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Baicalein protects the brain against neuron impairments induced by MPTP in C57BL/6 mice

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ABSTRACT

Many studies of Parkinson's disease suggest that oxidative stress is involved in the neurodegenerative process. Baicalein has been shown to have antioxidant effects. The present study examines the effect of baicalein on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity in C57BL/6 mice. MPTP treatment impaired spontaneous motor activity and rotarod performance, but baicalein improved this deficit. Moreover, baicalein at 280 and 560 mg/kg exhibited a protective effect against the MPTP-induced decrease in tyrosine hydroxylase (TH)-positive fibers in the substantia nigra, demonstrated by the immunohistological, morphological and behavioral outcomes. MPTP treatment also decreased dopamine levels in the striatum. However, treatment with baicalein attenuated these decreases in dopamine levels by changing dopamine catabolism and inhibiting dopamine turnover. The neuroprotective effect of baicalein on dopaminergic neurons may partly be due to its antioxidant properties. Therefore, we speculate that baicalein might be a promising candidate for prevention or treatment of oxidative stress-related neurodegenerative disorders such as Parkinson's disease.

1. Introduction

Parkinson's disease results from a loss of dopaminergic neurons in the substantia nigra pars compacta and is characterized by a set of neurological symptoms including tremor, postural instability, gait abnormality, bradykinesia and rigidity (Obeso et al., 2000; Olanow and Koller, 1998). Several biochemical mechanisms have been proposed to play critical roles in the pathogenesis of Parkinson's disease, one of which is the deleterious effects of oxidizing metabolites and free radicals (Jenner, 2003; Yuan et al., 2007). Antioxidants, as scavengers of reactive oxygen species and free radicals, may play an important role in the prevention of Parkinson's disease (Grimes et al., 1988; Zhao, 2009).

Baicalein is a flavonoid derived from the root of the traditional Chinese herbal medicine Huangqin, *Scutellaria baicalensis* Georgi. It has been widely employed for many centuries in traditional Chinese herbal medicine as a popular antibacterial, antiviral, and antioxidant agent (Chen et al., 2008; Cui et al., 2010; Wu et al., 2001). Recent studies have shown baicalein could prevent 6-hydroxydopamine-induced dopaminergic dysfunction through its antioxidative action (Im et al., 2005) and attenuate inflammation-mediated degeneration of dopaminergic neurons (Li et al., 2005). Therefore, on the basis of our previous studies (Cheng et al., 2008; Mu et al., 2009), we speculate that baicalein, through its antioxidant and anti-inflammatory properties, may exert the capacity to block the MPTP-induced neurotoxicity.

Neurotoxin to dopaminergic neurons such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) are usually applied to induce experimental parkinsonism. MPTP produces clinical, biochemical and neurochemical changes similar to those that occur in Parkinson's disease (Heikkila et al., 1984; Meredith et al., 2008). The MPTP-induced parkinsonian mouse is one of the most commonly used animal models for analyzing the effect of drugs which act on dopaminergic neurons (Betarbet et al., 2002; Przedborski and Vila, 2003). To examine whether baicalein could prevent neuronal cell death in the substantia nigra pars compacta and depletion of dopamine in the striatum of MPTP-induced parkinsonian mice model, the effects of baicalein on the survival and function of dopaminergic neurons in the model were investigated.

2. Materials and methods

2.1. Drugs and reagents

Baicalein was purchased from Mianyang High-tech Dongfangyuan Biotechnology Co., Ltd. and repurified and its β crystal form was prepared by Prof. Lu Yang in Institute of Materia Medica. The purity of baicalein is 98% tested by high-performance liquid chromatography (HPLC) method and the crystal purity is >98% tested by powder X-ray diffraction. MPTP, dopamine (DA), homovanilic acid (HVA) and 3,4-

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dihydroxyphenylacetic acid (DOPAC) were purchased from Sigma-Aldrich.

2.2. Animals and drug treatments

Adult male C57BL/6 mice (Institute of Laboratory Animal Science, Chinese Academy of Medical Sciences; ~25 g, 8 weeks of age; license: SCXK(JING) 2005-0013) were used in this study. They were housed at 22 °C, under 12-h light/12-h dark conditions with ad libitum access to food and water. All experiments were performed in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals and were approved by our local Animal Ethics Committee.

Mice were divided into six groups with 12 in each: Group A, control mice; Group B, MPTP challenged; Group C, MPTP challenged and then baicalein treated (140 mg/kg i.g.); Group D, MPTP challenged and then baicalein treated (280 mg/kg i.g.); Group E, MPTP challenged and then baicalein treated (560 mg/kg i.g.). Mice were injected with MPTP for 5 consecutive days (30 mg/kg/day, i.p.) and control animals received five injections of vehicle. After MPTP injection, the mice of the last three groups were treated with baicalein by intragastric administration alone for 7 days, while the control and MPTP group received an equivalent volume of vehicle. Seven days after the last administration of MPTP or saline, mice were subjected to a spontaneous motor activity test and a rotarod test.

