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Hydroxysafflor yellow A ameliorates depression-like behavior in Parkinson's disease mice

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Abstract: Depression is a common non-motor symptom of Parkinson's disease. Previous studies demonstrated that hydroxysafflor yellow A had properties of improving motor symptoms of Parkinson's disease. The effect of hydroxysafflor yellow A on depression in Parkinson's disease mice is investigated in this study. To induce Parkinson's disease model, male Swiss mice were exposed to rotenone (30 mg/kg) for 6 weeks. The chronic unpredictable mild stress was employed to induce depression from week 3 to week 6. Sucrose preference, tail suspension, and forced swimming tests were conducted. Golgi and Nissl staining of hippocampus were carried out. The levels of dopamine, 5-hydroxytryptamine and the expression of postsynaptic density protein 95, brain-derived neurotrophic factor in hippocampus were assayed. It showed that HSYA improved the depression-like behaviors of Parkinson's disease mice. Hydroxysafflor yellow A attenuated the injury of nerve and elevated contents of dopamine, 5-hydroxytryptamine in hippocampus. Treatment with hydroxysafflor yellow A also augmented the expression of postsynaptic density protein 95 and brain-derived neurotrophic factor. These findings suggest that hydroxysafflor yellow A ameliorates depression-like behavior in Parkinson's disease mice through regulating the contents of postsynaptic density protein 95 and brain-derived neurotrophic factor, therefore protecting neurons and neuronal dendrites of the hippocampus.

Keywords: Hydroxysafflor yellow A, Parkinson's disease, depression, rotenone

INTRODUCTION

Parkinson's disease (PD) mainly manifests motor symptoms including bradykinesia, tremor, postural instability, and rigidity (Okano *et al*., 2019). These motor dysfunctions are caused by injuries of dopaminergic nerve in substantia nigra and striatum. PD patients are considered to be affected only by motor dysfunction. This idea is deeply embedded not only in the minds of patients and their family members, but also in many physicians. Recently, researchers found that a great number of PD patients suffer from depression which is one of non-motor symptoms (Ryman and Poston, 2020). In fact, non-motor features are the source of considerable discomfort and disability for PD. However, the non-motor aspects have often received insufficient attention in current clinic.

There are 90% of PD patients experiencing non-motor symptoms. Depression is the most common psychological disturbance of PD patients. At some point during PD, depression affects up to 50% of people. And depression often occurs in the earliest stages of PD. The cause of depression in PD is not clear. But it is likely closely associated with imbalances of dopamine, serotonin, and norepinephrine in brain (Prange *et al*., 2022). Depression reduces the quality of life of PD. It not only worsens the neurological function, but also increases the risk of death. Some PD patients with depression will improve with adequate treatment of motor symptoms. However, many others need to be treated with antidepressants (Su *et al*., 2021).

Hippocampus is the portion of the temporal lobe cortex. It plays a key role in memory and reward. Recent studies demonstrated that the hippocampus of depressed patients was smaller than those of healthy controls. This finding has also been confirmed by the studies of meta-analysis (Liu *et al*., 2021). Altered hippocampus is an emerging marker of depression. The hippocampus shrinks in people with recurrent and poorly treated depression (Roddy *et al*., 2019). It reported that antidepressants and electroconvulsive therapy can augment the volume of the hippocampus in depression patients, suggesting that protection of nerves of hippocampus is a promising way to attenuate the clinical symptoms of depression (Wu and Zhang, 2023). Additionally, fMRI test showed that the activity of the hippocampus in depressive patients was decreased. The reduction of functional activity of hippocampus causes a negative emotion in patients (Zacková *et al*., 2021). Hippocampus dysfunction is associated with the pathogenesis of depression (Sanchez-Mendoza *et al*., 2020). And hippocampus is associated with mood-related brain region such as the amygdala (Song, 2023). Previous study also demonstrated that

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hippocampal neuroplasticity was closely related to antidepressant effects (Tartt *et al*., 2022). Many studies have linked the presence of depressive symptoms to the hippocampus, including the reduced number of hippocampal granule neurons and neural stem cells (Boldrini *et al*., 2019). In depression condition, non-pharmacological interventions such as diet, exercise, or certain antidepressants can increase hippocampal neurogenesis (Rosenberg *et al*., 2020; Berger *et al.*, 2020).

