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Ginkgolide-Platinum(II) Complex GPt(II) Exhibits Therapeutic Effect on Depression in Mice via Upregulation of DA and 5-HT Neurotransmitters

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Depression is the 5th most prevalent disorder adversely affecting the health of humans worldwide. The present study evaluated the antidepressant effect of ginkgolide-platinum(II) complex *in vivo* in a mice model of CMS-induced depression.

Material/Methods: Depression was induced in mice by social isolation followed by chronic mild stress. After stress, the mice were assigned randomly to a model group, a 3 mg/kg group, a 6 mg/kg group, and a 12 mg/kg group. The mice in the 3 treatment groups were intraperitoneally injected with a single dose of 3.0, 6.0, or 12.0 mg/kg GPt(II) on day 11 of stress. The behavioral changes in mice were analyzed on day 21 of GPt(II) treatment by suspension and open field tests.

Results: The GPt(II) treatment significantly increased the numbers of crossings and rearings in CMS mice. Treatment of mice with GPt(II) significantly elevated dopamine, BDNF, and serotonin levels in hippocampus tissues. The CMS-mediated reduction of neuropeptide production in the hippocampus tissues was significantly alleviated by GPt(II) treatment ($P<0.05$). The GPt(II) treatment suppressed the effect on CMS-induced elevated level of MAO-A in hippocampus tissues. Treatment with GPt(II) significantly repressed caspase-3 activation induced by CMS in the hippocampus tissues of mice. The GPt(II) treatment significantly ($P<0.05$) upregulated Hsp70 mRNA level in depression model mice. The levels of dopamine, serotonin, and BDNF were increased from 187.83±8.53, 289.65±10.76, and 7.98±1.87 ng/g, respectively, in the model group to 657.63±24.47, 720.54±28.09, and 22.56±3.11 ng/g, respectively, in the 12 mg/kg GPt(II) treatment group.

Conclusions: GPt(II) treatment significantly relieved characteristics of depression in the mice through upregulation of neurotransmitter, neuropeptide, and Hsp70 expression. Moreover, GPt(II) downregulated monoamine oxidase-A levels in the mouse hippocampus tissues. Therefore, further research is warranted on the possible therapeutic effect of GPt(II) in the treatment of depression.

MeSH Keywords: **Depression • Monoamine Oxidase • Neuropeptide Y**

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Background

Depression is the 5th most prevalent disorder adversely affecting the health of humans worldwide [1,2]. It is a chronic neurological disorder characterized by frequent recurrence, high prevalence, and low rate of treatment success [1,2]. The etiology of depression involves multiple factors, including genetics, social environment, personality, and endocrine secretions involved in development of this disorder. The disease is associated with suppression of neurotransmitters like dopamine and serotonin, as well as reduction of neurotrophic factors such as neuropeptide-Y in brain tissues [3–5]. Thus, upregulation of dopamine, serotonin, and neuropeptide-Y has immense importance for the treatment of depression. Heat shock protein 70 (Hsp70) induces most conserved pathways of cellular response to different types of oxidative stress [6]. Hsp70 is immediately induced during cell stress to regulate homeostasis [7,8]. In animal models of nervous system injury, the Hsp70 level is elevated and acts as a protective agent [8]. Studies have revealed that Hsp70 alleviates depression through regulation of glucocorticoid receptor activity [9]. The defect in the Hsp70 gene due to deletion of 162-base from 5'-flanking region is responsible for development of depression [10]. The mechanism of antidepressant activity of some therapeutic compounds involves upregulation of Hsp70 expression [11].

