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Protective effects of pseudoginsenoside-F_{11} on methamphetamine-induced neurotoxicity in mice

Chun Fu Wu[a,*], Yan Li Liu[a], Ming Song[c], Wen Liu[a], Jin Hui Wang[b], Xian Li[b], Jing Yu Yang[a]

[a]*Department of Pharmacology, Shenyang Pharmaceutical University, Wenhua Road 103, 110016 Shenyang, People's Republic of China*
[b]*Department of Chemistry for Natural Products, Shenyang Pharmaceutical University, 110016 Shenyang, People's Republic of China*
[c]*Liaoning Institute of Crime Detection, 110032 Shenyang, People's Republic of China*

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Abstract

In the present study, pseudoginsenoside-F_{11} (PF_{11}), a saponin that existed in American ginseng, was studied on its protective effect on methamphetamine (MA)-induced behavioral and neurochemical toxicities in mice. MA was intraperitoneally administered at the dose of 10 mg/kg four times at 2-h intervals, and PF_{11} was orally administered at the doses of 4 and 8 mg/kg two times at 4-h intervals, 60 min prior to MA administration. The results showed that PF_{11} did not significantly influence, but greatly ameliorated, the anxiety-like behavior induced by MA in the light–dark box task. In the forced swimming task, PF_{11} significantly shortened the prolonged immobility time induced by MA. In the appetitively motivated T-maze task, PF_{11} greatly shortened MA-induced prolonged latency and decreased the error counts. Similar results were also observed in the Morris water maze task. PF_{11} significantly shortened the escape latency prolonged by MA. There were significant decreases in the contents of dopamine (DA), 3,4-dihydroxyphenacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindoacetic acid (5-HIAA) in the brain of MA-treated mice. PF_{11} could partially, but significantly, antagonize MA-induced decreases of DA. The above results demonstrate that PF_{11} is effective in protection of MA-induced neurotoxicity and also suggest that natural products, such as ginseng, might be potential candidates for the prevention and treatment of the neurological disorders induced by MA abuse.
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Keywords: PF_{11}; Methamphetamine; Neurotoxicity; Memory impairment; Anxiety; Depression; Dopamine

1. Introduction

Methamphetamine (MA) is a drug that is significantly abused by humans worldwide. Many reports have demonstrated that MA causes neurotoxicity in rodents and nonhuman primates by producing long-term depletion of dopamine (DA) and its metabolites (Ellison et al., 1978; Seiden et al., 1975; Ricaurte et al., 1982) and decreasing the number of high-affinity DA uptake sites and the activity of tyrosine hydroxylase in striatum (Hotchkiss et al., 1979; Johnson et al., 1992). DA transporters are reduced in the postmortem striatum of chronic MA users (Imam et al., 1999; Volkow et al., 2001).

Previous studies have shown that ginseng extracts or its principles exert some antagonistic effects on the neurochemical and behavioral toxicities of dependence-liable drugs. For example, it is reported that total saponins of ginseng can modulate morphine-, MA-, and cocaine-induced dopaminergic dysfunction (Tokuyama et al., 1992; Oh et al., 1997), and ginseng extracts can inhibit MA-induced behavioral sensitization (Tokuyama et al., 1996). It is suggested that inhibitory effects of ginseng extracts on MA-induced reverse tolerance are related to the recovery of dysfunction in the dopaminergic system.

Recently, our studies have shown that pseudoginsenoside-F_{11} (PF_{11}), an ocotillol-type saponin found in *Panax quinquefolium* (American ginseng), but not in *Panax ginseng* (Chen et al., 1981), possesses antagonistic actions on morphine-induced behavioral changes in mice (Li et al., 2000). Further investigation shows that PF_{11} antagonizes morphine-induced intracellular cAMP production (Li et al., 2001a). Preliminary studies also show that PF_{11} antagonizes morphine-induced decreases in DA levels in the limbic area of rat (unpublished data). Because MA-induced neurotoxicities are closely related to the dopaminergic

* Corresponding author. Tel./fax: +86-24-2384-3567.
E-mail addresses: wucf@syphu.edu.cn (C.F. Wu), wuchunf@21cn.com (C.F. Wu).

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system, it is interesting to investigate whether PF_{11}, like other ginseng saponins, has an antagonistic effect on MA-induced neurotoxicities.

