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Full Length Research Paper

Effects of salidroside on the protection of diabetic encephalopathy and improvement of abilities of learning and memory in rat

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Salidroside, a phenol glycoside isolated from *Rhodiola rosea*, has been reported to have many pharmacological properties, among which are the protective effects against neuronal death. Salidroside has the best pharmacological effects at the concentration of 50 mg/kg Salidroside (po) for rodents. A diabetic encephalopathy rat model has been generated in this research. After treating with salidroside, the blood glucose reduced and body weight increased in rats. Morris water maze test indicated that salidroside could improve memory and learning ability, because it can protect the brain, promote neurons growth and balance neuron growth factors. Salidroside can also keep biochemistry markers and morphology normal in hippocampus. All these suggest that salidroside may be a potential drug for the treatment of diabetic encephalopathy and other nervous system diseases.

Key words: *Diabetes mellitus*, salidroside, hippocampus, Morris water maze tests, oxidative stress, signal pathway.

INTRODUCTION

Diabetes, short name for diabetes *mellitus*, is a chronic disease caused by lack of or inability to use insulin, which is normally produced in the pancreas, a gland attached to the small intestine. The function of insulin is to convert carbohydrates into glucose, the compound used by body to obtain energy and other functions. Diabetes could be divided into 3 main types: type 1 diabetes, which results from the inability to produce insulin; type 2 diabetes, which results from insulin resistance; and gestational diabetes. Diabetes, without proper treatments, can cause many complications, among which are hypoglycemia, diabetic ketoacidosis and nonketotic hyperosmolar coma (Asche et al., 2011). Adequate treatment of diabetes is thus important. Without this, patients would be in danger.

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Diabetic encephalopathy is caused by diabetes. The complications of diabetic encephalopathy include memory loss, dementia, coma, seizures and finally death. The defects in patients include lethargy, poor judgment and coordinations of limbs, dementia, and muscle twitching (McFarland and Cripps, 2010).

Rhodiola rosea has been used widely in traditional Chinese medicine. Salidroside ($C_{14}H_{20}O_7$), with the IUPAC name of 2-(4-hydroxyphenyl) ethyl β-D-glucopyranoside, is the main active constituent isolated from *R. rosea* (Panossian and Wagner, 2005; Li et al., 2011). Salidroside has been reported to be one of the compounds responsible for the neuroprotective, antidepressant and anxiolytic actions *in vitro* (Zhong et al., 2011; Guo et al., 2010). However, the effect of salidroside on the animal level remains unclear. This research mainly focused on the effects of salidroside on the protection of diabetic encephalopathy and improvement of abilities of learning and memory in rats.

MATERIALS AND METHODS

The root and stem of *R. rosea* were collected at the weight of 100 g, crushed and soaked in 10 times volume of 70% alcohol for 72 h. Circulation refluxed with reduced pressure twice, each for 40 to 60 min until no alcohol was detected. Proper water was added and then the aqueous solution was extracted by n-butyl alcohol. 2.5 g powder was got after volatilization; this was salidroside (Purity 99%). Streptozocin (STZ) was purchased from Sigma-Aldrich Inc. (St. Louis, MO, U.S.A.). 2-month-old male rats were kept in an environmentally controlled room with temperature near 22°C and relative humidity of 50%.

Rat model establishment and administration

After 1 week adaptive feeding, rats were kept out of food for 12 h, and then given intraperitoneal injection with STZ (60 mg/kg). Blood glucose was detected after 3 days treatment. Rats with more than 16.67 mmol/L blood glucose were considered successfully. Equal volume of buffer was injected into another 10 rats as control group. The diabetes rats were divided into 3 groups randomly: Diabetes mellitus group (DM), Diabetes mellitus + insulin (DM +I) and Diabetes mellitus + Salidroside (DM +S), each group for 10 rats. The dose of insulin (ih) was 10 U/kg in DM +I group while 50 mg/kg salidroside (po) for DM +S group. In control and DM groups, there was equal volume of saline using gavage, once per day for 12 weeks. At the end of 0 and 12 week, the blood glucose and body weight of rats were detected 2 h after drug treatment.

