributed in Asia. Traditionally, the stem bark of *A. julibrissin* was dried and boiled with water. Asians administered this *A. julibrissin* soup to patients as a folk medicine to treat insomnia, diuresis, sthenia, and confusion (Zhu, 1998). It has been reported that saponins (Kinjo et al., 1992; Chen et al., 1997), phenolic glycosides (Jung et al., 2004b), triterpenes (Chen and Zhang, 1997), flavonoids, and other compounds (Kang et al., 2000) have been isolated from the stem bark of *A. julibrissin*. A previous study showed that the saponin-containing fraction of *Albizzia lebbeck* improves object recognition (Chintawar et al., 2002). Brain concentrations of GABA and dopamine were decreased whereas serotonin levels were increased after treatment with the saponin-containing fraction of *A. lebbeck* (Chintawar et al., 2002). Recently, it was reported that the aqueous extract of *A. julibrissin* stem bark has anxiolytic-like activity in rats in the elevated plus maze test (Kim et al., 2004). Moreover, we recently reported that 5-HT_{1A} receptor binding after *A. julibrissin* treatment was markedly increased in the frontal cortex, hippocampus (CA2 and CA3 regions), and in the lateral septum compared to vehicle-treated animals (Jung et al., 2005). Therefore, a psychopharmacological role for *A. julibrissin* has been suggested.

5-HT_{1A} receptors play a critical role in the pathophysiology of anxiety and depression as well as in the mode of action of anxiolytic and antidepressant drugs (Lesch and Mossner, 1999). Binding potential values were reduced across many of the regions examined, including frontal, temporal, and limbic cortex in both unmedicated and medicated depressed patients compared to healthy volunteers (Sargent et al., 2000). Given the fact that the 5-HT system continues to be an important target for drug development and production, strategies aimed at the development of natural products to modify 5-HT function are likely to be exploited by enterprises participating actively in the introduction of alternative therapeutic approaches. The results described above suggest that *A. julibrissin* may control

* Corresponding author. Tel.: +82 31 290 7780; fax: +82 31 292 8800.
E-mail address: jang@skku.ac.kr (C.-G. Jang).

0091-3057/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2007.03.018

depressive responses via activation of the serotonergic system. However, there have been no reports of antidepressant-like effects from the methylene chloride fraction of *A. julibrissin*.

Furthermore, the World Health Organization predicts that depression will be the second-most common chronic condition in clinical practice, exceeded only by hypertension by the year 2020 (Nowak et al., 2003). Despite the progress made in recent years in the development of clinically relevant antidepressant drugs, currently available antidepressants are not totally effective and are associated with many undesirable adverse effects (Nestler et al., 2002). In addition, only 60% of patients are responsive to treatment with available antidepressants (Gareri et al., 2000). For this reason, new drugs capable of controlling the symptoms associated with depressive disorders are needed. Little is known about the antidepressant-like effects of *A. julibrissin*. In the present work, we assessed the possible antidepressant-like effects of *A. julibrissin* using in vivo pharmacological procedures, and examined whether the 5-HT_{1A} receptor system is involved in these antidepressant-like effects.

2. Materials and methods

2.1. Animals

Male ICR mice (MJ Ltd. Co., Seoul) weighing 20–25 g were used in all experiments. Mice were housed ten per cage. All animals were acclimatized for 1 week prior to the experiments and were used only once. Mice were maintained in an animal room on a 12 h light/dark cycle at 22±2 °C. All animal care procedures were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals, and were approved by the Institutional Animal Care and Use Committee of Sungkyunkwan University. All animals were introduced to the testing room 1 h before being tested and all behavioral tests were performed in the light phase between 9 a.m. and 5 p.m.

2.2. Sample preparation

The stem barks of *A. julibrissin* were collected in Hwaseong City, South Korea in July 2001. The plant was identified by Dr. Changsoo Yuk, College of Pharmacy, Kyung Hee University. A voucher specimen (#KHUHP-12) was deposited at the herbarium of the Graduate School of East–West Medical Science, Kyung Hee University. The dried powdered stem barks (750 g) of *A. julibrissin* were extracted twice (each time for 3 h followed by heating) with a mixture of EtOH and water (1:1) in a reflux apparatus. The extract was concentrated to dryness under vacuum. The yield of the 50% ethanolic mixture extract was 18% (w/w, 132 g). Part of the ethanolic extract (68 g) was suspended in 1 L of distilled water, and partitioned successively with methylene chloride and BuOH. The yields of the methylene chloride, butanol and water soluble fractions were 13.3, 16.4 and 38.3%. The methylene chloride soluble fraction (MCAJ, 13.3 g) was used in the animal experimental model. This fraction was prepared by boiling the ethanolic extract with 1 L CH_2Cl_2. The final yield of the methylene chloride fraction was 3.6%.