Panax ginseng consists of several plant species belonging to the *Panax* genus and *Araliaceae* family found in north-eastern Asia. In Japan and Korea, *P. ginseng* has been used in traditional medicine as a revitalizing agent [12]. Later on, triterpenoid compounds like ginkgolides were isolated from *P. ginseng,* which demonstrated neuroprotective activities [12]. The inorganic complexes of platinum have been found to possess various biological properties, but have the limitation of inducing adverse effects [13,14]. The modification of these platinum complexes led to avoidance of adverse effects and increase of biological activity [13,15]. Complexes of platinum were synthesized by linking it to the natural compound and screening for efficacy in treating various diseases [16,17]. The complex of jatrorrhizine, an active constituent of *Tinospora capillipes Gagnep* with platinum has shown a broad spectrum of biological properties [18,19]. In the present study, we assessed the antidepressant effect of ginkgolide-platinum(II) complex GPt(II) *in vivo* in the mouse model of CMS-induced depression.

Material and Methods

Animals

Fifty C57BL/6 mice (7–8 weeks old) were obtained from the Shanghai Slac Laboratory, Shanghai, China. The mice were acclimated to the facilities in the Animal Center laboratory for 7 days before experiments were started. The mice were housed with 12/12 h light/dark cycle and provided free access to food and water. The study was approved by the Animal Ethics Committee, Xinxiang Medical University (Xinxiang, China; Approval number MU/2017/0027). The procedures were performed in accordance with the guidelines of the National Institutes of Health, China.

Mouse depression model preparation and treatment

The mouse depression model was prepared using social isolation in combination with chronic mild stress. The mice were individually housed in cages and daily subjected to stress for 3 weeks. The methodology of stress was: a) 24-h fasting; b) 24-h water deprivation; c) 24-h cage tilting at 30°; d) 1-min pinching of tail; e) 2-h restraint in a 10×2.5 cm fixator; f) 3-min continuous soaking in water at 17°C; g) 3=min continuous soaking in water at 40°C; and h) alteration of day with night. Following stress, the mice were randomly assigned to the model group, 3 mg/kg group, 6 mg/kg group, and 12 mg/kg group. Each group contained 10 mice, and 10 mice without stress treatment were used as controls. The mice in the 3 treatment groups were given a single dose of 3.0, 6.0, or 12.0 mg/kg GPt(II) on day 11 of stress, administered intragastrically in normal saline. The model and control mice were injected with equal volumes of normal saline at the same time. The behavioral changes in mice were analyzed on day 21 of GPt(II) treatment.

Suspension test

A black plexiglass box was used to determine immobility time for each mouse after suspension. Briefly, the mouse tail at the distal end was fixed with the crossbar kept at 30 cm height from the base. The mice were continuously kept in inverted position with head down for 6 min. The mice were adapted for 2 min, followed by measurement of immobility time.

Open field test

The test was conducted on day 21 of GPt(II) treatment using a 100×100×50 cm box. The 4-sided box contained 25 equilateral squares, and each mouse was put on the center square. The activity of each mouse in the box was monitored carefully to count the numbers of crossings and rearings during 5 min.

ELISA assay for dopamine, serotonin, and BDNF levels

Five mice from each group were subjected to exsanguination following anesthesia (pentobarbital anesthesia at 35 mg/kg) on day 21 of GPt(II) injection. The brain tissues were carefully excised, washed with saline and subjected to homogenization. The homogenized tissues were centrifuged at 4°C for 15 min at 13 000×g to collect supernatant. The levels of

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dopamine, serotonin, and BDNF in the supernatant were analyzed using ELISA kits.

Western blot analysis

The mice were sacrificed by exsanguination following anesthesia on day 21 of GPt(II) injection to excise the brain tissues. The tissues were lysed, homogenized, kept for 40 min on ice, and centrifuged at 4°C for 40 min at 12 000×g. The supernatant was mixed with loading buffer 5X consisting of Tris-hydrochloric acid (60 mM, at pH 6.8), SDS (2%), bromophenol blue (0.1%), trihydroxy propanol (25%), and β-mercaptoethanol (14 mM). The mixture was boiled in a water bath for 20 min, followed by separation of proteins on SDS-PAGE using electrophoresis. The proteins were subsequently transferred onto PVDF membranes, which were blocked on incubation with dry milk (5%) for 1.5 h. The membranes were incubated overnight with primary antibodies for anti-neuropeptide, anti-MAO-A, anti-caspase-3, and anti-Hsp70 at 4°C. After washing 3 times in PBST, the membranes were incubated with HRP-labeled rabbit anti-mouse secondary antibodies at room temperature for 2 h. The illumination of bands was performed using an ECL system (Santa Cruz Biotechnology) and the blots were normalized to β-actin.