Test of abilities of learning and memory

Morris water maze tests were performed after training for 12 weeks. After the rats were familiar with the testing environment, normal training was performed from the second day. The experiments were divided into 2 parts: Orientation test and Space exploration test. In the former, ats were trained twice per day, one time in the morning and one time in the afternoon. Each training lasted for 120 s and the gap time was 30 s. This training lasted for 4 days. Starting area was randomly selected and the number of times rats touch the platform in 120 s was recorded. Space exploration test: The platform was removed, and the rats were put into water at the opposite side of the platform. The percent of residence time in the center area and number of time of passing the former platform in 120 s were recorded.

Biochemistry markers test

The brains of rats in each group after the test of abilities of learning and memory were collected on the ice and then the hippocampus was dissected. Tissues were crushed and centrifuged at the speed of 2000 r/min for 10 min. The supernate was collected and the activities of SOD, GSH-Px, CAT and content of MDA in the rat, hippocampal gyrus were detected. Coomassie brilliant blue staining was used to detect protein concentration.

HE staining test

30 μm brain coronal sections were collected from every 200 μm. The sections were deparaffinized, with two changes of xylene, 10 min each. They were re-hydrated in 2 changes of absolute alcohol, for 5 min each; 95% alcohol for 2 min and 70% alcohol for 2 min; and then washed briefly in distilled water and stained in Harris hematoxylin solution for 8 min. They were washed in running tap water for 5 min and differentiated in 1% acid alcohol for 30 s. After which they were washed in running tap water for 1 min, and blued in 0.2% ammonia water or saturated lithium carbonate solution for 30 to 60 s. Again they were washed in running tap water for 5 min, rinsed in 95% alcohol, at 10 dips and then counter-stained in eosin-phloxine solution for 30 s. They were dehydrated in 95% alcohol, 2 changes of absolute alcohol, 5 min each. They were cleared in 2 changes of xylene, 5 min each, and mounted with xylene based mounting medium. The neurons in CA1 in hippocampus were observed using optical microscope.

Ultra-structure observation

Hippocampus tissue was cut into 1mm3, deparaffinized and washed with 0.1 mol/L PBS 5 to 6 times. Frozen sections were cut into 30 μm thick and collected in every 200 μm. They were deparaffinized using 1% osmic acid at 4°C for 2 h and washed with 0.1 mol/L PBS 5 to 6 times. Gradient dehydration was done on them using ethylalcohol and acetone, and then they were embedded and cut. They were double stained using uranyl acetate and lead citrate; and pictures were taken using electron microscope.

IHC staining test

After dissecting tissues at 5 μm, and fixed in 4% paraformaldehyde for 10 m, slides were incubated 2 to 3 times in xylene for 10 m each and then incubated twice in 100% ethanol for 2 m each. They were hydrated by placing in 95, 70, 50 and 30% ethanol for 2 min each. Slides were placed into buffer containing 5% normal goat serum for 10 min. Slides were incubated in a humidified chamber overnight with primary antibody (Rabbit anti rat Akt/PKB 1:500, Rabbit anti rat pCREB 1:1000). They were washed in 5 m in buffer for 3 times and incubated with secondary antibody in a humidified chamber for 30 min. DAB and hematoxylin staining, 5 discontinue brain sections were selected and 5 fields were selected randomly. The numbers of Akt/PKB and pCREB positive cells in CA1 were counted.