Hydroxysafflor yellow A (HSYA) is a compound with a monochalcone glycoside structure. In China, HSYA is used for treating cerebrovascular disease. HSYA attenuated the injury of cerebral ischemia, effectively reducing infarct volume, inhibiting apoptosis, and promoting neurological recovery (Fangma *et al*., 2021). Emerging evidence revealed that HSYA possessed an anti-PD property. Previous study reported that HSYA attenuated the neurotoxicity by reducing oxidative stress in mice (Han and Zhao, 2010). HSYA also reduced defects of the substantia nigra and striatum in a PD mouse model through decreasing the expression of inflammatory cytokines. HSYA ameliorated the degeneration of dopaminergic neurons via its anti-neuroinflammatory and anti-apoptotic effects (Yang *et al*., 2020). HSYA promoted the clearance of alpha-synuclein by regulating the autophagy in rotenone-induced PD mice (Han *et al*., 2018). Lipopolysaccharide-induced neuroinflammation is a major pathogenesis of PD. HSYA attenuated the damage of dopaminergic neurons induced by lipopolysaccharide via reducing the expression of inflammatory cytokines (Wang *et al*., 2018). HSYA elevated brain-derived neurotrophic factor (BDNF) level, protected dopaminergic neuron integrity, and then improved motor function in PD animal model (Han *et al*., 2013). It has been shown that HSYA improved depressive behavior by regulating HPA function, inhibiting oxidative stress and inflammation in hippocampus (Liu *et al.*, 2022). The present experiment clarified for the first time that HSYA ameliorated depression-like behavior in PD mice through regulating the levels of BDNF, PSD-95 and therefore protecting neurons and neuronal dendrites of the hippocampus.

MATERIALS AND METHODS

Animals

Jinan Pengyue Experimental Animal Breeding Company (Shandong, China) provided male Swiss mice (25 to 28 g). Animals were housed in a room with a controlled room temperature of 20~22ºC and a controlled room relative humidity of 40%~70%, with a light/dark cycle (12/12 h). The mice were allowed to access freely to water and food. The experiments were approved by the Institutional Animal Ethics Committee of Yantai University (No. YTDX20220309) and conducted in Yantai University (Shandong, China).

Experiment design

There were five groups (n =15 per group): control, model, HSYA (50, 100, or 200mg/kg) groups. To induce PD model, the mice were administered intragastrically with rotenone (30mg/kg) for 6 weeks. Then, chronic unpredictable mild stress (CUMS) was carried out from week 3 to week 6. From week 6, HSYA groups were intragastrically administered with HSYA (50, 100, or 200 mg/kg), once a day for 2 weeks. A flow chart (fig. 1) was provided to illustrate the experimental procedure.

CUMS

CUMS was carried out according to the study (Xie *et al.*, 2021). It included cage tilt (12 h), soiled cage (24 h), physical restraint (3 h), tail pinch (1 min), food deprivation (24 h), water deprivation (24 h), white noise. Two stressors were randomly employed each day. Body weight of mice was also recorded.

Forced swimming test

According to previous method (Cojocariu *et al.*, 2020), forced swimming test (FST) was performed. A tank (height: 30 cm, diameters: 20 cm) that is filled with water at 23 to 25ºC. A video was used to record the behavior of mice in the tank. SMART 3.0 (Panlab Harvard Apparatus, MA, USA) was used to analyze the immobility time.

Tail suspension test

According to the reference (Liu *et al.*, 2021), the tails of mice were adhered to a tape. Then the animals were suspended by placing the free end of the tape on a shelf. The behavior of mice will be recorded with a video. The immobility time of mice was analyzed using SMART 3.0.

Sucrose preference test

According to previous report (Mendonca *et al.*, 2021), mice were presented with 2 bottles. One contained water. The second contained 2% sucrose solution. The bottles were weighed and then let the animals drink water or sucrose solution. After 6 h, the bottles were weighed. Sucrose preference (%) = Sucrose intake (g)/Sucrose intake (g)+Water intake (g)×100%.

Golgi staining

Golgi staining procedure was carried out in accordance with the manufacturer's manual (https://fdneurotech.com/catalog/fd-rapid-golgistain-kit-small/).

Nissl staining

The brains of mice were coronally sectioned (5 µm). The slices of brain were rehydrated with alcohol and then stained in 0.5% Cresyl-Violet (Sigma, St. Louis, MO, USA) for 10 min. Dehydrated with alcohol and cleaned with xylene, slices were imaged. Neurons were counted by an experimenter who was blinded to the grouping using a microscopy (IX-70, Olympus Corp. Japan).