Reverse transcription-polymerase chain reaction (RT-PCR)

The mice were sacrificed by exsanguination following anesthesia on day 21 of GPt(II) injection. Right hippocampus tissues were excised, and frozen in liquid nitrogen until further analysis. The total RNA from hippocampus tissues was isolated by treatment with TRIzol reagent. The RNA was subjected to reverse transcription into cDNA using a reverse transcription kit (Tiangen Biotech, Co., Beijing, China) according to the manufacturer's instructions. The qPCR was carried out using SYBR Green PCR Master mix (Tiangen Biotech, Co.) on an ABI 7300 PCR Instrument (Thermo Fisher Scientific, Inc.). The primers used were:
HSP-70 forward, 5'-GCTGGTGAGCCACTTCGTG-3' and
reverse, 5'-TGGATCTGCGCCTTGTCC-3';
MAO-A forward, 5'-ATTGGAGGCGGCATC TCAGGAT-3' and
reverse, 5'-AGGTGGGAATGCACC ACGGAAT-;
caspase-3 forward, 5'-AACGAACGGACCTGTGG-3' and
reverse, 5'-TTT GCATGGAAA GTGGC-3'.
The cycling conditions used were: activation of polymerase at 93°C for 10 min, then 93°C for 25 s and 58°C for 25 s. The changes in RNA by relative fold change were normalized to β-actin and calculated by $2^{-\Delta\Delta Cq}$ method.

Immunohistochemical analysis

The mice were sacrificed by exsanguination following anesthesia on day 21 of GPt(II) injection to excise the brain tissues. The tissues were immediately fixed in 4% paraformaldehyde overnight. The tissues were washed, dehydrated using a gradient ethyl alcohol series, and then embedded in paraffin. The paraffin-embedded brain tissues were cut into 3-µm sections and treated with hydrogen peroxide (3%) for 20 min. The tissue sections were incubated for 2 h with mouse anti-rabbit polyclonal antibodies against Hsp70 at 4°C. Then, the sections were incubated at room temperature with biotinylated goat anti-rabbit IgG secondary antibody for 1.3 h. PBS washing was followed by incubation for 1 h with horseradish peroxidase. The tissues were then treated with DAB solution followed by hematoxylin counterstaining, and then were examined under a light microscope (magnification ×400).

Statistical analysis

Data are expressed are mean ± standard deviations (mean±SD). Comparisons between groups were made using one-way analysis of variance (ANOVA) and *t* test. Data analysis was performed using SPSS 17.0 statistical software (SPSS, Inc., Chicago, IL, USA). Differences were regarded as statistically significant at $P<0.05$.

Results

Improvement of locomotor activity by GPt(II) in CMS mice

Locomotor activity was significantly reduced in mice after 21 days of CMS relative to the sham control group. CMS significantly decreased the numbers of crossings in mice ($P<0.05$) relative to the sham group (Figure 1A). The numbers of rearings was also significantly ($P<0.05$) lower in CMS mice relative to controls (Figure 1B). However, GPt(II) treatment significantly increased the numbers of crossings and rearings ($P<0.05$) in CMS mice, and the effect was in dose-dependent. The CMS-mediated reduction in numbers of crossings and rearings was completely reversed in the 12.0 mg/kg GPt(II) treatment group.