2.3. Drugs

Imipramine (a tricyclic antidepressant), WAY-100635, and pindolol were purchased from Sigma (Sigma Chemical Co., St Louis, USA). GR55562 and ketanserin were purchased from Tocris (Tocris Cookson Ltd., UK). All drugs were dissolved in 0.9% saline. MCAJ (50, 100, or 200 mg/kg, p.o.) and imipramine (10 mg/kg, i.p.) were administered 1 h before testing. The animals were pretreated with WAY-100635 (0.1, 0.3, or 1 mg/kg, s.c.), pindolol (1.25, 2.5, or 5 mg/kg, s.c.), GR55562 (1.25, 2.5, or 5 mg/kg, s.c.), ketanserin (0.5, 1, or 2 mg/kg, s.c.) or saline control 30 min before MCAJ treatment. Imipramine was used as a reference drug.

2.4. Measurements of locomotor activity in the open field

Animals were introduced to the test room 1 h before being tested. Locomotion was evaluated in transparent activity cages (opaque plastic, 30×30×30 cm), and video-tracking was conducted under subdued illumination (25 lx) 1 h after administration of 200 mg/kg MCAJ, locomotor activity in the open field chamber was recorded for 5 min using a computer. Imipramine (10 mg/kg) was used as a positive control. Each test group consisted of nine mice. Activity cages and floor surfaces were thoroughly cleaned with 70% ethanol between tests.

2.5. Measurement of tail suspension test

The tail suspension test (TST) was performed according to the method described by Steru et al. (1987) with modifications. Briefly, mice were suspended by the tail from a metal rod using adhesive tape. The rod was fixed 45 cm above the surface of a table in a sound-isolated room. The mice were at least 15 cm apart from each other and a styrofoam divider was placed between them so that they could not see each other during testing. Mice were considered immobile only when they hung passively and were completely motionless. Test sessions were videotaped for 6 min and immobility times were noted by an observer. The duration of immobility was observed during the final 4 min of the test. TST was measured 1 h after MCAJ treatment. The allocations to treatment groups were randomized within each TST session.

2.6. Measurement of body temperature in mice

Body temperature was determined using a rectal probe thermometer (TH-5, Physitemp, Clifton, NJ, USA) inserted 2.5 cm into the rectum. Animals received either saline or MCAJ 200 mg/kg orally 30 min after an s.c. injection of saline or antagonist (WAY-100635, 1 mg/kg). Rectal temperature was measured immediately before the injection and then again at 60, and 120 min after the injection of MCAJ. The difference in rectal temperature between pre-value and post-value was calculated.

2.7. Statistical analysis

The data are expressed as mean±SEM. Statistical significance of differences were assessed by one-way ANOVA

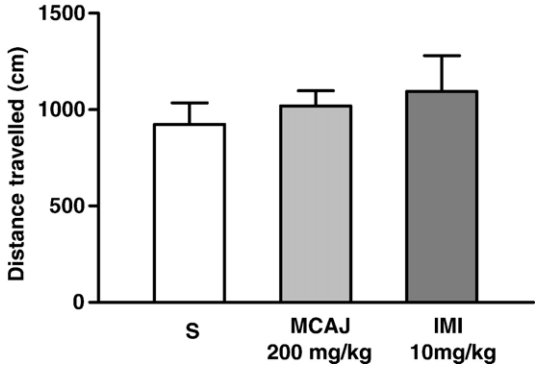

Fig. 1. The effect of MCAJ on locomotor activity in the open field test. Data are expressed as means and standard errors (n=9). S, saline; IMI, imipramine.

followed by the Student–Newman–Keuls post-hoc test. Differences were considered to be statistically significant when p-values were <5%.

3. Results

3.1. Effect of MCAJ on locomotor activity in the open field test

The saline-treated group traveled a mean distance of 922.8±112.7 cm. The group treated with 200 mg/kg MCAJ showed no change in distance traveled (1019±78.4 cm) compared to the saline control group. Similarly, the group treated with 10 mg/kg imipramine traveled 1094±186.4 cm [F(2,24)=0.4143, p<0.05, Fig. 1].

3.2. Antidepressant-like effect of acute MCAJ treatment on TST

A single treatment with 200 mg/kg MCAJ significantly reduced the TST immobility time, showing antidepressant-like effect when compared to the saline control group [F(4,30)=4.053, p<0.05, Fig. 2]. This effect of MCAJ was comparable to that of the antidepressant imipramine at 10 mg/kg [F(4,30)=4.250, p<0.05, Fig. 2].