Western blot

Run 20 μg protein/lane after heating at 100°C for 5 min. Run on an SDS-PAGE gel until the blue front is at the bottom of the gel. Transfer to a nitrocellulose membrane for 0.5 A-h. Block the membrane for 1 h in 5% non-fat dry milk in 1X TPBS, in a small Tupperware dish on a shaker. Incubate with primary antibody (Rabbit anti rat pCREB 1:500, Rabbit anti rat Bcl-2 1:1000, Rabbit anti rat Bax 1:1000, β-actin 1:200) at 4°C overnight. Wash 3 times for 5 to 10 min in 50 ml 1× PBS with 0.1% Tween 20 at RT. Incubate with goat anti rabbit 1:200 for 1 h at RT in 1X TPBS. Wash 3 × 10 min. Rinse with ddH2O.Detect protein with ECL kit (2 ml/membrane). In a separate tube, mix black and white ECL solutions in a 1:1 ratio. Then add aliquot solution onto membranes and wait for 1 min. Drain the ECL, wrap in plastic and expose to film. The value of protein would be compared with β-actin, and the relative potency ratio would stand for the expression of protein.

RESULTS

The change of blood glucose and body weight

As shown in Table 1, at the beginning of generating animal model, the values of blood glucose in DM and DM+S groups were much higher than control group ($P<0.01$), while the body weight of mice in 3 groups

Table 1. Blood glucose and body weight of mice in 3 groups (± s，n=1). Different letter represent the significant difference at p<0.05.

Group	Blood Glucose (mmol/L)		Body weight (g)	
	0 w	12 w	0 w	12 w
CON	5.31±0.42	5.47±0.35	240.62±8.75	341.15±31.57
DM	21.13±1.64[a]	22.64±1.42[a]	238.43±7.38	212.82±13.66[a]
DM+S	22.42±1.76[a]	17.83±1.27[b]	239.56±8.17	234.24±17.21[b]

Table 2. The abilities of learning and memory of mice in 3 groups ($\bar{x}$ ±s，n=10).

Group	Time of escape (t/s)	Centre area (%)	Times of passing target zone
CON	15.23±5.42	31.24±4.13	3.48±1.34
DM	27.18±6.11[a]	16.06±5.21[a]	2.57±1.07[a]
DM+S	19.45±1.75[b]	24.57±4.63[c]	3.12±1.23[c]

Different letter represent the significant difference at p<0.05.

remained the same(*P*>0.05). After the treatment, the values of blood glucose in DM+S group were decreased while body weight increased compared with DM group. The difference was significant (P<0.05).

Comparation of study and memory ability

In the experiment of orientation swimming，the escape latent period in DM group was much longer compared with control group (P<0.01), while the escape latent period in DM+S group was much shorter compared with DM group (P<0.01). In the experiment of space searching, compared with control group, the percent of residence time and the time of passing platform were decreased obviously in DM group (P<0.01), but increased obviously in DM+S group compared with DM group (P<0.05) (Table 2).

Changes on biochemistry

Compared with the control group, the activities of SOD, GSH-Px and CAT in the rat hippocampal gyrus in DM group were decreased obviously (P<0.01). Compared with DM group , the activities of SOD, GSH-Px and CAT in the rat hippocampal gyrus were increased while MDA decreased obviously in DM+S group (P<0.05 or P<0.01 (Table 3).

Changes on morphology

The neurons in CA1 in hippocampus in control group were normal with clear outline and well arrangement. The staining of cytoplasm was well-distributed and nuclei were observed clearly (Figure 1A). The indistinct neuronal structure, swelling cytoplasm and confused cell arrangement were observed. The numbers of nissl bodies and neurons were reduced (Figure 1B). The pathological changes were slight obviously in DM+S group (Figure 1C).

The ultra-structure changes of CA1 in hippocampus were observed by electron microscope. The pyramidal cells in CA1 in hippocampus in control group were normal (Figure 2A). The degenerative changes and apoptosis of pyramidal cells in DM group were observed with the damaged organelle (Figure 2B). After the treatment of salidroside, the increscent nucleus and intact karyotheca of pyramidal cells were observed. The cells returned to normal (Figure 2C).

Analysis on the results of IHC

The results of IHC indicated that, compared with the control group, the Akt/PKB positive cells in hippocampus in DM group were reduced while the staining was light. The results of IHC staining in DM+S group were similar with the control group (Figure 3). The numbers of Akt/PKB positive cells in hippocampus in 3 groups are shown in Table 4.