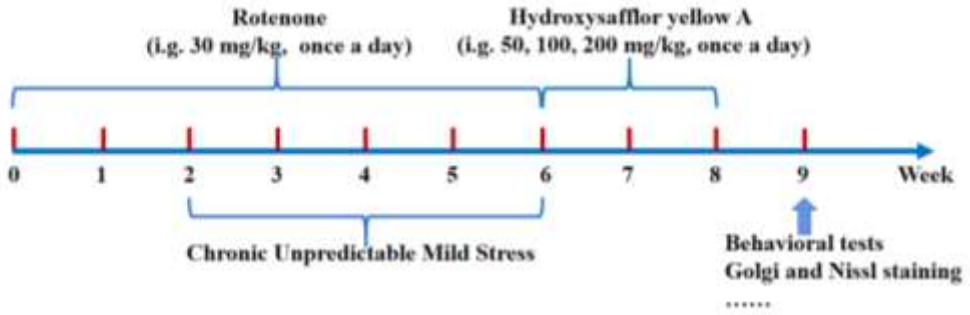

Fig. 1: Schematic diagram of the experimental timeline.

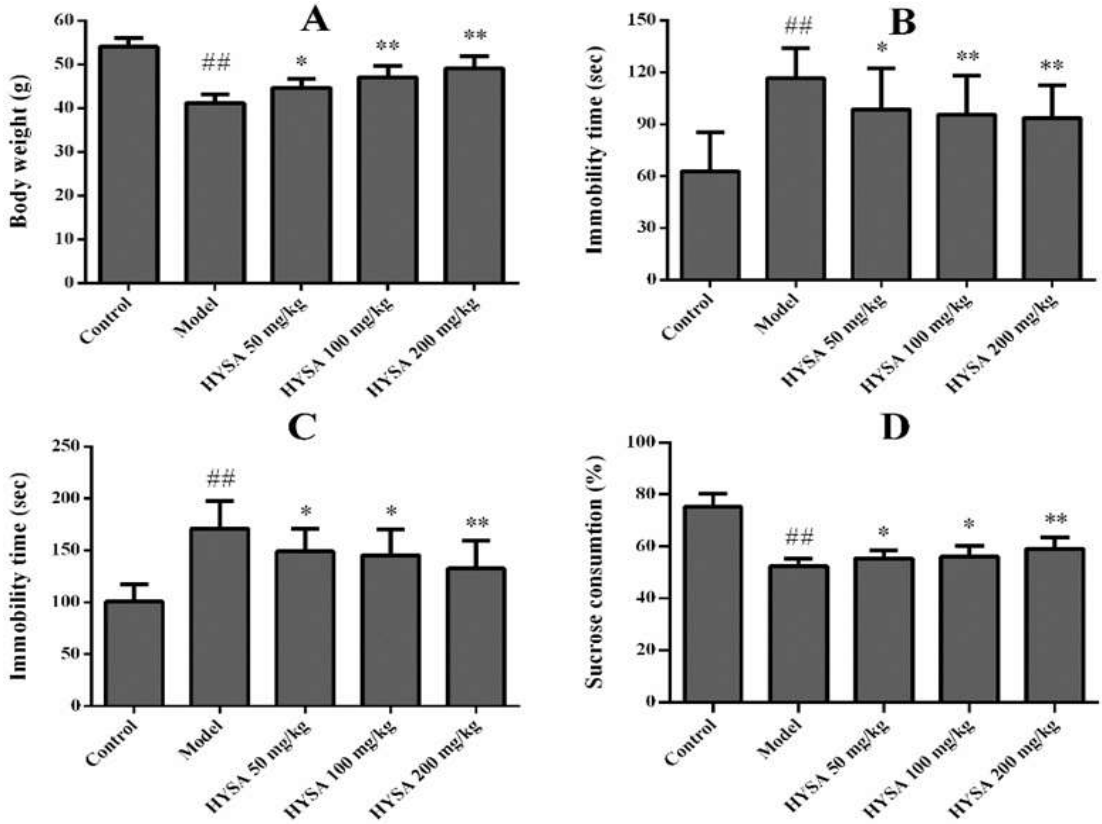

Fig. 2: Effects of HSYA on body weight and depression-like behavior. A: Body weight. B: Forced swimming test. C: Tail suspension test. D: Sucrose preference test. The data were expressed with Mean ± SD, (n = 15). $^{\#\#}p<0.01$ compared with the control group. $^{*}p<0.05$, $^{**}p<0.01$ compared with the model group.