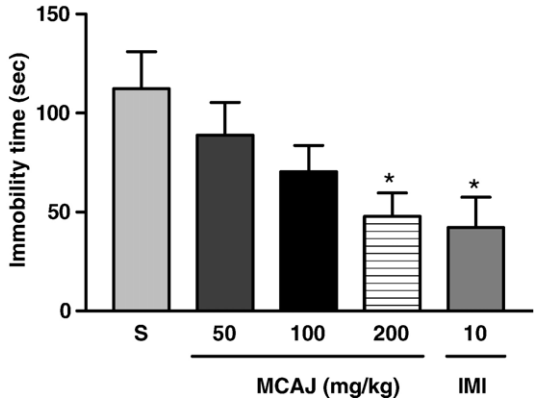

Fig. 2. Antidepressant-like activity of acute MCAJ treatment on TST. Data are expressed as means and standard errors (n=6–8). S, saline; IMI, imipramine. *p<0.05, compared with the saline control group.

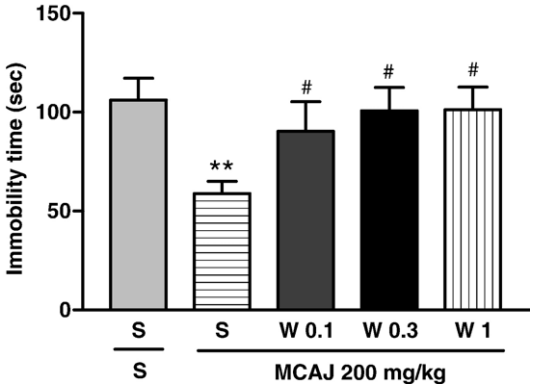

Fig. 3. The effect of WAY-100635 on antidepressant-like effect of MCAJ. Data are expressed as means and standard errors (n=9–17). S, saline; W, WAY-100635. **p<0.01, compared with the saline control group. $^{\#}p$<0.05, compared with the MCAJ control group.

3.3. Effect of WAY-100635 on the antidepressant-like effect of MCAJ

The administration of 200 mg/kg MCAJ significantly reduced immobility times compared to the saline controls [F(4,60)=5.025, p<0.01, Fig. 3]. This effect of MCAJ was blocked by pretreating with the 5-HT_{1A} receptor antagonist, WAY-100635, at 0.1 mg/kg [F(4,60)=3.006, p<0.05], 0.3 mg/kg [F(4,60)=3.800, p<0.05], and 1 mg/kg [F(4,60)=4.004, p<0.07].

3.4. Effect of pindolol on the antidepressant-like effect of MCAJ

The administration of 200 mg/kg MCAJ significantly reduced immobility times compared to saline controls [F(4,48)=4.979, p <0.01, Fig. 4]. This effect of MCAJ was abolished by pretreating with the 5-$HT_{1A/1B}$ receptor antagonist, pindolol, at 1.25 mg/kg [F(4,48)=3.542, p<0.05], 2.5 mg/kg [F(4,48)=5.373, p<0.01], and 5.0 mg/kg [F(4,48)=3.583, p<0.05].

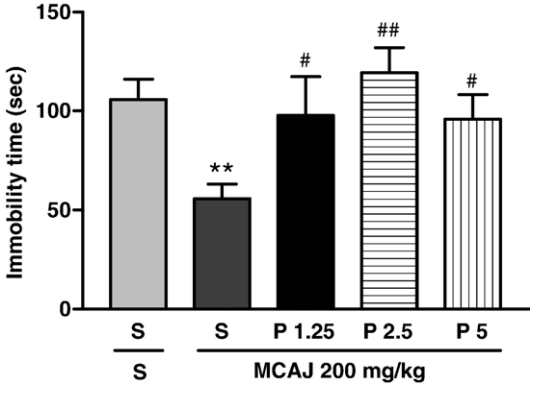

Fig. 4. The effect of pindolol on the antidepressant-like effect of MCAJ. Data are expressed as means and standard errors (n=8–14). S, saline; P, pindolol. **p<0.01, compared with the saline control group. $^{\#}p$<0.05, $^{\#\#}p$<0.01, compared with the MCAJ control group.

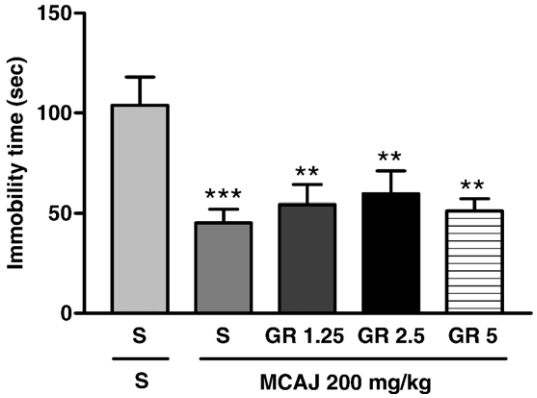

Fig. 5. The effect of GR55562 on the antidepressant-like effect of MCAJ. Data are expressed as means and standard errors (n=8–15). S, saline; R, GR55562. **p<0.01, ***p<0.001, compared with the saline control group.