2. Materials and methods

2.1. Animals and drugs

Male, 7-week-old Swiss mice, weighing 20–22 g at the start of experiment, were used. The animals were supplied by the Experimental Animal Center of Shenyang Pharmaceutical University. They were housed 10 per cage under a 12:12-h light–dark cycle and constant temperature (20 ± 2 °C), with water and food freely available. The experimental protocol was approved by the Committee for the Use of Experimental Animals of Shenyang Pharmaceutical University, and all animal use procedures were in accordance with the Regulations of Experimental Animal Administration issued by the State Committee of Science and Technology of the People's Republic of China on November 14, 1988.

PF_{11} was isolated from the aerial parts of *P. quinquefolium* by the Department of Chemistry for Natural Products of Shenyang Pharmaceutical University. The method for isolation of PF_{11} was the same as that described previously (Tanaka and Yahara, 1978). PF_{11} was dissolved in distilled water and administered intragastrically. MA (purity >98%, provided by Liaoning Institute of Crime Detection, People's Republic of China) was dissolved in physiological saline and injected intraperitoneally. In order to test the effect of PF_{11} on MA-induced neurotoxicity in mice, MA (10 mg/kg × 4 ip) was administered four times at 2-h intervals. Two doses of PF_{11} (4 and 8 mg/kg) were administered two times at 4-h intervals. The first administration of PF_{11} was 60 min before the first injection of MA or saline. All subjects were tested 1 week after treatment.

2.2. Anxiety test

The apparatus consisted of two 20 × 10 × 14 cm plastic boxes, divided by a black plate. One box was dark and the other was transparent. There was a 3-cm diameter hole in the middle at the bottom of the plate. A 100-W light bulb 30 cm above the floor of the apparatus was the only light source in the room. One mouse was put into the light box facing the hole. The transitions and time spent in the dark box were recorded for 5 min immediately after the mouse stepped into it.

2.3. Behavioral despair test

A cylinder (19-cm height, 14-cm inside diameter) was filled with water to 9 cm of height, and the water temperature was maintained at 25 ± 1 °C. A mouse was placed in the cylinder for a total of 6 min. The time of immobility in the last 4 min was recorded. A mouse was judged to be immobile when it was floating motionlessly in the water, making only those movements necessary to keep its head above the water (Yates et al., 1991).

2.4. Swimming-ability test

This experiment was performed in an iron pool (86 × 17 × 37 cm) filled with water to a depth of 20 cm. Water temperature was maintained at 25 ± 1 °C. At the end of the pool, there was a platform on which there was food and where mice could climb. The location of the platform was made visible by a blue-colored picture mounted above the platform.

During the test, the mouse was put into the water at the starting point. The swimming time from the starting point to the end of the pool was recorded (Li et al., 2001b).

2.5. T-maze test

The T-maze had a start (45 × 15 × 20 cm), left, and right arm (50 × 15 × 20 cm), all painted black. At the end of each arm, a 5-cm diameter, 0.5-cm deep food cup was located on the floor. Only one arm of the T-maze was baited with the food. The food was in the left arm for one half of the mice, while it was in the right arm for the other half. The T-maze was located in a dimly lit room. The animals were familiarized with the maze, food, and food containers for 10 min each day on two consecutive days. Before the test, the weight of mice was limited to 85–90% of normal mice. Then, the animals were food-deprived for 24 h. On three consecutive days, 10 trials per mouse were performed each day. The mouse was put into the start arm. A correct trial ended with the mouse eating the food. An incorrect trial ended with the mouse reaching the error arm. Then it was removed from the maze and put into a separate waiting box for 10 s and then returned to the maze as before. The number of errors and time taken for correct trials also were noted (Chen et al., 2002).

2.6. Morris water maze task

The task was carried out as previously described (Watanabe and Satoh, 1995). A circular pool (40-cm height, 120-cm diameter) was filled to a depth of 20 cm with room temperature (20 ± 0.5 °C) water. The water was made opaque by the addition of 15 ml India ink. Four equally spaced points around the edge of the pool were designed as four starting positions: east (E), south (S), west (W), and north (N). An escape platform (6.5-cm diameter) was set 1 cm below the surface of the water and placed in a constant position in the middle of the SW quadrant. The mouse in the pool was trained to find the platform using a variety of water maze cues, including the desk, wall, window, observer, etc. The observer always sat in the same position.