Western blot

The hippocampus of mouse was lysed in RIPA buffer (4ºC, 30 min). After centrifugation (4ºC, 12,000 g, 20 min), the supernatant was harvested. Proteins (50μg) was subjected to electrophoresis. Transferring membranes were carried out for 1 h at 110V. Incubated with the primary antibodies (BDNF, 1:1000, Sigma, St. Louis, MO, USA or PSD95, 1:2000, Cell Signaling, Danvers, MA, USA) followed by incubation with the secondary antibody (1:3000, Beyotime, Shanghai, China). Bands were visualized using an ECL kit (Beyotime, Shanghai, China) and quantified with Image Quant LAS 4000 (GE, Tokyo, Japan). β-actin was a loading control.

Analysis of the neurotransmitters

The levels of dopamine and 5-HT in hippocampus were assayed using UHPLC-MS/MS (Agilent, California, USA). The hippocampus was homogenized with 0.1% formic acid. The homogenate was centrifuged (4ºC, 16,000 g, 10 min). Then separation of 100μL of sample was conducted using a Waters Acquity UPLC HSS PFP column. The mobile phase was composed of 0.1% formic acid in acetonitrile and water, respectively. With column temperature (40ºC) and flow rate (0.3 mL/min), gradient elution was carried out. Sample (2μL) was assayed with mass spectrometry and quantitative analysis. The data were analyzed with Data Processing software version 1.6.2 (AB Sciex).