The results of IHC indicated that there were lots of pCREB positive cells in hippocampus with intensive zonal distribution. pCREB is mainly expressed in nucleolus, while there was no expression in cytoplasm and synapse. The expression of pCREB in hippocampus in control group was highest with the deepest clay bank colour, mostly distributed in dentate gyrus and then in CA1. Compared with the control group, the pCREB positive cells in DM group were decreased obviously with significant differences (p<0.01). Compared with the DM group, the pCREB positive cells in DM+S group were increased (p<0.05) (Figure 4). The numbers of pCREB

Table 3. Changes on biochemistry of rats in 3 groups ($\bar{x} \pm s$，n=10).

Group	SOD (U/mg.pro)	GSH-Px (U/mg.pro)	CAT (U/mg.pro)	MDA (nmol/mg.pro)
CON	61.22±10.41	0.067±0.023	5.73±0.71	8.33±1.57
DM	46.73±9.25[a]	0.044±0.012[a]	2.42±0.87[a]	13.86±2.62[a]
DM+S	65.74±11.52[b]	0.058±0.005 [c]	4.24±0.68[b]	9.25±1.83[c]

Different letter represent the significant difference at p<0.05.

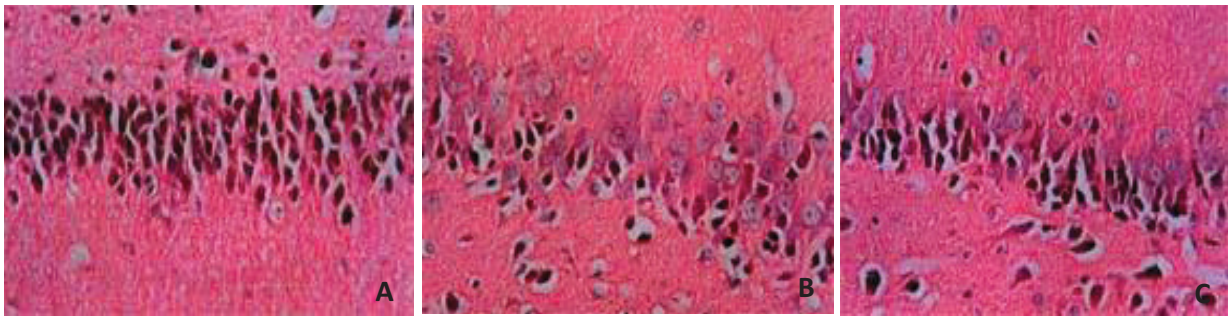

Figure 1. HE staining on morphology of neurons in CA1 in hippocampus of rats in 3 groups (HE，400×) A：CON Group；B：DM Group；C：DM+S Group.

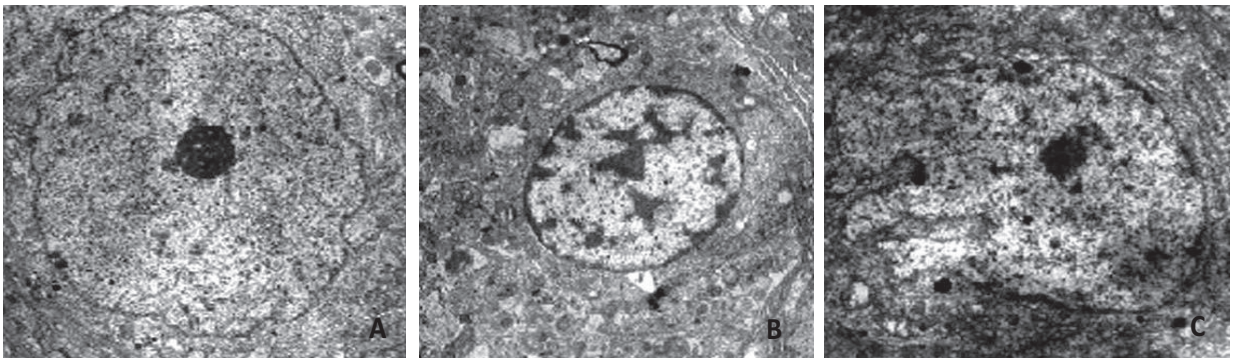

Figure 2. The ultrastructure changes of CA1 in hippocampus of rats in 3 groups (TEM，5000×). A: CON Group; B: DM Group；C: DM+S Group.