During the experiment, each mouse was trained four times daily. The mice were placed in the water facing away

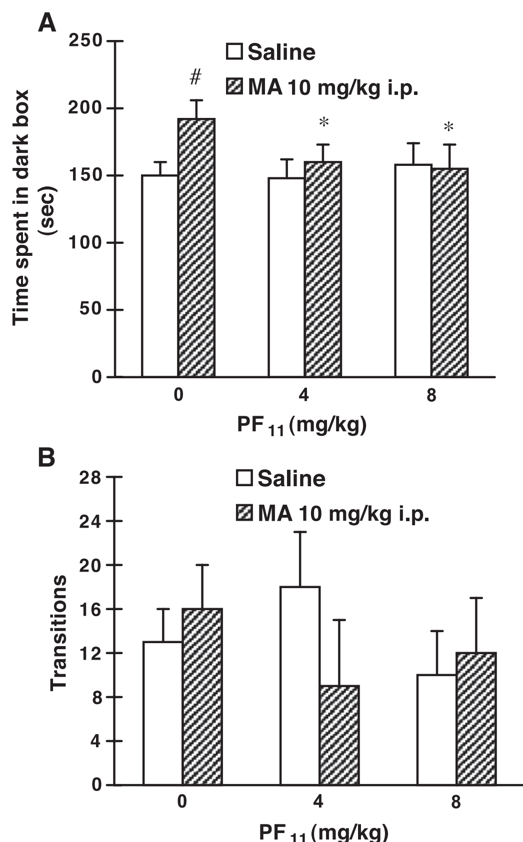

Fig. 1. Effect of PF_{11} on anxiety-like behavior in the light–dark test in MA-treated mice. MA (10 mg/kg ip) was administered four times at 2-h intervals between each injection. PF_{11} (4 and 8 mg/kg) was orally administered two times at 4-h intervals. The first administration of PF_{11} was performed 60 min before the first injection of MA or saline. Results are expressed as mean ± S.E.M. ($n = 10$). $^{\#}P < .05$ versus saline group. * $P < .05$ versus MA group.

from the wall from one of four starting sites in a random sequence, and each site was used once each day. The latency to find the escape platform was measured during each trial. Upon finding and climbing on the platform, the mice stayed there for 30 s. If the mice failed to find the platform within 60 s, they were placed there by the observer and a maximum score of 60 s was given. After a 30-s rest on the platform, the next trial was initiated. The test continued for 5 days. The escape latency was recorded (Li et al., 2001b).

2.7. Determination of DA and 5-HT levels

DA and 5-HT levels in the whole brain without cerebellum were determined by using high-performance liquid chromatography (HPLC) with electrochemical detection (Yamanaka et al., 1986). The mice were sacrificed by decapitation 1 week after the last administration of MA. The brain was removed and frozen on dry ice and stored at − 60 °C, until analyzed. On the day of the experiment, the brain was homogenized in 400 μl of 0.4 mmol/l perchloric acid solutions (containing 0.5 mmol/l EDTA-Na_2, 0.4 mmol/l perchloric acid, and 0.01% L-cysteine) and centrifuged (11,500 × g, 15 min). An aliquot (20 μl) of the supernatant was injected into the HPLC. A reverse-phase column (ODS C_{18}, 5 μm column, Dalian Chem-Physi. Inst. China) was used. The mobile phase was composed of 100 mmol/l sodium acetate, 85 mmol/l citric acid, 0.2 mmol/l EDTA-Na_2, and 15% methanol. The flow rate was 1.0 ml/min, and the electrode potential of the detector (L-ECD-6A, Shimadzu, Japan) was set at + 0.75 V.

2.8. Statistics

The results were expressed as the mean ± S.E.M. Data from the experiments were analyzed using a two-way analysis of variance (ANOVA) followed by Duncan test for multiple comparisons between groups. Differences with $P < .05$ were considered statistically significant.

3. Results

3.1. Effect of PF_{11} on MA-induced anxiety-like behavior in the light–dark box test

Compared to the saline group, MA (10 mg/kg × 4 ip) significantly prolonged the time spent in the dark box. PF_{11} (4 and 8 mg/kg) did not prolong the time spent in the dark box but it significantly shortened the time spent in the dark box induced by MA (Fig. 1).