2.3. Spontaneous motor activity test

The spontaneous motor activity was measured with a computerized locomotion detection system equipped with two infrared video web cameras (ZIL-2 spontaneous system, manufactured by the Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College). Mice were individually placed in a transparent plexiglass cylinder (23–30 cm, diameter–height) and allowed to habituate to the environment for 3 min before the test, and then numbers of horizontal and vertical movements were recorded for 5 min. The results are expressed as the 5-min cumulative counts (Sundstrom et al., 1990).

2.4. Rotarod test

The rotarod system (Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College) for assessing locomotor skills measures the time that an animal maintains balance on a moving Lucite rod (2.5-cm diameter). The following general conditioning and testing procedures were employed in the different treatment and control groups: animals were first conditioned on a stationary rod for 30 s and during this time any animal that fell was placed back on the rod. Animals were next conditioned at a constant speed of 16 rpm for a period of 180 s. Animals that failed the first conditioning were given two additional conditioning periods. The same basic conditioning methodology was employed in testing treatment and control groups. Thirty minutes after the last conditioning, animals were placed on the rod and timed to determine their locomotor skill, using a constant speed of 16 rpm three times per day with an interval of 30 min.

2.5. Measurement of dopamine and its metabolites in the striatum by HPLC with electrochemical detection

Six of the mice were decapitated 3 days after the last behavioral assessment and the brains were removed immediately. The striatum was dissected and frozen in liquid nitrogen before assay. One side of the striatum was homogenized in 200 μL of 0.02 M perchloric acid ($HClO_4$) and centrifuged at 12 000 × *g* at 4 °C for 30 min to precipitate proteins. The supernatant was used to determine the concentration of DA and its metabolites DOPAC and HVA by HPLC with electrochemical detection. The mobile phase consisted of 0.1 M NaH_2PO_4 buffer, 0.85 M octane sulfonic acid, methanol 11%, and 0.5 mM EDTA·Na_2, and the pH of the mobile phase was set to 3.25. The column temperature was set at 35 °C and the flow rate was 1.2 ml/min.

2.6. Measurement of MDA, SOD and GSH-Px levels

The other side of the striatum of these brains was homogenized in 9 volumes of ice-cold saline, and the homogenate was further diluted with an appropriate buffer solution for determination of the relevant biochemical index. The activities of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and malondiadehycle (MDA, a product of lipid peroxidation) level were determined with specific kits (Nanjing Jiancheng Bioengineering Institute, China). The BCA Protein Assay Kit (PIERCE) was used for protein measurement.

2.7. Immunohistochemistry

For the immunohistochemical study, four of the mice were perfusion-fixed with 4% paraformaldehyde following a heparinized saline flush 7 days after behavioral assessment. Brains were dissected and postfixed in paraformaldehyde overnight at 4 °C, after which they were transferred into 30% sucrose in 0.1 M PB at 4 °C for 24 h. Then using a cryostat, series of 20-μm-thick coronal sections were cut through the ventral mesencephalon. Nigral brain sections were rinsed in PBS + Triton X-100 (PBST), quenched in 3% H_2O_2 and then incubated in blocking solution. After incubation with the anti-tyrosine hydroxylase (TH, monoclonal mouse, Chemicon, 1:500) at 4 °C overnight, the sections were treated with biotinylated secondary antibody for 1 h at 37 °C, then with streptavidin-peroxidase for 1 h. Subsequently the sections were incubated with 3,4-diaminobenzidine. The results were analyzed by counting the numbers of positive cells at 200× magnifications on an Olympus microscope (1X-70, Olympus Corp., Japan). The average number of positive cells was used to represent cell density.

2.8. Electron microscopic analysis

Mice were perfused with 4% paraformaldehyde and 2% glutaraldehyde 7 days after behavioral assessment. Substantia nigra was dissected and postfixed in the same fixative, and then blocks were processed by osmium tetroxide, dehydrated, and embedded in epoxy resin. Ninety nanometer sections were cut and examined under Hitachi H600 transmission electron microscope at 70 kV.

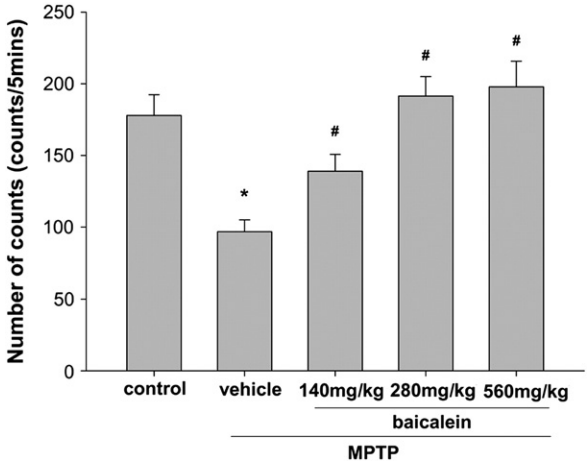

Fig. 1. Effect of baicalein on the spontaneous motor activity counts in MPTP-treated mice. Measurement of spontaneous motor activity was conducted 7 days after the last administration of MPTP or saline. Spontaneous motor activity was measured for 5 min as described in the text. Values are expressed as mean ± S.E.M. ($n = 12$). $^{*}P<0.05$ compared with control group, $^{\#}P<0.05$ compared with MPTP/vehicle treatment group.