GPt(II) promotes dopamine and serotonin expression in mouse hippocampus tissues

ELISA results showed that CMS exposure significantly ($P<0.05$) suppressed dopamine and serotonin in hippocampus tissues of mice (Figure 2). Treatment with 3.0, 6.0, or 12.0 mg/kg GPt(II) significantly elevated dopamine and serotonin levels in the hippocampus tissues in a dose-dependent manner. The BDNF level was also significantly ($P<0.05$) suppressed by CMS in hippocampus tissues relative to the sham group (Table 1). However, GPt(II) treatment significantly prevented CMS-mediated suppression of BDNF level at 3.0 ($P<0.01$), 6.0 ($P<0.02$), and 12.0 ($P<0.05$) mg/kg doses.

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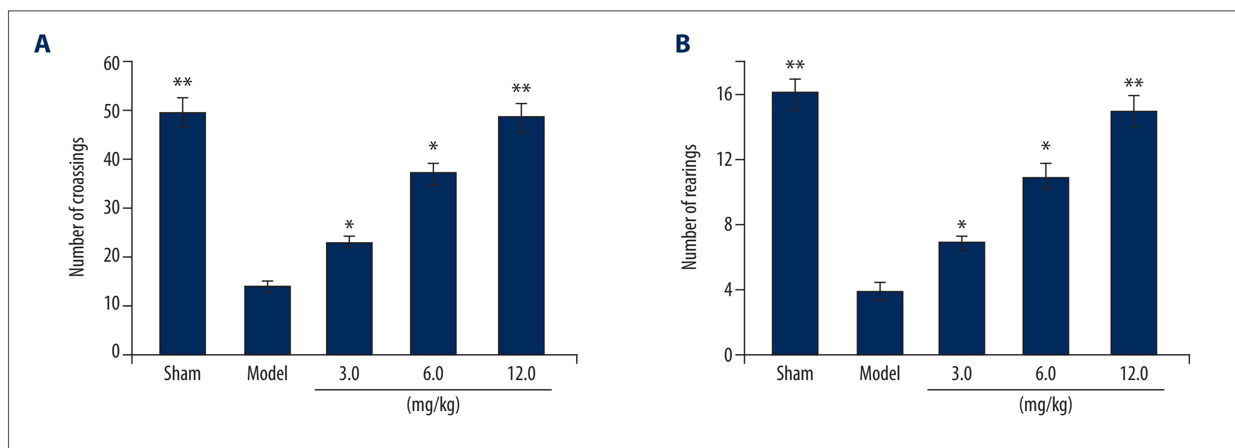

Figure 1. Effect of GPt(II) on numbers of crossings and rearings in mice. The mice were subjected to CMS and then intraperitoneally injected with 3.0, 6.0, or 12.0 mg/kg of GPt(II). The (**A**) crossings and (**B**) rearings were counted for each animal for 5 min. * P<0.05, and ** P<0.05 *vs.* sham control.

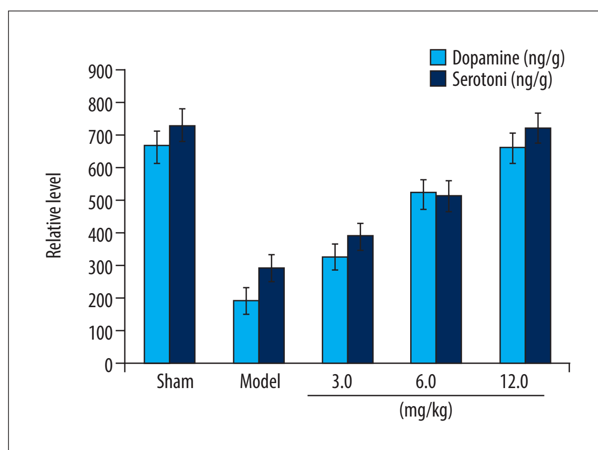

Figure 2. Effect of GPt(II) on dopamine and serotonin levels in mice. The mice were subjected to CMS and then intraperitoneally injected with 3.0, 6.0, or 12.0 mg/kg doses of GPt(II). The dopamine and serotonin levels were determined by ELISA. * P<0.05, and ** P<0.05 *vs.* sham control.