3.2. Effect of PF_{11} on forced swimming in MA-treated mice

MA (10 mg/kg × 4 ip) significantly prolonged the immobility time in the forced swimming test in mice. PF_{11}

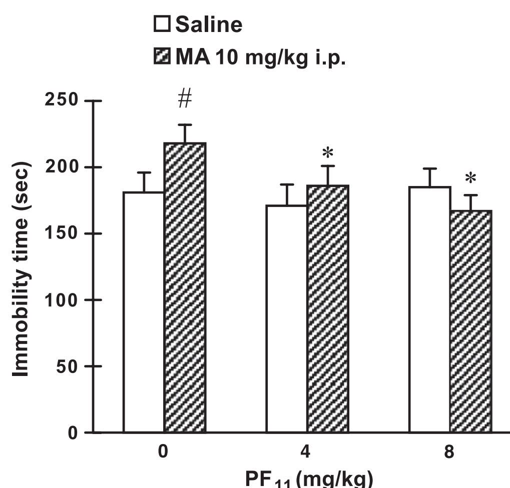

Fig. 2. Effect of PF_{11} on forced swimming in MA-treated mice. MA (10 mg/kg ip) was administered four times at 2-h intervals between each injection. PF_{11} (4 and 8 mg/kg) was orally administered two times at 4-h intervals. The first administration of PF_{11} was performed 60 min before the first injection of MA or saline. Results are expressed as mean ± S.E.M. ($n = 10$). $^{\#}P < .05$ versus saline group. * $P < .05$ versus MA group.

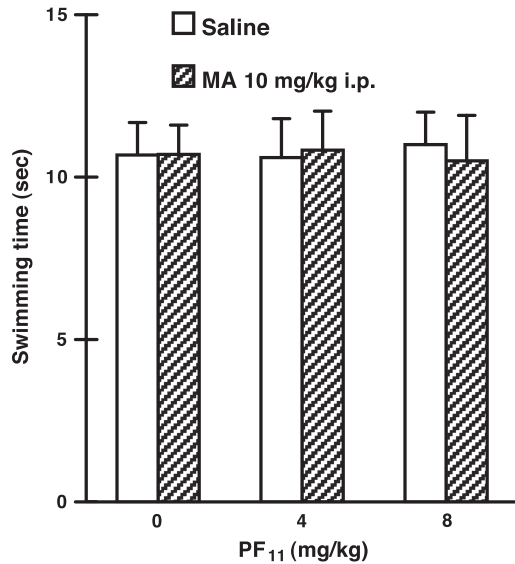

Fig. 3. Effect of PF_{11} on swimming ability in MA-treated mice. MA (10 mg/kg ip) was administered four times at 2-h intervals between each injection. PF_{11} (4 and 8 mg/kg) was orally administered two times at 4-h intervals. The first administration of PF_{11} was performed 60 min before the first injection of MA or saline. Results are expressed as mean ± S.E.M. ($n = 10$).

(4 and 8 mg/kg) had no significant effect on the immobility time compared to that of the saline group. However, PF_{11}, at both doses, recovered the immobility time induced by MA (Fig. 2).

3.3. Effect of PF_{11} on swimming ability in MA-treated mice

The results showed that PF_{11}, at the doses of 4 and 8 mg/kg, or MA, at four injections of 10 mg/kg with 2-h intervals, did not inhibit the swimming ability of the mice. The combination of PF_{11} and MA had no effect on the swimming ability (Fig. 3).

3.4. Effect of PF_{11} on MA-induced memory impairment in an appetitively motivated task in T-maze

Compared to the saline group, PF_{11} (4 and 8 mg/kg) changed neither the latency to find the food nor the number of errors of entering the wrong arm. However, in MA (10 mg/kg × 4)-treated mice, the latency to find the food was significantly prolonged and the number of errors of entering the wrong arm was significantly increased. Administration of PF_{11} markedly shortened the prolonged