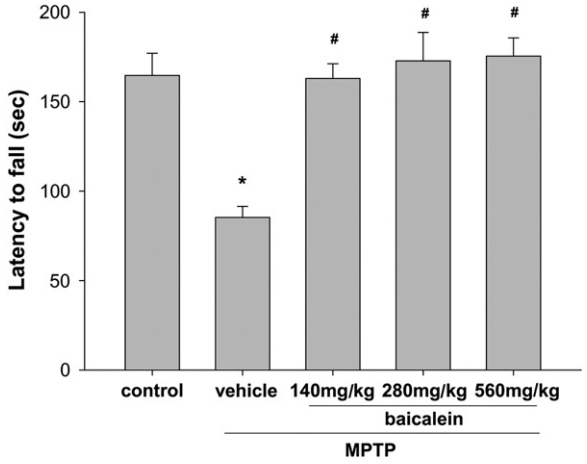

Fig. 2. Effect of baicalein on the rotarod performance in MPTP-treated mice. Testing was conducted after the spontaneous motor activity test. The latency to fall from the rotarod with a constant speed of 16 rpm was measured three times per day with intervals of 30 min. Values are expressed as mean ± S.E.M. ($n = 12$). $^{*}P<0.05$ compared with control group, $^{\#}P<0.05$ compared with MPTP/vehicle treatment group.

2.9. Statistical analysis

Values were expressed as means ± S.E.M. To analyze the differences between groups, statistical analysis was conducted with one-way ANOVA tests followed by Dunnett's test. A P value <0.05 was considered significant.

3. Results

3.1. Effects of baicalein on MPTP-induced behavioral deficits

The results of spontaneous motor activity and rotarod test performance were shown in Figs. 1 and 2, respectively. Compared with control mice, the MPTP-treated mice displayed a significant decrease in spontaneous motor activity and latency to fall of the rotarod test ($P<0.05$). However, baicalein treatment significantly ameliorated these behavioral deficits induced by MPTP toxicity ($P<0.05$).

3.2. Effect of baicalein on the changes of neurons in the substantia nigra

The morphology of the neurons was confirmed by analysis at an ultrastructural level. As shown in Fig. 3A, the normal-appearing neurons were easily detectable in the substantia nigra of control mice. The nucleus contained a large, rounded, and distinctly bounded chromatin clump. Numerous intact mitochondria and endoplasmic reticulum (ER) were observed in the cytoplasm. In MPTP-treated mice, morphological alterations were observed in both the nucleus and the cytoplasm (Fig. 3B). The nucleus showed an overall increase in electron density, and there was dilatation of the perinuclear cisternal space. In the cytoplasm, there were vacuoles and layered structures consisting of dilated cisternae of ER alternating with regions densely packed with ribosomes. The mitochondria were most often abnormal in appearance with poorly defined cristae. Baicalein treatment could ameliorate neuronal degeneration induced by MPTP. As shown in Fig. 3C, D and E, neurons showed milder abnormalities. There was a slight increase in the electron density of the nucleus and cytoplasm. Within the cytoplasm, rare vacuoles were seen, and mitochondria were of normal size and shape.

3.3. Effect of baicalein on MPTP-induced reduction of tyrosine hydroxylase immunoreactivity in the substantia nigra

Tyrosine hydroxylase immunoreactivity is a marker of dopaminergic neurons. Representative microphotographs of TH immunostaining in the substantia nigra were shown in Fig. 4A. Animals that received vehicle-only treatment with MPTP injection showed a marked loss of TH-immunopositive neurons, and the survival ratio of TH-immunopositive neurons in the Substantia nigra pars compacta was only 34.50% compared with the normal controls. In contrast, baicalein at the dose of 280 mg/kg and 560 mg/kg could increase TH-