3.5. Effect of GR55562 on the antidepressant-like effect of MCAJ

The administration of 200 mg/kg MCAJ significantly reduced immobility times compared to the saline controls [F(4,46)=6.403, p<0.001, Fig. 5]. This effect of MCAJ was not changed by pretreating with the 5-HT_{1B} receptor antagonist, GR55562 at 1.25, 2.5, or 5 mg/kg.

3.6. Effect of ketanserin on antidepressant-like effect of MCAJ

The administration of 200 mg/kg MCAJ significantly reduced immobility times compared to saline controls [F(4.35)=3.744, p<0.05, Fig. 6]. This effect of MCAJ was unchanged by pretreating with the 5-HT_{2A} receptor antagonist, ketanserin, at 0.5, 1, or 2 mg/kg.

3.7. Effects of WAY-100635, pindolol, GR55562, and ketanserin on the TST

The immobility time of the group treated with saline was 129±11.2 s. The immobility time of the mice treated with 1 mg/kg WAY-100635, 5 mg/kg pindolol, 5 mg/kg GR55562, or 2 mg/kg ketanserin were 137±15.0, 147±13.6, 142±13.0, and 168±8.2 s, respectively. Administration of these drugs did not change the immobility time in the TST compared to the saline control group [F(4.41)=1.184, p<0.33, Fig. 7].

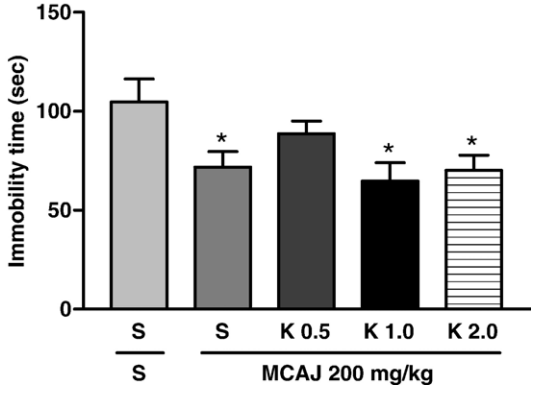

Fig. 6. The effect of ketanserin on the antidepressant-like effect of MCAJ. Data are expressed as means and standard errors (n=8). S, saline; K, ketanserin. *p<0.05, compared with the saline control group.

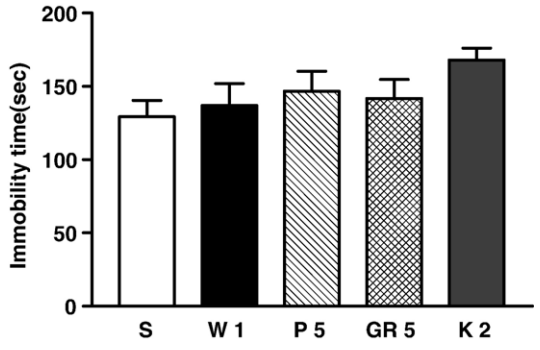

Fig. 7. The effects of WAY-100635, pindolol, GR55562, and ketanserin on tail suspension test. Data are expressed as means and standard errors (n=9–10). S, saline; W, WAY-100635; P, pindolol; R, GR55562; K, ketanserin.

3.8. Effect of WAY-100635 on MCAJ induced hypothermia in mice

Rectal temperature was measured 60 and 120 min after vehicle or MCAJ (200 mg/kg, p.o.) administration. MCAJ