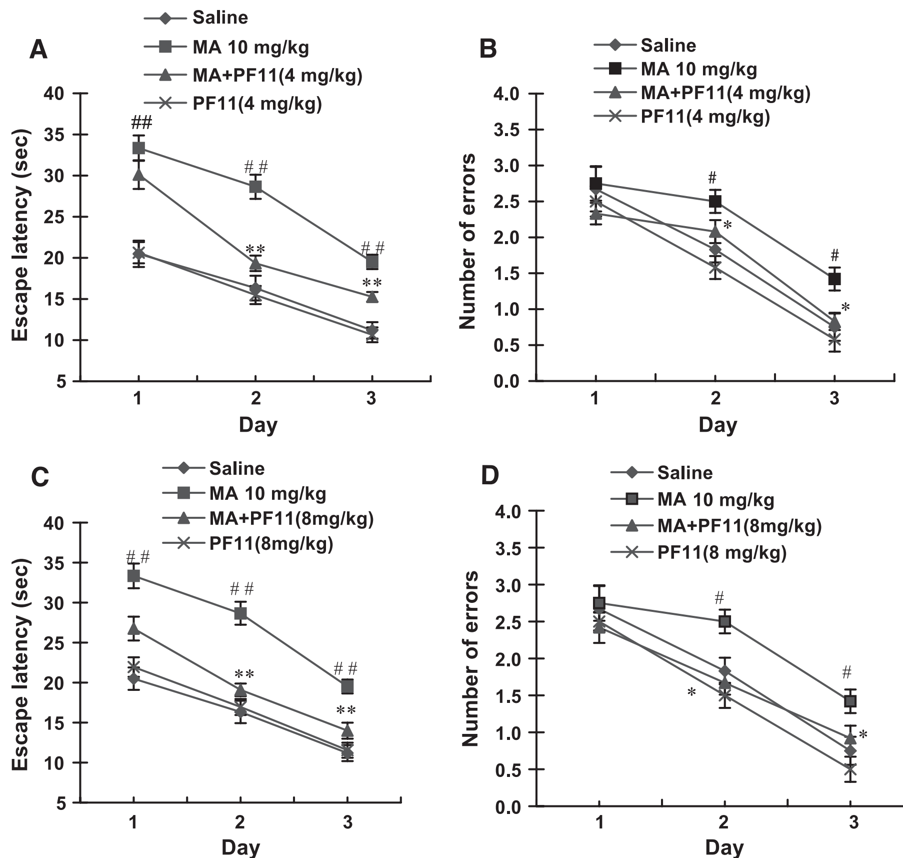

Fig. 4. Effect of PF_{11} on memory function in an appetitively motivated task in the T-maze in MA-treated mice. MA (10 mg/kg ip) was administered four times at 2-h intervals between each injection. PF_{11} (4 and 8 mg/kg) was orally administered two times at 4-h intervals. The first administration of PF_{11} was performed 60 min before the first injection of MA or saline. Each point is the mean ± S.E.M. ($n = 10$). $^{\#}P < .05$, $^{\#\#}P < .01$ versus saline group. $*P < .05$, $**P < .01$ versus MA group.

latency induced by MA and decreased the number of errors (Fig. 4).

3.5. Effect of PF_{11} on MA-induced memory impairment in Morris water maze

PF_{11}, at the doses used, did not affect the latencies to locate the platform when compared with the saline group. However, the latencies of mice to locate the platform were significantly prolonged after MA (10 mg/kg × 4) administration, on Days 1 to 5, when compared with the saline group, and the prolonged latencies could be markedly shortened after administration of PF_{11}, 4 and 8 mg/kg (Fig. 5).

3.6. Effect of PF_{11} on DA and 5-HT contents in the brain of MA-treated mice

As seen in Fig. 6, in mouse brain, the contents of DA and its metabolites 3,4-dihydroxyphenacetic acid (DOPAC) and homovanillic acid (HVA), as well as 5-hydroxyindoacetic acid (5-HIAA), a metabolite of 5-HT, significantly decreased after the treatment of MA (10 mg/kg × 4). The percentage of decrease of these substances was 85.86, 53.85, 60.00, and 33.00, respectively. Administration of PF_{11} alone, at the doses of 4 and 8 mg/kg, had no significant effect on the contents of DA, 5-HT, and their metabolites. However, PF_{11} could partially but significantly antagonize the MA-induced decrease of DA. The recovery percentage of DA was 23.22 (Fig. 6).