GPt(II) increased neuropeptide-Y level in mouse hippocampus tissues

The level of neuropeptide in mouse hippocampus tissues was significantly suppressed (P<0.05) by CMS relative to the sham group (Figure 3). However, GPt(II) treatment significantly (P<0.05) alleviated CMS-mediated reduction of neuropeptide-Y in the hippocampus tissues of mice. The CMS-mediated suppression of neuropeptide-Y level was significantly alleviated by treatment with 3.0, 6.0, and 12.0 mg/kg GPt(II).

Table 1. The level of BDNF in sham, model, and GPt(II)-treated mice.

Groups	BDNF (ng/g)
Sham	23.76±5.14
Model	7.98±1.87
3.0 mg/kg	11.67±2.87
6.0 mg/kg	19.43±2.90
12.0 mg/kg	22.56±3.11

Inhibition of MAO-A by GPt(II) in the hippocampus of mice

The CMS caused a marked elevation in MAO-A level in the mouse hippocampus tissues relative to the sham group (Figure 3). The GPt(II) treatment suppressed the CMS-induced elevated level of MAO-A in mouse hippocampus tissues. The level of MAO-A protein and mRNA induced by CMS was significantly suppressed by GPt(II) treatment at 3.0 (P<0.01), 6.0 (P<0.02), and 12.0 (P<0.05) mg/kg doses.

Inhibition of caspase-3 activation by GPt(II) in mouse hippocampus

The caspase-3 level was significantly elevated (P<0.05) in the hippocampus of mice by CMS relative to the sham control group (Figure 5). Treatment with GPt(II) significantly repressed caspase-3 activation induced by CMS in the hippocampus tissues of mice. The suppression of CMS-mediated caspase-3 level by GPt(II) treatment in mice was significant at 3.0 (P<0.01), 6.0 (P<0.02), and 12.0 (P<0.05) mg/kg doses compared to the untreated group.

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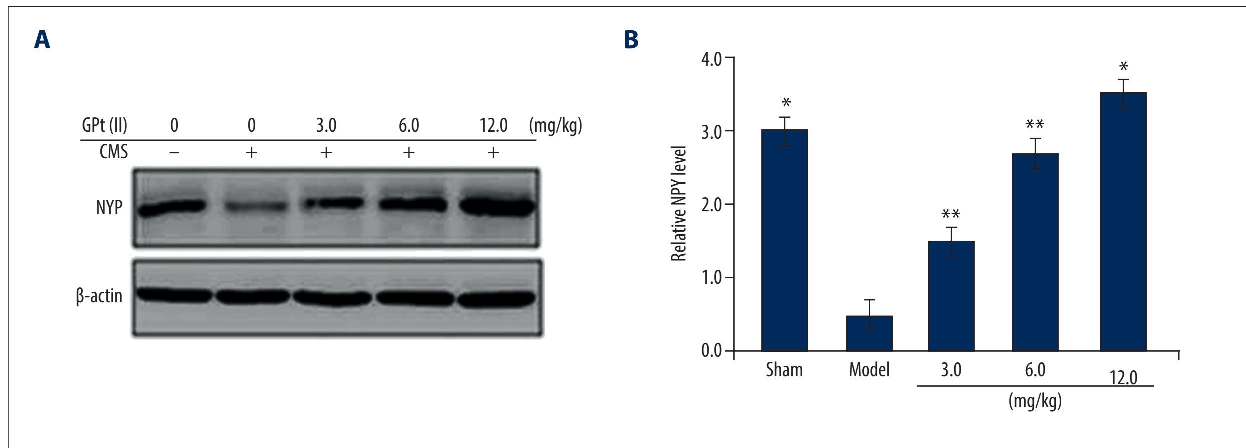

Figure 3. Effect of GPt(II) on neuropeptide-Y level in hippocampus tissues. The mice were subjected to CMS and then intraperitoneally injected with 3.0, 6.0, or 12.0 mg/kg doses of GPt(II). The neuropeptide-Y level was determined using (**A**) Western blot assay and (**B**) data were quantified. * P<0.05, and ** P<0.05 *vs.* sham control.