Figure 3. The distribution of Akt/PKB positive cells in hippocampus of rats in 3 groups（IHC，×200）A：CON Group；B：DM Group；C：DM+S Group.

Table 4. The number of positive cells of neurons in CA1 in hippocampus of rats in 3 groups ($\bar{x}$ ±s).

Group	Numbers of rats	Akt/PKB	pCREB
CON	10	32.74±4.13	36.38±4.56
DM	10	20.16±2.51[1)]	22.52±3.16[1)]
DM+S	10	30.01±3.86[2)]	33.02±5.03[2)]

Different letter represent the significant difference at p<0.05.

Figure 4. The distribution of pCREB positive cells in hippocampus of rats in 3 groups (IHC，×400). A：CON Group；B：DM Group；C：DM+S Group.

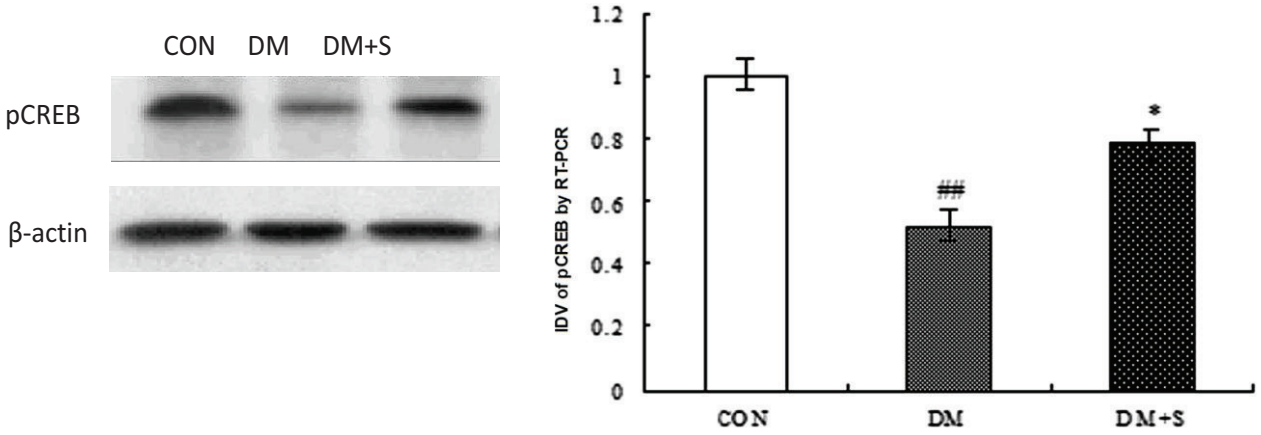

Figure 5. The protein expression of pCREB in hippocampus of rats in 3 groups. Different mark represent the significant difference at p<0.05.

positive cells in hippocampus in 3 groups are shown in Table 4.

Western blot

Compared with the control group, the expression of pCREB was obviously decreased in the rat hippocampal gyrus in DM group (P<0.01). Compared with DM group, the expression of pCREB was obviously increased in the rat hippocampal gyrus in DM+S group (P<0.05) (Figure 5).

As shown in Figure 6, the expression of Bcl-2 was only 1/3 value of the control group in the rat hippocampal gyrus in DM group (P<0.01). However, the expression of Bcl-2 was 2 times higher than DM group after the treatment of salidroside (P<0.01). As shown in Figure 7, the expression of Bax was opposite to Bcl-2.