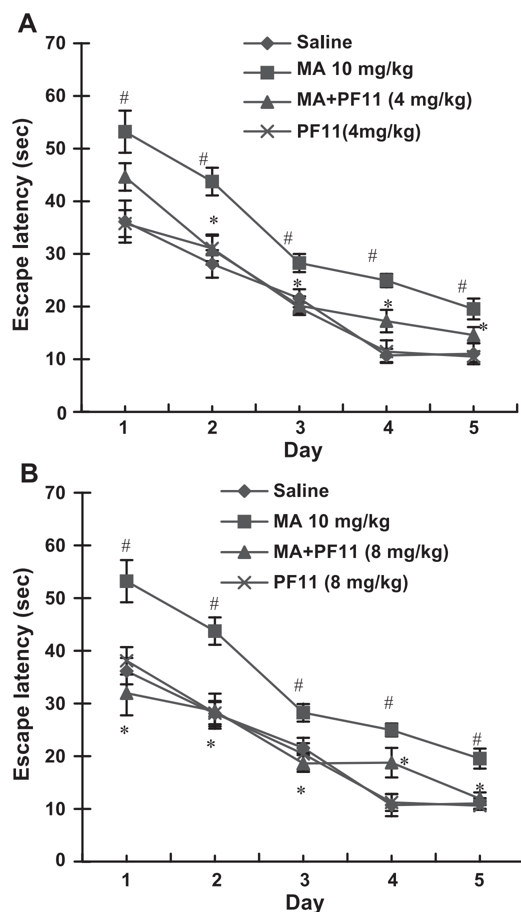

Fig. 5. Effect of PF_{11} on MA-induced memory impairment in the Morris water maze in mice. MA (10 mg/kg ip) was administered four times at 2-h intervals between each injection. PF_{11} (4 and 8 mg/kg) was orally administered two times at 4-h intervals. The first administration of PF_{11} was performed 60 min before the first injection of MA or saline. Each point is the mean ± S.E.M. ($n = 10$). #$P < .05$ versus saline group. * $P < .05$ versus MA group.

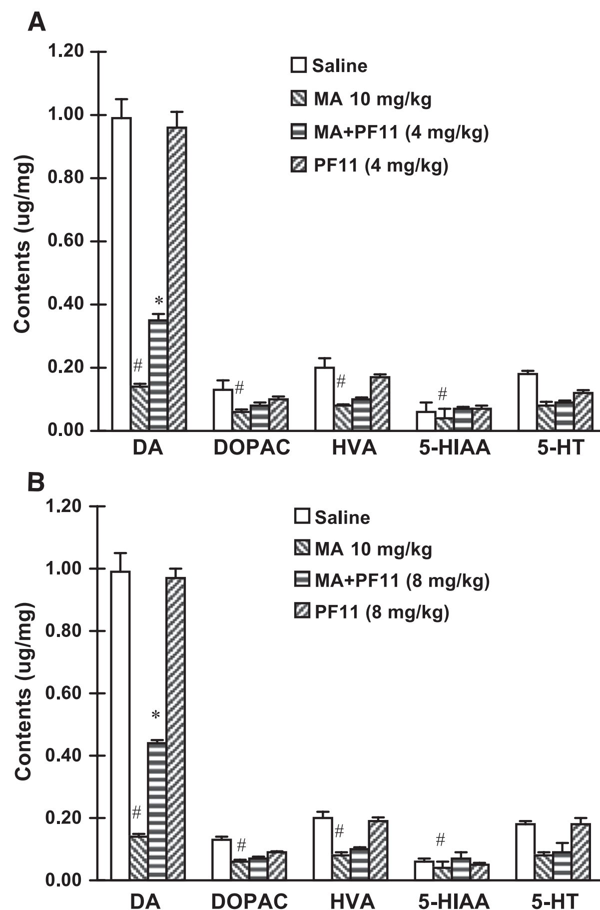

Fig. 6. Effect of PF_{11} on changes of monoamine and their metabolite levels in the brains of MA-treated mice. MA (10 mg/kg ip) was administered four times at 2-h intervals between each injection. PF_{11} (4 and 8 mg/kg) was orally administered two times at 4-h intervals. The first administration of PF_{11} was performed 60 min before the first injection of MA or saline. Results are expressed as mean ± S.E.M. ($n = 10$). #$P < .05$ versus saline group. * $P < .05$ versus MA group.