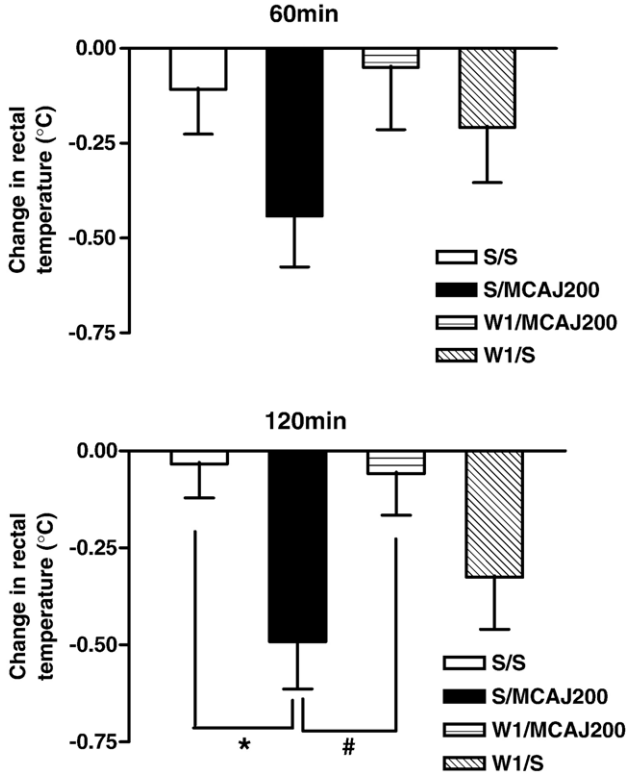

Fig. 8. The effect of WAY-100635 on MCAJ induced hypothermia in mice. The first measurement was made just prior to the saline or WAY-100635 injection and was repeated before saline or MCAJ dosing and then 60 and 120 min after injection. Data are expressed as difference of body temperature between pre- and post-measurement of MCAJ injection at 0, 60, and 120 min in mice (n=15). S, saline; W, WAY-100635. *p<0.05, compared with the saline control group. #p<0.05, compared with the MCAJ control group.

(200 mg/kg) significantly decreased the rectal temperature by − 0.5±0.08 °C 120 min after the MCAJ administration [$F(3,45)=3.710$, $p<0.05$, Fig. 8]. WAY-100635 antagonized the response at a dose of 1 mg/kg (s.c.) ($p<0.05$), which itself had no effect on rectal temperature.

4. Discussion

Depression is a common, debilitating, life-threatening illness with a high incidence. Numerous antidepressant compounds are now available, which presumably act via different mechanisms involving the serotonergic, noradrenergic and/or dopaminergic systems. Heterogeneity of clinical response to antidepressant and mood-stabilizing drugs and susceptibility to adverse effects are major clinical problems (Lerer and Macciardi, 2002). Therefore, new drugs are still needed for the control of depression-related disorders.

In the present study, our results demonstrate that treatment with MCAJ produced a significant antidepressant-like response. This effect was comparable to that of the classical antidepressant imipramine at 10 mg/kg. Moreover, the administration of MCAJ did not affect locomotor activity in the open field test. Kasture et al. (2000) reported a convulsive, ataxic and sedative profile and narrow window of safety for a methanolic extraction of *A. lebbeck*. In our experiment, however, no change in locomotor activity and no myorelaxant effect were seen in any MCAJ-treated group compared to the saline control group (data not shown). These results suggest that MCAJ has an antidepressant-like effect but that it does not stimulate locomotor activity. Furthermore, we saw no signs of the serotonin syndrome, such as the head twitch response, when we observed animals treated with MCAJ (data not shown). The absence of the side effects seen with *A. lebbeck* may be due to the species difference (*A. lebbeck* vs. *A. julibrissin*) and/or to the extraction method used (methanol vs. methylene chloride).

The brain serotonin (5-HT) system projects widely throughout the cortex and limbic system, and 5-HT neurotransmission is believed to play a major role in the control of mood and behavior (Tork, 1990;Jacobs and Azmitia, 1992;Barnes and Sharp, 1999). It is known that depression results in part from reduced activity of the serotonin system (Blier and de Montigny, 1999; Lesch and Heils, 2000; Veenstra-VanderWeele et al., 2000). Therefore, reversal of the reduced 5-HT transmission is important in terms of recovery from depression. It has been reported that the methanolic fraction of Albizzia increased GABA and 5-HT content in mouse brain (Kasture et al., 2000). Therefore, further study on the change in 5-HT release by MCAJ is needed to elucidate the neurochemical mechanism underlying the antidepressant-like effect of MCAJ.

More recently, several lines of evidence have suggested that a deficiency in the function and expression of 5-HT_{1A} receptors is an important factor in the development of depression (Leitch et al., 2003). 5-HT_{1A} receptors are located at presynaptic and postsynaptic sites (Blier et al., 1993). The somatodendritic autoreceptor, when activated by systemic stimulation, is believed to down-regulate the 5-HT_{1A} receptors and reduce the level of 5-HT release both in the cell body and in the terminal regions of the serotonergic neurons (Laaris et al., 1997). When antidepressants are administered, the 5-HT_{1A} autoreceptors become desensitized, and so disinhibit neuronal firing. In this way extracellular 5-HT levels are elevated at synapse terminals.

The 5-HT_{1A} receptors localized postsynaptically to the serotonergic neurons in the hippocampus, septum, amygdala and cortex increase signal transfer, which leads to an inhibition of the firing activity (Okazawa et al., 1999). A decrease in 5-HT_{1A} binding potential, as determined by positron emission tomography, has been demonstrated in depressed patients in multiple forebrain areas, including the frontal cortex and hippocampus (Drevets et al., 1999; Sargent et al., 2000). Most antidepressant medications function by normalizing 5-HT_{1A} receptor density, so relieving depression (Leonard, 1992; Haddjeri et al., 1998). In support of this hypothesis, the 5-HT_{1A} agonists gepirone (Van et al., 1999) and MDL73005EF (Hajos-Korcsok et al., 1999), as well as the 5-$HT_{1A/1B}$ antagonist, pindolol (Olver et al., 2000) are used in antidepressant therapy.