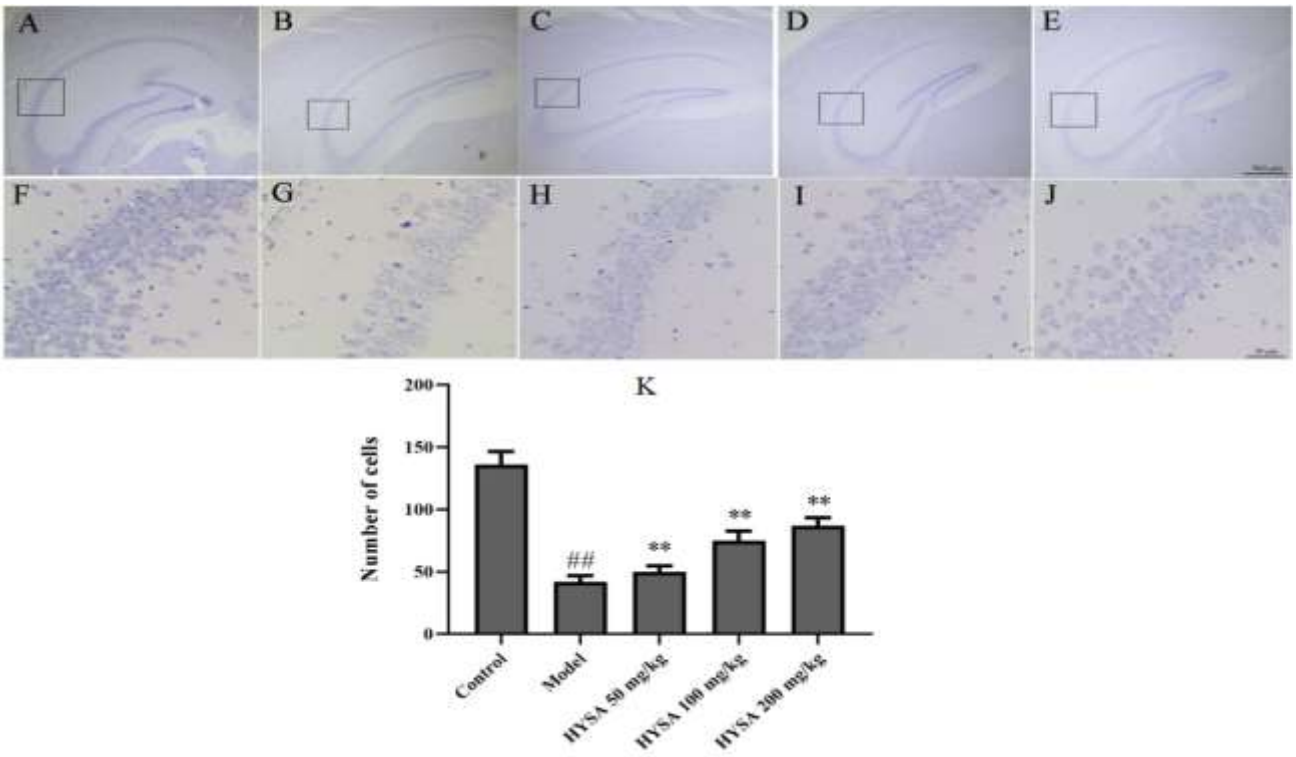

Fig. 3: Effects of HSYA on the number of normal neurons in hippocampus. A-J showed the representative pictures of Nissl staining. A, F: Control group. B, G: Model group. C, H: HSYA 50 mg/kg group. D, I: HSYA 100 mg/kg group. E, J: HSYA 200 mg/kg group. K: Bar graph of the number of normal neurons. The results were the Mean ± SD, (n = 3). $^{\#\#}p<0.01$ compared with the control group. $^{**}p<0.01$ compared with the model group.

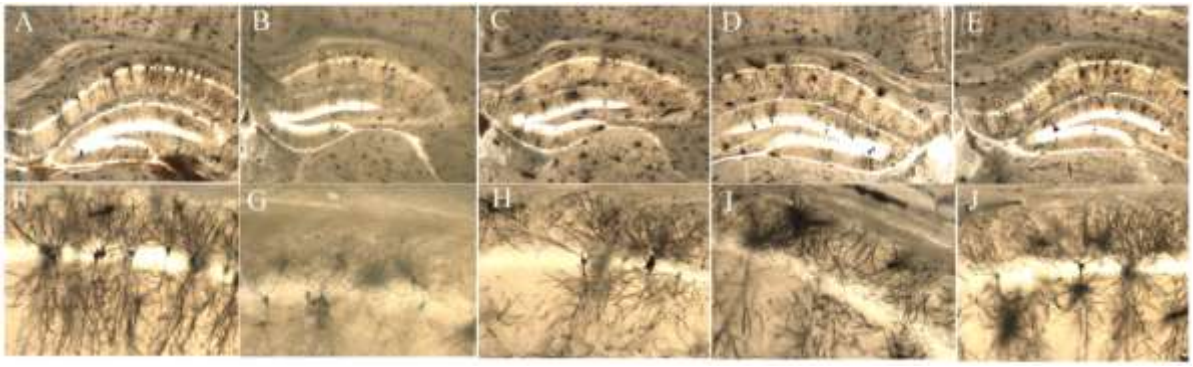

Fig. 4: Effects of HSYA on dendrite of hippocampus. A, F: Control group. B, G: Model group. C, H: HSYA 50 mg/kg group. D, I: HSYA 100 mg/kg group. E, J: HSYA 200 mg/kg group. Top: Bar = 500μm. Bottom: Bar = 200μm.

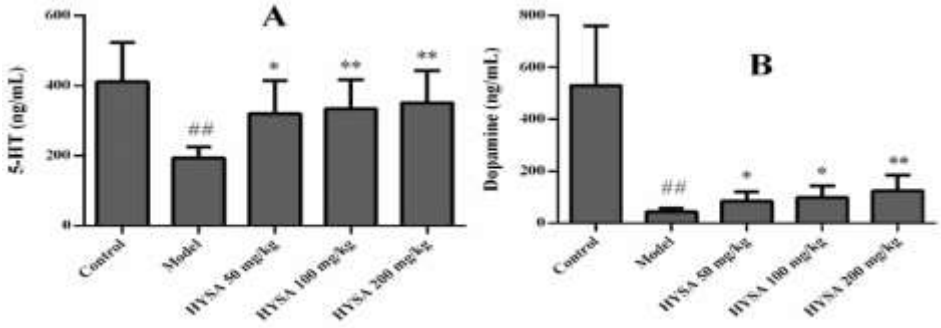

Fig. 5: Effects of HSYA on the levels of 5-HT and dopamine. The data were expressed as mean ± SD, (n = 6). $^{\#\#}p<0.01$, compared with control group. $^{*}p<0.05$, $^{**}p<0.01$, compared with model group.