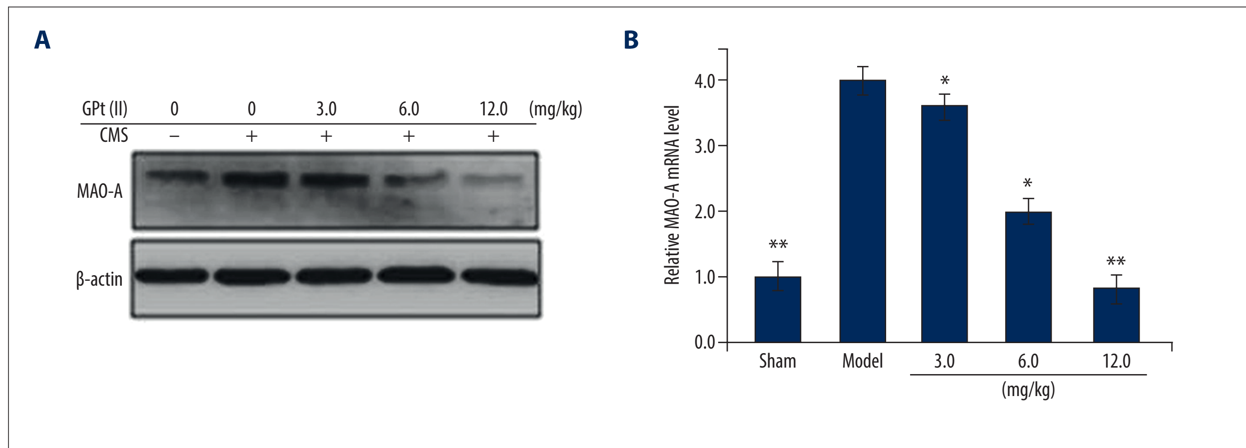

Figure 4. Effect of GPt(II) on MAO-A level in mouse hippocampus. CMS mice were intraperitoneally injected with 3.0, 6.0, or 12.0 mg/kg doses of GPt(II). The MAO-A (**A**) mRNA and (**B**) protein expression was detected by RT-PCR and Western blot assay in hippocampus tissues. * P<0.05, and ** P<0.05 *vs.* sham control.