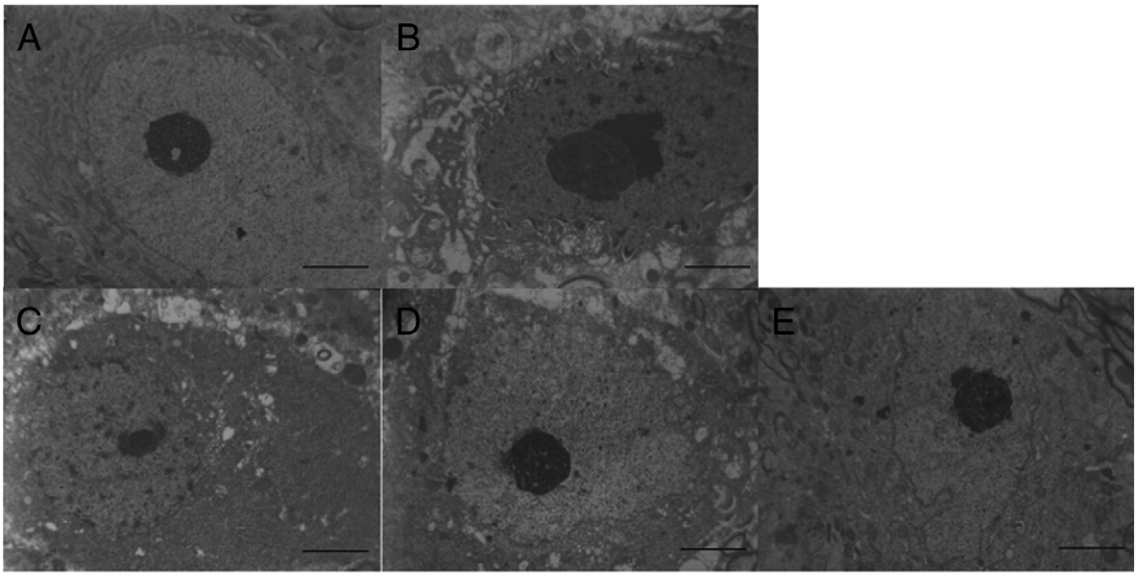

Fig. 3. Effect of baicalein on the changes of neurons in the substantia nigra. (A) Ultrastructure of a normal neuron in Substantia nigra pars compacta of normal control mice. The nucleus showed multiple, small clumps of heterochromatin, and normal-appearing rough endoplasmic reticulum (ER) and mitochondria are observed within the cytoplasm. (B) Ultrastructural appearance of degenerating neurons in MPTP-treated mice. The nucleus showed an overall increase in electron density, and numerous dilated ER and intact mitochondria were observed in the cytoplasm. (C, D, and E) Morphology changes in neurons of substantia nigra pars compacta in mice treated with baicalein at the dose of 140, 280, 560 mg/kg, respectively. The nucleus and organelles showed milder abnormalities. Scale bars: 2 μm.