4. Discussion

MA- and MA derivative-induced neurotoxicity can be demonstrated by behavioral and neurochemical tests. Acute administration of a high dose or multiple administration of MA in a short period can induce anxiety-like behavior, depression, tardive dyskinetic movements, memory impairment, and depletion of DA content from dopaminergic

neurons in man (Kolecki, 1998; Ornstein et al., 2000; Cho and Melega, 2002) and experimental animals (Strupp et al., 1991; Nakagawa et al., 1997; Imam et al., 2001). The neurotoxicity induced by MA and its derivatives is one of the main causes of Parkinson's disease observed in abusers of these substances (Fornai et al., 1997). The present study, after multiple administration of MA, which can deplete DA contents in the mouse striatum (Imam et al., 1999), demonstrated that PF_{11}, a saponin found in American ginseng, could antagonize the neurotoxicity induced by MA. These results suggest the usefulness of natural products for the prevention and treatment of MA-induced neurological disorders and neurotoxicity.

Previously reported data have shown that chronic or multiple administrations of high doses of MA impaired memory function in MA abusers (Simon et al., 2002; Vorhees, 1994; Cho and Melega, 2002; Kolecki, 1998; Ornstein et al., 2000) and rats (Robinson et al., 1990). Although lower doses of MA or its derivatives can improve memory function (Strupp et al., 1991), the present study employed two different task models to show that multiple administration of MA impaired appetitively motivated memory function in the T-maze and passive avoidance-motivated spatial memory function in the Morris water maze. These obvious impairments in memory function induced by MA were not due to the possible impairment of motor function because neither the transition number in the light–dark box test nor swimming ability was significantly changed in mice under the same MA dosage protocol. PF_{11} did not alter motor memory function in mice but could significantly antagonize this kind of memory impairment induced by MA. These results are consistent with previous observations that PF_{11} antagonized scopolamine- and morphine-induced memory dysfunction without any effect in naive animals (Li et al., 1999, 2000).

MA-induced deficits in spatial working memory may be related to its DA-depleting action. It is found that multiple administration of 1-mtheyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) caused about 60% depletion of striatal DA (Cadet et al., 1995; Morley et al., 2001). Mice treated with MPTP were comparable to controls in T-maze-delayed alternation with fixed delays but were impaired when trials with mixed 20- and 120-s delays were presented (Tanila et al., 1998). However, in the present study, PF_{11} could only partially inhibit MA-induced decrease of DA content in the brain, although in some behavioral parameters, it could almost reverse the abnormality induced by MA. Because memory function is mediated by many neuronal systems in the brain, the effect of PF_{11} on memory dysfunction might not be directly connected with the dopaminergic system. Our previous studies have demonstrated that PF_{11} can improve the memory function impaired by scopolamine (Li et al., 1999) and morphine (Li et al., 2000), suggesting that a complicated mechanism of action might be involved in the efficacy of PF_{11}.

The serotonergic system may be involved in MA- and MA derivative-induced anxiety and depression. Rats previously exposed to 3,4-methylenedioxymethamphetamine (ecstasy) show no difference in the anxiety from saline controls but lead to increased anxiety 3 months later. This might be due to a neurotoxic effect of the substance on brain serotonin systems (Morley et al., 2001). However, in the present study, we only found that PF_{11} significantly inhibited MA-induced anxiety-like behavior and depressive behaviors in mice but not MA-induced decrease of 5-HT and 5-HIAA contents in the mouse brain. It is reported that the dopaminergic system is also involved in anxiety-like and depressive behaviors in man and animals (Dazzi et al., 2001; Martinot et al., 2001; Suzuki et al., 2001). Therefore, besides the serotonergic system, the partial involvement of the dopaminergic system should be considered in such MA-induced behavioral changes.

In summary, the present study first provided evidence that PF_{11} antagonized MA-induced neurotoxicity, both behaviorally and neurochemically, in mice. These effects of PF_{11} partially resulted from its protection against MA-induced impairment in the dopaminergic system. These results, along with others (Tokuyama et al., 1992; Oh et al., 1997), suggest that natural products, such as ginseng, might have potential usefulness in the prevention and treatment of the neurological disorders in MA and MA derivative abusers.

Acknowledgements

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