DISSCUSSION

Diabetes is a serious and chronic disease. When the

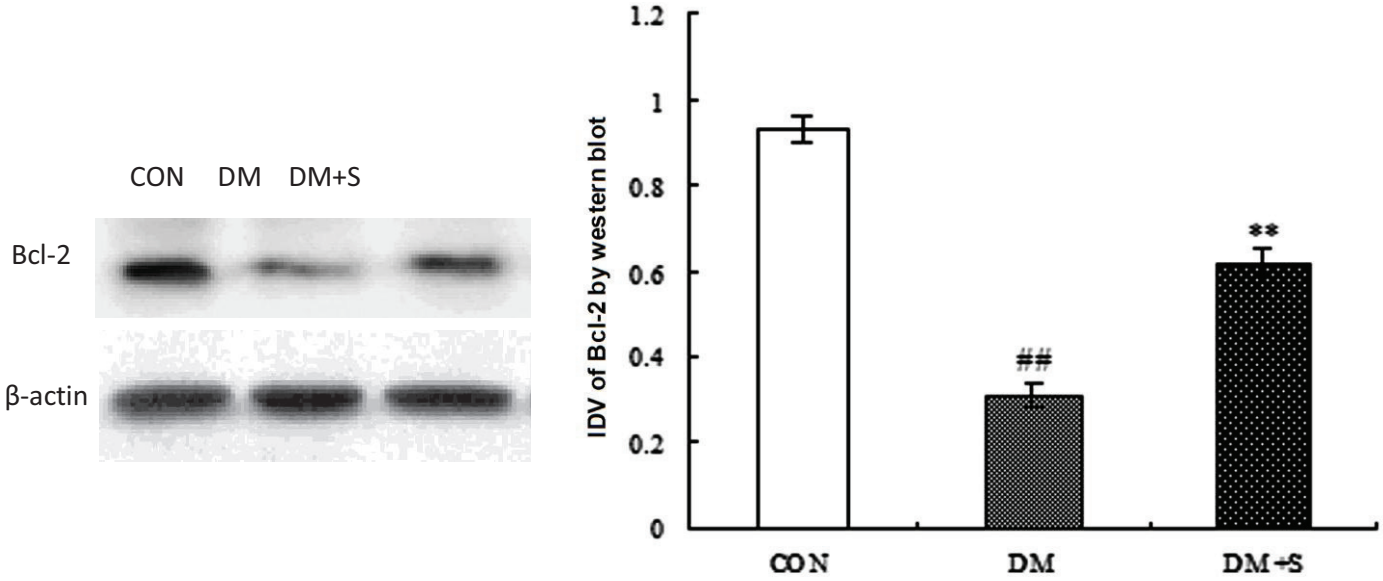

Figure 6. The protein expression of Bcl-2 in hippocampus of rats in 3 groups Different mark represent the significant difference at p<0.05.