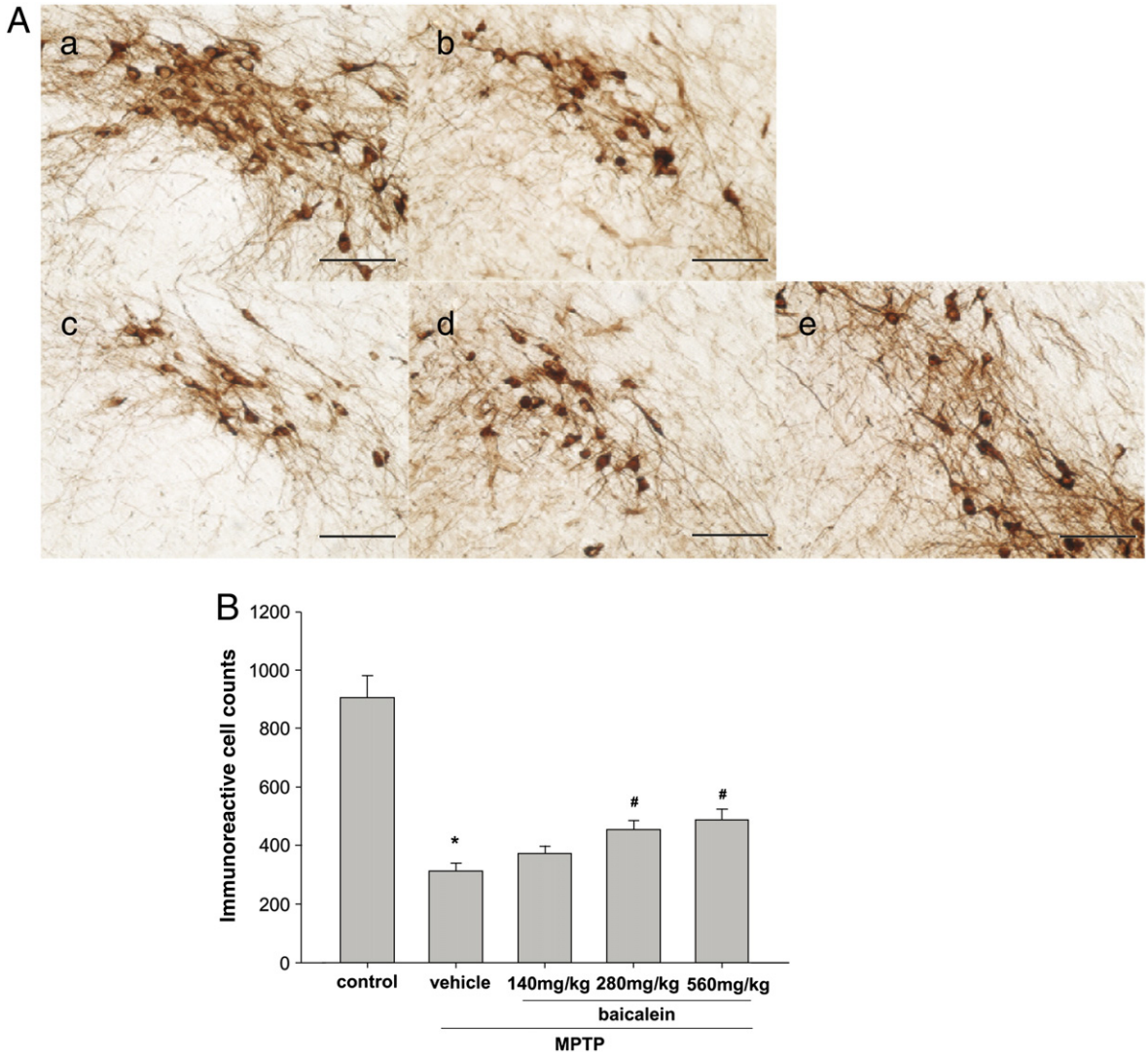

Fig. 4. Effect of baicalein on MPTP-induced reduction of tyrosine hydroxylase (TH) immunoreactivity in the substantia nigra of mice. (A) Representative microphotographs showing control (a), MPTP + vehicle (b), MPTP + baicalein (140 mg/kg) (c), MPTP + baicalein (280 mg/kg) (d), MPTP + baicalein (560 mg/kg) (e). (B) Summary of the effect of baicalein on MPTP-induced TH immunoreactive neurons in the substantia nigra. The TH positive neurons are expressed as mean ± S.E.M. ($n = 4$). $^{*}P<0.05$ compared with control group, $^{\#}P<0.05$ compared with MPTP/vehicle treatment group. Scale bars: 100 μm.

immunopositive neurons to 145.04%, 156.08% of the MPTP group, respectively ($P<0.05$, Fig. 4B).

3.4. Effects of baicalein on the levels of dopamine and its metabolites in the striatum

The results of catecholamine measurement were shown in Fig. 5. The present study confirmed that administration of MPTP induced a marked decrease in the levels of dopamine and its metabolites compared with the control group ($P<0.05$). Treatment with baicalein significantly attenuated the decrease in the levels of DA and HVA ($P<0.05$, Fig. 5A, C), but had no significant effect on the level of DOPAC ($P>0.05$, Fig. 5B). In addition, the DOPAC : DA ratio, indicating the monoamine oxidase (MAO)-dependent dopamine catabolism, was enhanced by MPTP, and intragastric administration of baicalein strongly depressed the MPTP-evoked acceleration of MAO-dependent dopamine catabolism ($P<0.05$, Fig. 6A). The rate of the total dopamine catabolism measured as the HVA/DA ratio was significantly enhanced by MPTP and the degree of enhancement of the ratio by MPTP was also decreased with increasing concentrations of baicalein ($P<0.05$, Fig. 6B).

3.5. Effects of baicalein on the levels of MDA, SOD and GSH-Px in the striatum

To understand the mechanisms of the protective effects of baicalein, we measured the activities of SOD and GSH-Px and the MDA contents in the striatum of every group of mice. The results of these biochemical parameters were shown in Table 1. The contents of MDA in the striatum of MPTP-treated mice were significantly increased compared with those in the control group ($P<0.05$). However, this increase in MDA level was significantly ameliorated when mice received baicalein treatment ($P<0.05$). In addition, the SOD activity did not change after MPTP challenge, but the GSH-Px activity in MPTP-treated mice was significantly decreased compared with control group ($P<0.05$), and baicalein treatment largely attenuated this decrease ($P<0.05$).

4. Discussion

The MPTP model in mice is widely used to study neuroprotective effect of drugs because it recapitulates the primary pathological and