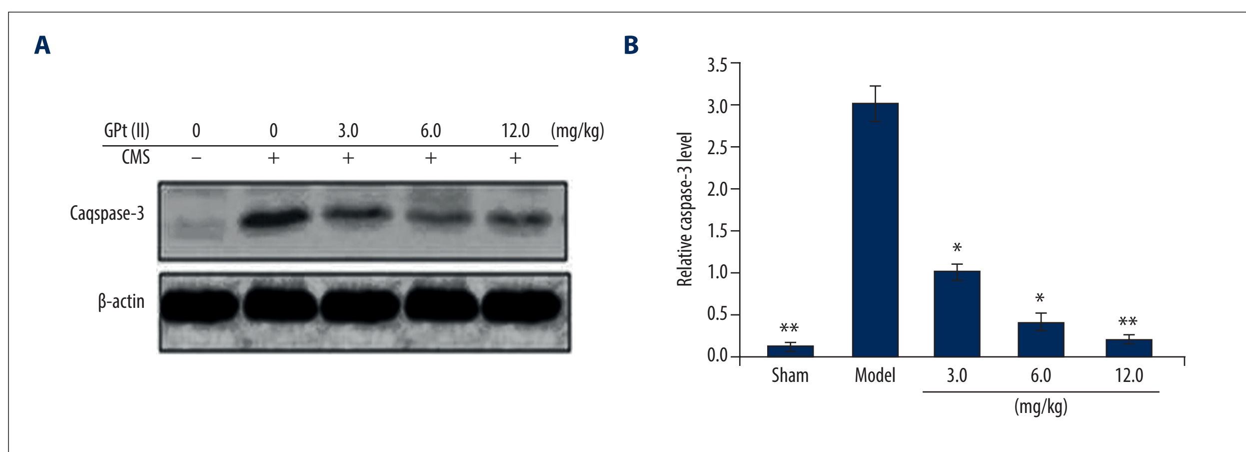

Figure 5. Effect of GPt(II) on caspase-3 activation induced by CMS in mice. CMS mice were intraperitoneally injected with 3.0, 6.0, or 12.0 mg/kg doses of GPt(II). The caspase-3 (**A**) mRNA and (**B**) protein expression was detected by RT-PCR and Western blot assay in hippocampus tissues. * P<0.05, and ** P<0.05 *vs.* sham control.

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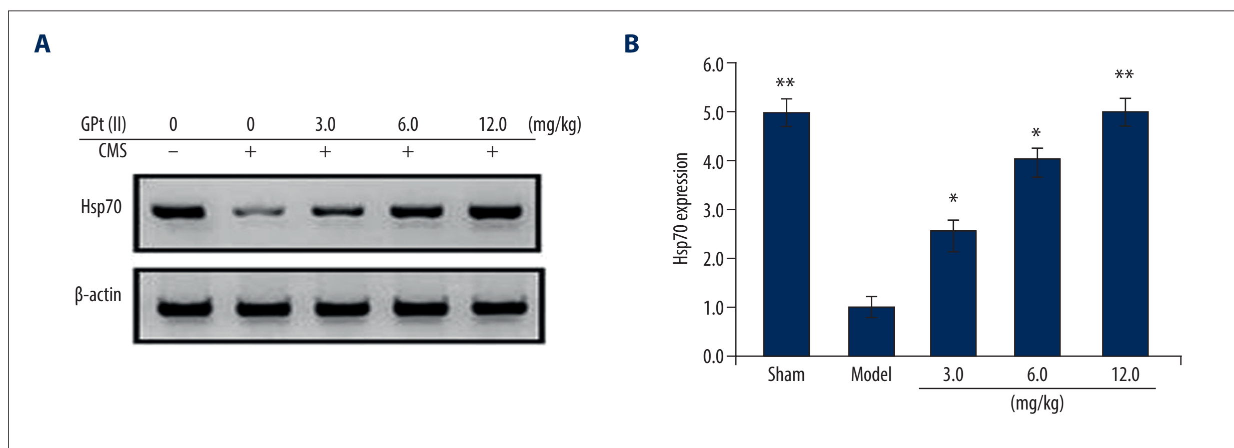

Figure 6. Effect of GPt(II) on Hsp70 level in depression model mice. The mice were intraperitoneally injected with 3, 6, or 12 mg/kg of GPt(II) following induction of depression. (**A**) The Hsp70 mRNA level was detected by RT-PCR in the hippocampus. (**B**) The Hsp70 protein expression was measured by Western blot assay. (* P<0.05, and ** P<0.05 *vs.* sham control.

Upregulation of Hsp70 expression by GPt(II) in mouse hippocampus tissues

The hippocampi of depression model mice showed markedly lower Hsp70 expression compared to the sham group (Figure 6). The GPt(II) treatment significantly (P<0.05) upregulated Hsp70 mRNA level in depression model mice in a dose-dependent manner (Figure 6A). Western blot analysis confirmed that stress-mediated suppression of Hsp70 protein expression was alleviated in the hippocampus of depression model mice by GPt(II) treatment (Figure 6B). Moreover, elevation of stress-mediated Hsp70 expression by GPt(II) treatment was also confirmed using immunohistochemical assay. The hippocampi of depression model mice treated with 10 mg/kg GPt(II) showed markedly higher Hsp70 expression compared to the model control mice.