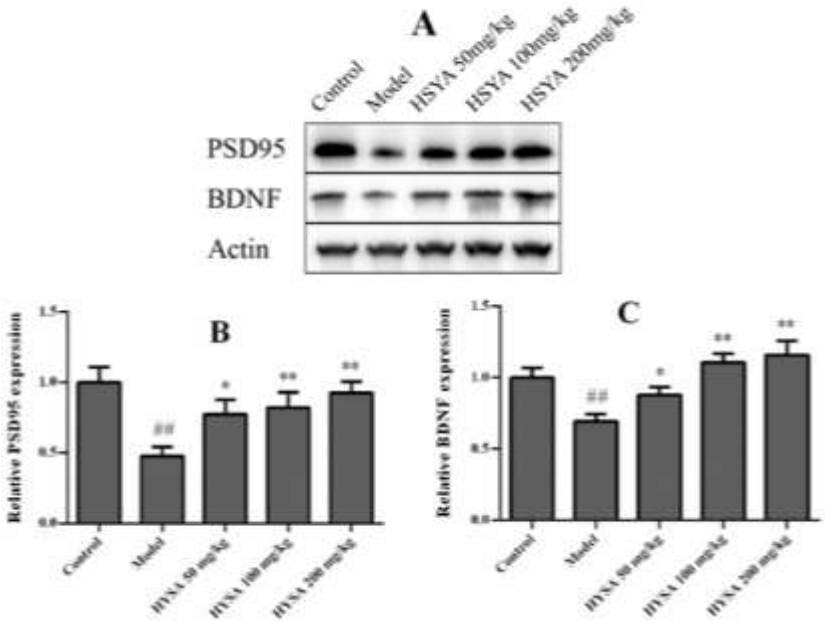

Fig. 6: Effects of HSYA on the expression of PSD-95 and BDNF. A: Representative strips of PSD-95 and BDNF proteins in Western blot. B: Histogram for quantitative analysis of PSD-95 protein expression. C: Histogram for quantitative analysis of BDNF protein expression. The data were the Mean ± SD, (n = 3). $^{\#\#}p<0.01$, compared with control group. $^{*}p<0.05$, $^{**}p<0.01$, compared with model group.

STATISTICAL ANALYSIS

The data were analyzed with GraphPad Prism 6.01. All data were expressed as mean ± SD. One-way analysis of variance (ANOVA) and Tukey's test are used to observe statistically significant differences among means of five groups and to determine statistical differences between the means of two groups (p-value < 0.05).

RESULTS

Effects of HSYA on body weight and depression-like behavior

The body weight of animals in model group significantly reduced (p=0.0001) when compared with the control group. Compared with the model group, the body weight of HSYA groups increased (p=0.0001, p=0.0001, p= 0.0001, respectively).

Compared with the control group, the immobility time in FST, TST significantly increased and the sucrose consumption decreased (p=0.0001, p=0.0001, p=0.0001) in the model group of mice. However, treatment with HSYA not only reduced the immobility time in FST (p= 0.0237, p=0.0074, p=0.0016), TST (p=0.0189, p= 0.0108, p=0.0005) but also augmented the sucrose consumption (p=0.0100, p=0.0101, p=0.0001), (fig. 2A, B, C, D).

Effects of HSYA on the number of normal neurons in hippocampus

Nissl-staining is widely used to observe the morphology and pathology of neurons. The hippocampus of mice was collected and then Nissl staining was carried out. In the control group, the neurons were arrayed normally, and the Nissl bodies were clear. There were damaged neurons and disintegrated Nissl body in the model group. The number of normal neurons in the model group significantly decreased (p=0.0001). However, HSYA treatment attenuate the changes of morphology and pathology of and increased the number of normal neurons in the hippocampus (p=0.0001, p=0.0001, p=0.0001), (fig. 3).

Effects of HSYA on dendrite of hippocampus

The branching of the neuronal dendrites within the hippocampus are associated with depression. Compared with the control group, the dendritic branching and dendritic length of the model group reduced. The dendritic branching and dendritic length of hippocampus in the HSYA (50, 100, 200mg/kg) groups augmented when compared with the model group (fig. 4).

Effects of HSYA on the levels of 5-HT and dopamine

Monoamine neurotransmitters are closely associated with depression. fig. 5 showed the levels of dopamine and 5-HT in the model group were decreased when compared with the control group (p=0.0042, p=0.0032). However, treatment with HSYA (50, 100, or 200 mg/kg) increased the levels of dopamine (p=0.0342, p=0.0280, p=0.0099) and 5-HT (p=0.0207, p=0.0032, p=0.0067) of hippocampus.