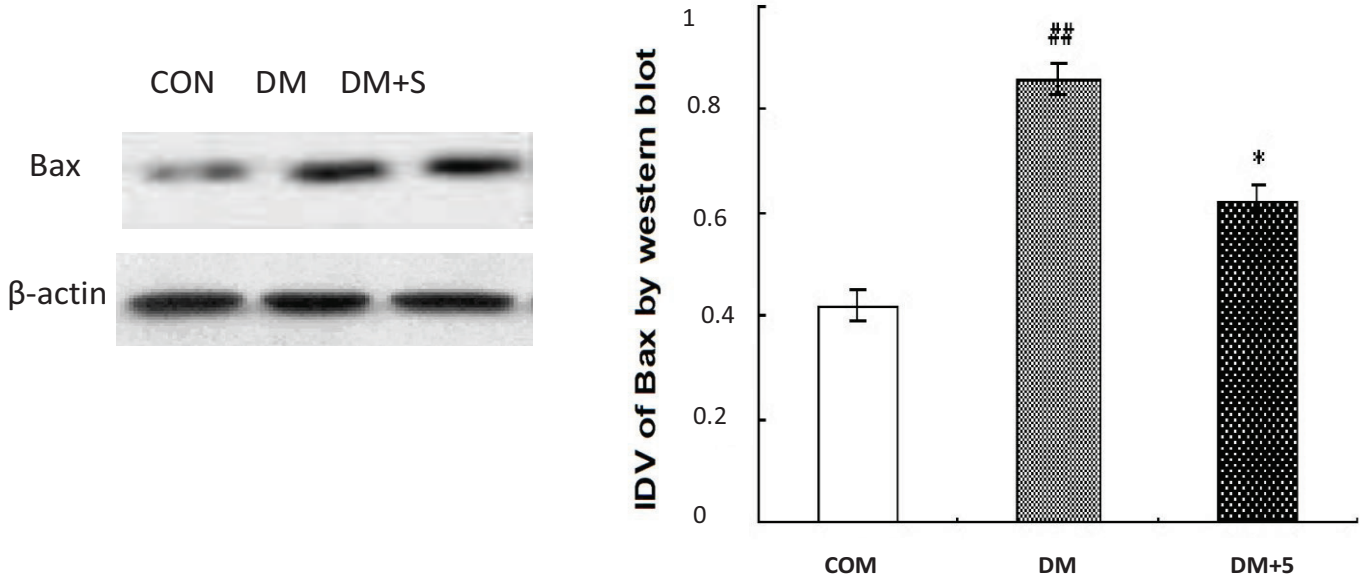

Figure 7. The protein expression of Bax in hippocampus of rats in 3 groups. Different mark represent the significant difference at p<0.05.

pancreas does not produce enough insulin or cannot effectively use the insulin, hyperglycaemia occurs, which is called diabetes. Diabetes could result in serious neural diseases. One of them is diabetic encephalopathy, the complications which include memory loss, dementia, seizures, and finally death. The defects observed in patients are complex, such as lethargy, dementia, poor judgment and coordination of limbs, muscle twitching, and so on. Diabetes without proper treatment could be lethiferous.

R. rosea is a plant which belongs to the Crassulaceae family. It grows in cold regions all around the world including China (Panossian et al., 2010). Salidroside is one of the most effective components in *R. rosea*. It may be effective for strength immunity, improving mood, alleviating depression and reducing fatigue. Former researches have indicated that salidroside protects neuronal PC12 cells from Aβ-induced cytotoxicity via its antioxidant pathway (Hoi et al., 2010). Protective effects of salidroside on hydrogen peroxide-induced apoptosis

have been reported in SH-SY5Y human neuroblastoma cells (Zhang et al., 2011). Salidroside has the property of potent antioxidant. It has protective effects against oxidative stress-induced cell apoptosis, and thus could be used for treating or preventing neurodegenerative diseases caused by oxidative stress (Qian et al., 2011). Most of these researches mainly are *in vivo* study that focuses on cell level. Salidroside has the best pharmacological properties at the concentration of 50 mg/kg salidroside (po) for rodents. However, whether it could improve physical and mental performance, and reduce the symptom of diabetic encephalopathy on the animal level, remains unknown.

First, we established the animal model and then tested the effects of salidroside on the blood glucose and body weight. After single injection of STZ at the concentration of 60mg/kg, the concentration of blood glucose in rat was more than 16.67 mmol/L and the symptom of diabetes was obvious. These indicated that the diabetes rats model were generated successfully. The blood glucose was reduced and the body weight increased in the rats after treating with salidroside. This means that salidroside could improve the symptom of diabetes.

Previous study reported that salidroside may have some effects on the body condition (Zhong et al., 2011; Yin et al., 2009). This research firstly reported that salidroside had some effects on the treatment of diabetes in diabetes rats induced by STZ. This may be one of the reasons of improving the brain function by reducing the risk of diabetic encephalopathy.