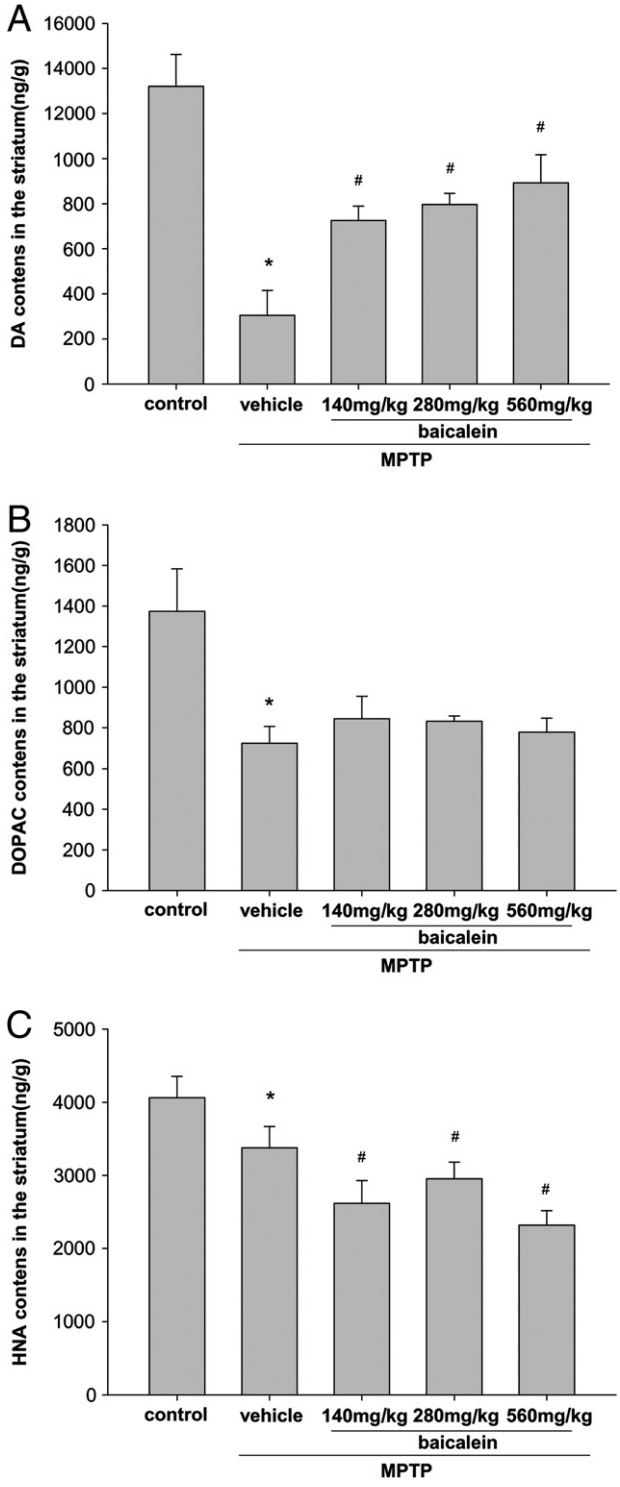

Fig. 5. Effects of baicalein treatment on the levels of DA (A), DOPAC (B) and HVA(C) in the striatum after MPTP treatment. Data are expressed as means ± S.E.M. ($n = 6$). *$P<0.05$ compared with control group, #$P<0.05$ compared with MPTP/vehicle treatment group.

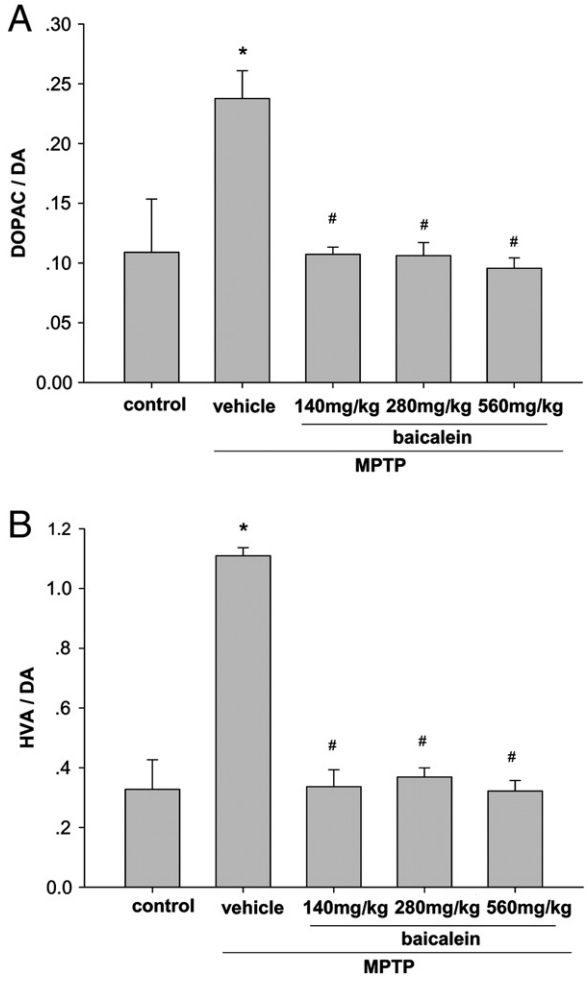

Fig. 6. Effects of baicalein treatment on the levels of DOPAC/DA (A) and HVA/DA (B) in the striatum after MPTP treatment. Data are expressed as means ± S.E.M. ($n = 6$). *$P<0.05$ compared with control group, #$P<0.05$ compared with MPTP/vehicle treatment group.

biochemical features of Parkinson's disease, such as oxidative stress, mitochondrial dysfunction and apoptosis (Schmidt and Ferger, 2001; Schober, 2004). In the present study, repeated treatment of MPTP-induced behavioral deficit in mice, i.e., a reduction of spontaneous motor behavior and motor incoordination in the rotard test. These behavioral alterations were consistent with a previous report (Sundstrom et al., 1990). The present study demonstrated that baicalein, a flavonoid extracted from a traditional Chinese herbal *Scutellaria baicalensis* Georgi (Huangqin), ameliorated behavioral abnormalities in C57BL/6 mice induced by MPTP. Moreover, it was revealed that this effect of baicalein was closely associated with the protection of nigrostriatal dopaminergic neurons against MPTP-induced neurotoxicity in the brain.