In a previous study, it was noteworthy that after repeated treatment with the aqueous extract of *A. julibrissin* [^{3}H]8-OH-DPAT binding of the 5-HT_{1A} receptor was markedly increased in the rat frontal cortex, hippocampus, and lateral septum compared to vehicle-treated controls (Jung et al., 2005). This result implies a possibility that the antidepressant-like effect of MCAJ may be mediated by modulation of the 5-HT_{1A} receptor, although in our study the mice received a single dose of the methylene chloride fraction of *A. julibrissin*. This hypothesis is supported by one of the findings of our present pharmacological manipulation study that the 5-HT_{1A} antagonist WAY-100635 abolished immobility time reduced by MCAJ. The 5-$HT_{1A/1B}$ antagonist pindolol also reversed the reduction of immobility time by MCAJ. However, the 5-HT_{1B} antagonist, GR55562, did not reverse this antidepressant-like effect by MCAJ. In addition, in another experiment the 5-HT_{2A} receptor antagonist, ketanserin, did not change the immobility time reduction induced by MCAJ. Furthermore, 5-HT antagonists administered alone did not have any effect on the duration of immobility in this experiment. These results suggest that the 5-HT_{1A} receptor is implicated in the antidepressant-like effects of MCAJ, and that the 5-HT_{1B} and 5-HT_{2A} receptors are not.

It has been reported that 5-HT_{1A} receptor activation by a wide range of agonists produces hypothermia and this has been postulated to be a robust method for detecting 5-HT_{1A} agonists (Cryan et al., 1999). In fact, our experiment showed that MCAJ administration produced a mild hypothermia in mice, suggesting some 5-HT_{1A} agonist properties of MCAJ. Furthermore this hypothermic response was completely blocked by WAY-100635, a specific 5-HT_{1A} receptor antagonist. It has been demonstrated that the receptors mediating the hypothermia in the mouse appear to be located presynaptically upon 5-HT-containing neurons since selective lesions of serotonergic terminals by injection of 5-HT neurotoxin, 5-DHT, largely prevented the hypothermic responses of 8-OH-DPAT (Bill et al., 1991). Chronic administration of 5-HT synthesis inhibitor, *p*-chlorophenylalanine also blocked the decrease in temperature induced by 8-OH-DPAT (Goodwin et al., 1987). In addition,

Martin et al. (1992) confirmed that repeated administration of antidepressants down-regulated the hypothermic response. Therefore, there is a possibility that antidepressant-like effect of MCAJ may due to the modulation via 5-HT_{1A} receptor presynaptically.

To date, 5-HT_{1A} agonists have been only moderately successful antidepressants in the clinic in comparison to selective serotonin reuptake inhibitors (SSRIs). However, most SSRIs suffer from a variety of drawbacks, such as a delay in the onset of efficacy (Kinney et al., 2000) and several adverse effects, such as sexual dysfunction, anxiogenic action, headache, gastrointestinal cramps, and diarrhea (Stahl, 1998; Rosen et al., 1999). Therefore, a herbal extract acting on the 5-HT_{1A} receptors should provide a lead for new antidepressants, because of low adverse effects evidenced by its use as a traditional folk medicine. Meanwhile, several recent human studies have reported changes in 5-HT_{2C} receptor in major depression, but the results are variable and inconclusive (Serretti et al., 2000; Gardiner and Du, 2006). Nevertheless further study would seem warranted as to whether the antidepressant-like effect of MCAJ is partially mediated by 5-HT_{2C}.

At present, it is not clear which constituent of MCAJ exerts its antidepressant-like effect. Several compounds have been isolated from *A. julibrissin* stem bark. These include flavone derivatives, unsaturated acids, lignan glycosides and triterpenoidal saponin (Kinjo et al., 1992; Jung et al., 2003, 2004a). *A. lebbeck* is a different species from *A. julibrissin* (Jung et al., 2004a). Acacic acid lactone saponins and triterpenoidal saponins were isolated from *A. lebbeck* (Pal et al., 1995). However, similarities with regard to active fractions between these two species may be due to the effects of triterpenoidal saponins isolated from these species of Albizzia Genu. Further study is needed to identify the compound that causes these antidepressant-like effects. We are currently examining the major components of MCAJ in this respect.

Taken together, the findings of the present study indicate that MCAJ has an antidepressant-like effect, and that its effects are mediated mainly by the 5-HT_{1A} receptor system.