Then we detected the effects of salidroside on the abilities of learning and memory of rats. The Morris water maze test is a behavioral procedure widely used in behavioral neuroscience to study spatial learning and memory (Holmes et al., 2002). For Morris water maze test, the learning and memory abilities of diabetes rats were decreased compared with normal rats which obviously improved after the treatment of salidroside. This test indicated that salidroside could improve the memory, learning ability and function of the brain. The concentration of salidroside was high in hippocampus, which indicated that salidroside could protect the CNS and promote the growth of neurons.

SOD, GSH-Px and CAT could clear the O-, OH-, H_2O_2 and reduce the damage by diabetes. Compared with the control group, the activities of SOD, GSH-Px and CAT in hippocampus in DM group were decreased obviously, while MDA increased obviously. These indicated that hyperglycaemia would induce the metabolic disturbance，while the damaged neurons could not clear oxygen radical in time. The anti-oxygenization was inhibited. After salidroside treatment, the activities of SOD, GSH-Px and CAT in hippocampus were increased obviously, while MDA decreased. These means salidroside could reduce neuron damage by clearing oxygen radical in time and thus improve the function of hippocampus.

The hippocampus, which belongs to the limbic system in CNS, is a major component of the brains in mammals. It plays very important roles in the consolidation of information, from short-term memory to long-term memory and spatial navigation (Koehl and Abrous, 2011; Vassort and Turan, 2010). In rodents, hippocampus has been studied extensively as part of the brain system responsible for behavioral inhibition and attention, navigation, memory, learning ability and spatial memory (Aaseb et al., 2011). The neurons in CA1 in hippocampus in control group were normal with clear outline and well arrangement. The staining of cytoplasm was well-distributed and nuclei were observed clearly. The indistinct neuronal structure, swelling cytoplasm and confused cell arrangement were observed. The numbers of nissl bodies and neurons were reduced. The pathological changes were slight obviously in DM+S group. All these indicated that salidroside could improve the damage in hippocampus caused by diabetic encephalopathy.

Neuronal survival factors are necessary for neurons. These factors make the neurons survive normally and work by many special signal transduction pathways, which mainly include phosphorplylinositol 3 kinase and Ras pathways. In these pathways, Akt/PKB, p CREB, and Bcl-2/Bax are related with nervous system. Akt/PKB is a serine/threonine protein kinase that plays a key role in multiple cellular processes. Akt/PKB could promote growth factor-mediated cell survival (Bhattacharya et al., 2011). CREB (cAMP response element-binding protein) is a cellular transcription factor. It has many important functions in different organs, especially in the brain (Kwon et al., 2011). Both Akt/PKB and CREB proteins in neurons are thought to be involved in the formation of learning and memories. Compared with control group, the expression of Akt/PKB and pCREB decreased in DM group. However, compared with DM group, the expression of Akt/PKB and pCREB increased in DM+S group. This means the expression of Akt/PKB and pCREB became normal after the treatment of salidroside. Bcl-2 (B-cell lymphoma 2) is the member of the Bcl-2 family of apoptosis regulator proteins. The Bcl-2–associated X protein, or short for Bax, is one of the proteins in the Bcl-2 gene family. It promotes apoptosis by competing with Bcl-2 (Krishna et al., 2011). The balance of Bcl-2 and Bax plays very important role in cell growth and apoptosis (Llambi and Green, 2011). After treatment of salidroside, the increased expression of Bax in DM group was decreased obviously in DM+S group while it was opposite with Bcl-2. All these indicated that the apoptosis of neurons was inhibited after the treatment of salidroside. In other words, salidroside could protect the neurons from apoptosis and death. Salidroside is a potential neuron protective drug and could be used to treat neuro-degeneration and other neural diseases. This research mainly focused on the effects of salidroside on the memory, learning ability, growth of neurons, balance

of biochemistry markers and neuronal survival factors, morphology, and other functions of the brain. The results will help us to better understand the function of salidroside as a neuron protective drug and for developing new drugs.

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