We observed that intragastric administration of baicalein produced an effective rescue of the dopaminergic neuronal death,

Table 1
Effects of baicalein on the levels of MDA, SOD and GSH-PX in the striatum.

Group	MDA (nmol/mg protein)	SOD (U/mg protein)	GSH-Px (U/mg protein)
Control	8.53 ± 0.33	4.75 ± 0.48	133.31 ± 16.00
MPTP + vehicle	13.34 ± 0.73*	4.61 ± 0.46	53.45 ± 6.23*
MPTP + baicalein (140 mg/kg)	6.84 ± 0.56#	6.81 ± 0.56#	72.62 ± 5.31#
MPTP + baicalein (280 mg/kg)	6.37 ± 0.29#	7.50 ± 0.91#	83.41 ± 8.03#
MPTP + baicalein (560 mg/kg)	5.81 ± 0.43#	7.71 ± 0.71#	89.87 ± 7.34#

Mice were decapitated 3 days after the last behavioral assessment and the striatum was dissected for biochemical evaluation. Values are expressed as mean ± S.E.M. ($n = 6$).
* $P<0.05$ compared with control group.
# $P<0.05$ compared with MPTP/vehicle treatment group.

demonstrated by the immunohistological, morphological and behavioral outcomes. The possible mechanism involved in neuroprotective action of baicalein may be its catechol-like structure, since it is known that catechol containing compounds are potent radical scavengers and chelators of ferric ion (Mandel and Youdim, 2004). Excessive free radical formation or antioxidant deficiency can result in oxidative stress and is a possible mechanism of the toxicity of MPTP (Lotharius and O'Malley, 2000). To investigate whether baicalein protected dopaminergic neurons through inhibiting oxidative stress, we determined the activity of the antioxidant enzymes, SOD, GSH-Px and the levels of lipid peroxidation. The present study showed that baicalein treatment could prevent the lipid peroxidation and improve abnormal GSH-Px activities induced by MPTP. In addition, although we did not observe the change in SOD activity induced by MPTP, baicalein treatment did significantly increase the SOD activity. Taken together, these results suggested that the neuroprotective effect of baicalein as demonstrated by the increasing number of dopaminergic neurons may partly owe to its antioxidant properties.

MPTP caused a partial lesion of the substantia nigra and a significant reduction in striatal dopamine levels. Our results suggested that baicalein could attenuate the decrease in the levels of DA and HVA in the striatum of MPTP-lesioned mice. Moreover, the present study showed that baicalein strongly depressed the MPTP-evoked acceleration of MAO-dependent dopamine catabolism, indicated by the decreased DOPAC/DA ratio. It is well known that the enzymatic catabolism of dopamine by mitochondrial enzyme MAO results in the production of DOPAC and hydrogen peroxide, which can form highly toxic hydroxyl radicals via the iron-catalyzed Fenton reaction (Chiueh et al., 1992). The suppressed oxidative catabolism of dopamine could thereby prevent an excessive production of hydrogen peroxide. The inhibition of the MAO-dependent pathway of dopamine catabolism observed in this study suggested that baicalein, through changing dopamine catabolism, may contribute to the protection of dopaminergic neurons against the effect of free radicals.

Furthermore, the decrease in dopamine turnover induced by baicalein administration, demonstrated by the HVA/DA ratio, was also observed in this study. HVA is a product of both extra- and intraneuronal dopamine metabolism and hence, may reflect the extent of dopamine transmission. In the present study, the HVA levels of the MPTP-lesioned animals were reduced, but less than dopamine levels, so that HVA/DA ratios were increased as discussed in a previous report (Zigmond and Stricker, 1989). Our data showed that, after baicalein administration, an increase in the HVA concentration compared with the MPTP-lesioned animals produced a decline in the HVA/DA ratio. Hence, it seems that baicalein is a potential therapeutic agent in Parkinson's disease with regards to the decline in dopamine turnover.

5. Conclusion

In conclusion, the present study confirmed some protective effects of baicalein in MPTP-induced neurotoxicity. The protective effects may be caused by increasing the levels of DA and HVA in the striatum, increasing the counts of dopaminergic neurons and inhibiting oxidative stress. Based on our previous studies (Cheng et al., 2008; Mu et al., 2009) and the current result of our investigation, we speculate that baicalein might be a promising candidate for the prevention or treatment of oxidative stress-related neurodegenerative disorders such as Parkinson's disease, but further studies to understand the basic mechanism are required.

6. Conflict of interest

There are no conflicts of interest.