Acknowledgment

This research was supported by a grant (M103KV010013-06K2201-01310) from the Brain Research Center of the 21st Century Frontier Research Program funded by the Ministry of Science and Technology, Republic of Korea.

References

Barnes NM, Sharp T. A review of central 5-HT receptors and their function. Neuropharmacology 1999;38:1083–152.

Bill DJ, Knight M, Forster EA, Fletcher A. Direct evidence for an important species difference in the mechanism of 8-OH-DPAT-induced hypothermia. Br J Pharmacol 1991;103:1857–64.

Blier P, de Montigny C. Serotonin and drug-induced therapeutic responses in major depression, obsessive–compulsive and panic disorders. Neuropsychopharmacology 1999;21:91S–8S.

Blier P, Lista A, De MC. Differential properties of pre- and postsynaptic 5-hydroxytryptamine1A receptors in the dorsal raphe and hippocampus: II. Effect of pertussis and cholera toxins. J Pharmacol Exp Ther 1993;265:16–23.

Chen SP, Zhang RY. Studies on the triterpene sapogenins from Albizziae Cortex. Yao Xue Xue Bao 1997;32:144–7.

Chen SP, Zhang RY, Ma LB, Tu GZ. Structure determination of three saponins from he stem bark of *Albizzia julibrissin* Durazz. Yao Xue Xue Bao 1997;32:110–5.

Chintawar SD, Somani RS, Kasture VS, Kasture SB. Nootropic activity of *Albizzia lebbeck* in mice. J Ethnopharmacol 2002;81:299–305.

Cryan JF, Kelliher P, Kelly JP, Leonard BE. Comparative effects of serotonergic agonists with varying efficacy at the 5-HT(1A) receptor on core body temperature: modification by the selective 5-HT(1A) receptor antagonist WAY 100635. J Psychopharmacol 1999;13:278–83.

Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, et al. PET imaging of serotonin 1A receptor binding in depression. Biol Psychiatry 1999;46:1375–87.

Gardiner K, Du Y. A-to-I editing of the 5HT2C receptor and behaviour. Brief Funct Genomic Proteomic 2006;5:37–42.

Gareri P, Falconi U, De Fazio P, De Sarro G. Conventional and new antidepressant drugs in the elderly. Prog Neurobiol 2000;61:353–96.

Goodwin GM, De Souza RJ, Green AR, Heal DJ. The pharmacology of the behavioural and hypothermic responses of rats to 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT). Psychopharmacology (Berl) 1987;91:506–11.

Haddjeri N, Blier P, de Montigny C. Long-term antidepressant treatments result in a tonic activation of forebrain 5-HT1A receptors. J Neurosci 1998;18:10150–6.

Hajos-Korcsok E, McQuade R, Sharp T. Influence of 5-HT1A receptors on central noradrenergic activity: microdialysis studies using (±)-MDL 73005EF and its enantiomers. Neuropharmacology 1999;38:299–306.

Jacobs BL, Azmitia EC. Structure and function of the brain serotonin system. Physiol Rev 1992;72:165–229.

Jung JW, Cho JH, Ahn NY, Oh HR, Kim SY, Jang CG, et al. Effect of chronic *Albizzia julibrissin* treatment on 5-hydroxytryptamine1A receptors in rat brain. Pharmacol Biochem Behav 2005;81:205–10.

Jung MJ, Kang SS, Choi JS. A new (E)4-hydroxy-dodec-2-enedioic acid from the stem bark of *Albizzia julibrissin*. Arch Pharm Res 2003;26:207–9.

Jung MJ, Kang SS, Jung HA, Kim GJ, Choi JS. Isolation of flavonoids and a cerebroside from the stem bark of *Albizzia julibrissin*. Arch Pharm Res 2004a;27:593–9.

Jung MJ, Kang SS, Jung YJ, Choi JS. Phenolic glycosides from the stem bark of *Albizzia julibrissin*. Chem Pharm Bull (Tokyo) 2004b;52:1501–3.

Kang TH, Jeong SJ, Kim NY, Higuchi R, Kim YC. Sedative activity of two flavonol glycosides isolated from the flowers of *Albizzia julibrissin* Durazz. J Ethnopharmacol 2000;71:321–3.

Kasture VS, Chopde CT, Deshmukh VK. Anticonvulsive activity of *Albizzia lebbeck*, *Hibiscus rosa sinesis* and *Butea monosperma* in experimental animals. J Ethnopharmacol 2000;71:65–75.

Kim WK, Jung JW, Ahn NY, Oh HR, Lee BK, Oh JK, et al. Anxiolytic-like effects of extracts from *Albizzia julibrissin* bark in the elevated plus-maze in rats. Life Sci 2004;75:2787–95.