Effects of HSYA on the expression of PSD-95 and BDNF

In fig. 6, the expression of BDNF, PSD-95 in the model reduced (p=0.0020, p=0.0035). Compared with the model group, the expression of BDNF (p=0.0134, p=0.0010, p= 0.0020), PSD-95 (p=0.0140, p=0.0090, p=0.0016) in HSYA groups increased.

DISCUSSION

Previous results of our studies demonstrated that HSYA had the properties of ameliorating the motor symptoms of PD. However, PD patients often experience depression, and it will worsen the quality of life and motor function. To our knowledge, this study shows for the first that HSYA can improve the depression-like behavior in PD mice. And the mechanism of action of HSYA is associated with regulating the levels of BDNF, PSD-95 and therefore protecting neurons and neuronal dendrites of the hippocampus.

Using a rotenone-induced PD model with chronic unpredictable mild stress and three different tests of depression-like behavior, this study showed that HSYA attenuated the depression-like behavior in PD mice. Our results demonstrated that mice of PD depression model showed an increase of immobility in the TST, FST and a decrease of sucrose consumption. However, treatment with HSYA prevented not only the augmentation of immobility time but also the reduction of sucrose consumption. The findings mentioned above indicated HSYA elicited an antidepressant-like effect.

In addition to playing a key role in learning and memory, the hippocampus is closely associated with the etiology of depression. The shrinkage of hippocampus is a common feature of depression. Smaller hippocampal volume also indicates an increased risk of depression (Larosa and Wong, 2022). Preclinical and clinical reports demonstrate that there was often an impairment of hippocampal neurogenesis in depression. In animal models of depression, depression-like behaviors are accompanied by a decreased neuronal proliferation and differentiation in the hippocampus (Parul *et al.*, 2021). Several clinical studies got a consistent observation which demonstrated that patients with depression had a reduction of hippocampal volume (Evans *et al.*, 2024). Previous studies indicated that monoamine in brain played a role in depression (Rodríguez-Lavado *et al.*, 2022). The alteration of levels of monoamine including 5-HT and dopamine is a cardinal factor to cause depression (Bhatt *et al.*, 2021; Speranza *et al.*, 2021). The degeneration of serotonergic nervous system may be the pathogenesis of depression in PD (Wang *et al.*, 2023). The decreased level of the 5-HT, dopamine and norepinephrine in the limbic system played a role in PD-related depression (Assogna *et al.*, 2020; Laux, 2022). BDNF is the neurotrophic factor of brain, which is involved in neuronal survival, proliferation, and synaptic neuroplasticity (Rana *et al.*, 2021). Chronic stress will reduce the expression of BDNF, leading to a neuronal loss in the hippocampus and an impairment of hippocampal function. Chronic stress may cause an injury of neurons and therefore result in an atrophy dendritic cell (Chai *et al.*, 2019), which negatively affects neuronal plasticity of the hippocampus. PSD-95 is a synapse-associated protein. It is involved in regulating synaptic activity and acts as a marker reflecting prominent plasticity. The expression of PSD-95 may, to some extent, reflect synaptic transmission function. Therefore, the increase of expression of BDNF and PSD-95 will protect synaptic plasticity and then exert an antidepressant effect. In the present study, HSYA attenuated the changes of morphology and pathology of neurons in PD mice with depression. The dendritic branching and dendritic length of hippocampus in the HSYA groups were also augmented. In consistent with the results of histopathological observation, HSYA treatment increased the levels of 5-HT and dopamine of hippocampus. The consequent assay showed that the expression of PSD-95 and BDNF in HSYA groups increased. These findings suggested that HSYA had a property of ameliorating the depression-like behavior in PD mice through regulating the levels of BDNF, PSD-95 and therefore protecting neurons and neuronal dendrites of the hippocampus.

The current study has some limitations. Firstly, the findings cannot exclude the possibility that HSYA may improve the motor function of PD animals and then ameliorates the depressive-like behaviors. Secondly, this study did not observe the signaling pathway which may regulate the expression of BDNF, PSD-95. Further experiment should focus on elucidating the effect of HSYA on the molecular of signaling pathway which affects the levels of BDNF, PSD-95.

CONCLUSION

In summary, this study suggested that HYSA ameliorates depression-like behavior in PD mice through regulating the contents of BDNF, PSD-95, therefore protecting neurons and neuronal dendrites of the hippocampus.

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