Discussion

Depression is a serious and chronic neurological disorder that impairs human cognition, and its incidence is increasing rapidly due to high social and work pressure [20]. There are reports that impaired neurotransmission caused by downregulation of neurotransmitter production is the main cause of depression [21,22]. The 2 main neurotransmitters with prominent roles in the pathogenesis of depression are dopamine and serotonin [23]. The progression of depression depends on the downregulation of monoamines like dopamine and serotonin [24]. Post-mortem hypothalamic tissues obtained from depression patients also showed reduced dopamine and serotonin levels, suggesting the association of these monoamines with depression [25,26]. BDNF is associated with neuronal differentiation, promotes axonal growth, enhances survival of neurons, and promotes density of synaptic termini [27]. This neuropeptide, also called neuroendocrine polypeptide, regulates excitability of neurons during signal transmission [28]. The pathogenesis of depression is determined by secretion of MAO-A enzyme, which catalyses reduction of monoamine levels [29]. It is believed that overproduction of MAO-A can be inhibited by increasing the level of Hsp70 in hippocampus tissues [30]. The upregulation of Hsp70 by therapeutic molecules has been found to exhibit cytoprotection effects in various cells [31]. In the present study, the neurotransmitter (dopamine, BDNF, and serotonin) level decreased in the hippocampi of CMS mice. The inhibitory effect of CMS on neurotransmitter level in the mouse hippocampus was significantly alleviated by GPt(II) treatment. GPt(II) treatment also alleviated CMS-mediated reduction of neuropeptide in mouse hippocampus tissues. CMS exposure markedly increased monoamine oxidase-A secretion and elevated production of Hsp70 in the mouse hippocampus tissues. Treatment of the CMS-exposed mice with GPt(II) inhibited secretion of MAO-A. Moreover, GPt(II) treatment also alleviated CMS-mediated downregulation of Hsp70 production in the mice. These results suggest that the antidepressant effect of GPt(II) in mice involves suppression of MAO-A and upregulation of Hsp70 production. The behavioral assays showed that characteristics of depression were effectively relieved in mice after treatment with GPt(II) treatment. The loss of hippocampus cells like neurons and glial cells has been observed in post-mortem brain samples of patients with depression, which indicates apoptosis activation [32]. Neuronal apoptosis is also reported in the cerebral cortex of animals exposed to chronic stress [32]. The apoptotic process clearly contributes to reduction of hippocampal volume and development of depression [33]. The cellular apoptosis is effectively caused by activated caspase-3 [34]. In the present study, hippocampus tissues of CMS-exposed mice markedly overexpressed activated caspase-3 compared to the sham group. The increased caspase-3 served as a marker of apoptosis activation in the CMS mouse hippocampus tissues. Fortunately, GPt(II) treatment

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effectively suppressed CMS-mediated activation of caspase-3 in hippocampus tissues. Stress-induced cell apoptosis is effectively inhibited by Hsp70 in various types of tissues [35]. It was reported that Hsp70 targets ROS accumulation, alleviates the toxicity of amino acids, and inhibits apoptosis in various stressed tissues [36]. Therefore, GPt(II) may partly exhibit antidepressant effect by inhibiting apoptosis in hippocampus tissues through promotion of Hsp70 production.

Conclusions

GPt(II) treatment effectively relieved characteristics of depression in the mice through upregulation of neurotransmitter, neuropeptide, and Hsp70 expression. Moreover, GPt(II) downregulated monoamine oxidase-A level in the hippocampus tissues of mice. Further research is needed to elucidate the possible role of GPt(II) in the treatment of depression.

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