Kinjo J, Araki K, Fukui K, Higuchi H, Ikeda T, Nohara T, et al. Six new triterpenoidal glycosides including two new sapogenols from Albizziae Cortex. V. Chem Pharm Bull (Tokyo) 1992;40:3269–73.

Kinney GG, Taber MT, Gribkoff VK. The augmentation hypothesis for improvement of antidepressant therapy: is pindolol a suitable candidate for testing the ability of 5HT1A receptor antagonists to enhance SSRI efficacy and onset latency? Mol Neurobiol 2000;21:137–52.

Laaris N, Le PE, Hamon M, Lanfumey L. Stress-induced alterations of somatodendritic 5-HT1A autoreceptor sensitivity in the rat dorsal raphe nucleus—in vitro electrophysiological evidence. Fundam Clin Pharmacol 1997;11:206–14.

Leitch MM, Ingram CD, Young AH, McQuade R, Gartside SE. Flattening the corticosterone rhythm attenuates 5-HT1A autoreceptor function in the rat: relevance for depression. Neuropsychopharmacology 2003;28:119–25.

Leonard BE. Pharmacological differences of serotonin reuptake inhibitors and possible clinical relevance. Drugs 1992;43(2):3–9.

Lerer B, Macciardi F. Pharmacogenetics of antidepressant and mood-stabilizing drugs: a review of candidate-gene studies and future research directions. Int J Neuropsychopharmacol 2002;5:255–75.

Lesch KP, Heils A. Serotonergic gene transcriptional control regions: targets for antidepressant drug development? Int J Neuropsychopharmacol 2000;3:67–79.

Lesch KP, Mossner R. Knockout Corner: 5-HT(1A) receptor inactivation: anxiety or depression as a murine experience. Int J Neuropsychopharmcol 1999;2:327–31.

Martin KF, Phillips I, Hearson M, Prow MR, Heal DJ. Characterization of 8-OH-DPAT-induced hypothermia in mice as a 5-HT1A autoreceptor response and its evaluation as a model to selectively identify antidepressants. Br J Pharmacol 1992;107:15–21.

Nestler EJ, Gould E, Manji H, Buncan M, Duman RS, Greshenfeld HK, et al. Preclinical models: status of basic research in depression. Biol Psychiatry 2002;52:503–28.

Nowak G, Szewczyk B, Wieronska JM, Branski P, Palucha A, Pilc A, et al. Antidepressant-like effects of acute and chronic treatment with zinc in forced swim test and olfactory bulbectomy model in rats. Brain Res Bull 2003;61:159–64.

Okazawa H, Yamane F, Blier P, Diksic M. Effects of acute and chronic administration of the serotonin1A agonist buspirone on serotonin synthesis in the rat brain. J Neurochem 1999;72:2022–31.

Olver JS, Cryan JF, Burrows GD, Norman TR. Pindolol augmentation of antidepressants: a review and rationale. Aust N Z J Psychiatry 2000;34:71–9.

Pal BC, Achari B, Yoshikawa K, Arihara S. Saponins from *Albizia lebbeck*. Phytochemistry 1995;38:1287–91.

Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol 1999;19:67–85.

Sargent PA, Kjaer KH, Bench CJ, Rabiner EA, Messa C, Meyer J, et al. Brain serotonin1A receptor binding measured by positron emission tomography with [11C]WAY-100635: effects of depression and antidepressant treatment. Arch Gen Psychiatry 2000;57:174–80.

Serretti A, Lilli R, Lorenzi C, Lattuada E, Smeraldi E. Serotonin-2C and serotonin-1A receptor genes are not associated with psychotic symptomatology of mood disorders. Am J Med Genet 2000;96:161–6.

Stahl SM. Basic psychopharmacology of antidepressants, part 2: estrogen as an adjunct to antidepressant treatment. J Clin Psychiatry 1998;59(4):15–24.

Steru L, Chermat R, Thierry B, Mico JA, Lenegre A, Steru M, et al. The automated Tail Suspension Test: a computerized device which differentiates psychotropic drugs. Prog Neuro-Psychopharmacol Biol Psychiatry 1987;11:659–71.

Tork I. Anatomy of the serotonergic system. Ann N Y Acad Sci 1990;600:9-34.

Van RO, Olivares E, Zhang Y, Tripathi B, Turek FW. Chronobiotic effects of gepirone, a potential antidepressant with 5HT1A receptor partial agonist properties. Behav Pharmacol 1999;10:119–30.

Veenstra-VanderWeele J, Anderson GM, Cook Jr EH. Pharmacogenetics and the serotonin system: initial studies and future directions. Eur J Pharmacol 2000;410:165–81.

Zhu YP. Chinese materia medica chemistry, pharmacology and applications. Netherlands: Harwood Academic Publishers; 1998. p. 519–20.