Acknowledgements

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References

Betarbet R, Sherer TB, Greenamyre JT. Animal models of Parkinson's disease. Bioessays 2002;24:308–18.
Chen SF, Hsu CW, Huang WH, Wang JY. Post-injury baicalein improves histological and functional outcomes and reduces inflammatory cytokines after experimental traumatic brain injury. Br J Pharmacol 2008;155:1279–96.
Cheng Y, He G, Mu X, Zhang T, Li X, Hu J, et al. Neuroprotective effect of baicalein against MPTP neurotoxicity: behavioral, biochemical and immunohistochemical profile. Neurosci Lett 2008;441:16–20.
Chiueh CC, Krishna G, Tulsi P, Obata T, Lang K, Huang SJ, et al. Intracranial microdialysis of salicylic acid to detect hydroxyl radical generation through dopamine autooxidation in the caudate nucleus: effects of MPP^+. Free Rad Biol Med 1992;13:581–3.
Cui L, Zhang X, Yang R, Liu L, Wang L, Li M, et al. Baicalein is neuroprotective in rat MCAO model: role of 12/15-lipoxygenase, mitogen-activated protein kinase and cytosolic phospholipase A2. Pharmacol Biochem Behav 2010;96:469–75.
Grimes JD, Hassan MN, Thakar JH. Prevention of progression of Parkinson's disease with antioxidative therapy. Prog Neuropsychopharmacol Biol Psychiatry 1988;12: 165–72.
Heikkila RE, Hess A, Duvoisin RC. Dopaminergic neurotoxicity of 1-methyl-4- phenyl-1, 2, 5, 6-tetrahydropyridine in mice. Science 1984;224:1451–3.
Im HI, Joo WS, Nam E, Lee ES, Hwang YJ, Kim YS. Baicalein prevents 6-hydroxydopamine-induced dopaminergic dysfunction and lipid peroxidation in mice. J Pharmacol Sci 2005;98:185–9.
Jenner P. Oxidative stress in Parkinson's disease. Ann Neurol 2003;53:26–36.
Li FQ, Wang T, Pei Z, Liu B, Hong JS. Inhibition of microglial activation by the herbal flavonoid baicalein attenuates inflammation-mediated degeneration of dopaminergic neurons. J Neural Transm 2005;112:331–47.
Lotharius J, O'Malley KL. The parkinsonism-inducing drug 1-methyl-4- phenylpyridinium triggers intracellular dopamine oxidation. A novel mechanism of toxicity. J Biol Chem 2000;275:38581–8.
Mandel S, Youdim MB. Catechin polyphenols: neurodegeneration and neuroprotection in neurodegenerative diseases. Free Radic Biol Med 2004;37:304–17.
Meredith GE, Totterdell S, Potashkin JA, Surmeier DJ. Modeling PD pathogenesis in mice: advantages of a chronic MPTP protocol. Parkinsonism Relat Disord 2008;14: 112–5.
Mu X, He G, Cheng Y, Li X, Xu B, Du G. Baicalein exerts neuroprotective effects in 6-hydroxydopamine-induced experimental parkinsonism in vivo and in vitro. Pharmacol Biochem Behav 2009;92:642–8.
Obeso JA, Rodriguez-Oroz MC, Rodriguez M, Lanciego JL, Artieda J, Gonzalo N, et al. Pathophysiology of the basal ganglia in Parkinson's disease. Trends Neurosci 2000;23:8-19.
Olanow CW, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease: treatment guidelines. American Academy of Neurology. Neurology 1998;50:S1-S57.
Przedborski S, Vila M. The 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine mouse model: a tool to explore the pathogenesis of Parkinson's disease. Annals of the New York Academy of Sciences 2003;991:189–98.
Schmidt N, Ferger B. Neurochemical findings in the MPTP model of Parkinson's disease. J Neural Transm 2001;108:1263–82.
Schober A. Classic toxin-induced animal models of Parkinson's disease: 6-OHDA and MPTP. Cell Tissue Res 2004;318:215–24.
Sundstrom E, Fredriksson A, Archer T. Chronic neurochemical and behavioral changes in MPTP-lesioned C57BL/6 mice: a model for Parkinson's disease. Brain Res 1990;528:181–8.
Wu JA, Attele AS, Zhang L, Yuan CS. Anti-HIV activity of medicinal herbs: usage and potential development. Am J Chin Med 2001;29:69–81.
Yuan H, Zheng JC, Liu P, Zhang SF, Xu JY, Bai LM. Pathogenesis of Parkinson's disease: oxidative stress, environmental impact factors and inflammatory processes. Neurosci Bull 2007;23:125–30.
Zhao B. Natural antioxidants protect neurons in Alzheimer's disease and Parkinson's disease. Neurochem Res 2009;34:630–8.
Zigmond MJ, Stricker EM. Animal models of parkinsonism using selective neurotoxins: clinical and basic implications. Int Rev Neurobiol 1989;31:1-79.