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Skilled Aerobic Exercise Reduces Endoplasmic Reticulum Stress and Dopamine Neuron Apoptosis by Activating Wnt/β-Catenin Pathway and Improves Motor Function in Pd Model Rats

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Abstract

Objective: To observe whether skilled aerobic exercise (SAE) could reduce endoplasmic reticulum stress (ERS) and apoptosis of dopamine neuron by activating Wnt/β-catenin pathway and improves motor function in Parkinson's disease (PD) model rats.

Methods: The PD models were established by injection into the right SNC (substantia nigra, compact part) and VTA (ventral tegmental area) on the rat stereolocator with 6-hydroxydopamine (6-OHDA). A cylindrical test was used to was used to test motor function. The expression of tyrosine hydroxylase (TH) in midbrain was detected by immunohistochemistry, the expression of genes and proteins related to the Wnt/β-catenin pathway was detected by Western blot. The level of Irisin in serum was identified through an enzyme-linked immunosorbent assay (ELISA).

Results: It was determined that 28 days of SAE improved motor function from Parkinson disease. In model group, the expression of TH in midbrain and FNDC5 in skeletal muscle was significantly down-regulated, the content of Irisin in serum decreased, the expression level of Bip/Grp78 and CHOP was up-regulated, the expression level of Wnt, β-catenin and P-GSK3β (Ser9) were down-regulated, while P-GSK3β (Tyr216) was up-regulated, the movement ability of forelimbs decreased ($P<0.05$), and the rotation behavior induced by Apo significantly increased in model group ($P<0.05$).

Conclusion: Mid-long term SAE could up-regulate the expression of FNDC5 in skeletal muscle, increase the content of Irisin in serum, reduce the level of ERS in midbrain, increase the activity of Wnt/β-catenin pathway, down-regulate the activity of Gsk3β, reduce the apoptosis of DA neurons in midbrain substantia nigra, and improve the motor function of PD model rats.

Keywords: Rat model of Parkinson's disease • Skilled aerobic exercise • Endoplasmic reticulum stress • Tyrosine Hydroxylase • FNDC5/Irisin • Wnt/β-catenin pathway

Introduction

Parkinson disease (PD) is the most common neurodegenerative movement disorder. In Europe, prevalence and incidence rates for PD are estimated at approximately 108-257/100 000 and 11-19/100 000 per year, respectively [1]. The prevalence rate of Parkinson's disease in people over 65 years old is 170/100,000 in China and increases with age. PD leads to heavy burden of families and society [2]. This disease is the result of the interaction of aging, genetic defects and environmental toxins, its pathogenesis is still not fully understood, and there is no fundamental prevention and treatment [3]. ERS mediated apoptosis has been proven to be associated with the pathogenesis of neurodegenerative diseases, including Parkinson's disease [4]. The main pathological changes of Parkinson's disease are degeneration dopaminergic neurons in the substantia nigra compact, accumulation of α-synuclein (α-syn) and formation of Louis corpuscle. The accumulation of α-synuclein can induce oxidative stress and endoplasmic reticulum stress (ERS). It also mediates various signalling pathways to participate in degeneration of dopamine (DA) neurons [5]. This results in a large loss of striatum dopamine (DA) and motor control dysfunction of basal ganglia [6]. Rehabilitation and kinetotherapy may be helpful for improving motor and non-motor symptoms of Parkinson's disease and even delaying the progression of the disease, especially for PD patients who have axial symptoms such as gait disorders, postural balance disorders, speech and swallowing disorders [7]. Studies have shown that aerobic exercise can activate the central transcriptional coactivator (PGC-1α) in skeletal muscle [8]. Skeletal muscle releases the systemic factor fibronectin type III domain protein 5 (FNDC5) and its secreted form Irisin. FNDC5/Irisin plays a positive regulatory role in neuronal differentiation and maturation through the blood-brain barrier. Compared with simple non-skilled aerobic Exercise (NSAE), skilled aerobic exercise (SAE) animals can improve motor deficits better, through increasing cerebral blood flow in the prefrontal limbic cortex, somatosensory cortex and cerebellum regions [9].

Wnt signalling pathway is an autocrine-paracrine signalling pathway, which has been proved to be a key regulator of dopaminergic neuronal development [10]. Wnt signalling is also involved in neuronal degeneration, for example, Aβ may lead to leading to degeneration of β-catenin and hippocampal neurons by attenuation of Wnt signalling and activation of GSK3β [11]. The classical Wnt pathway called the Wnt/β-catenin signalling pathway is an important signalling branch of cell survival [12]. Glycogen synthase kinase-3 β (GSK3β) is a serine/threonine protein kinase, which is known to regulate a variety of cellular processes [13]. Down-regulating activity of GSK3β is a core function of the Wnt pathway and alleviates 6-OHDA-induced neuronal death and apoptosis [14].

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This experiment was conducted to observe the effects of SAE on the athletic ability of PD rats, the expression of FNDC5 in skeletal muscle, and tyrosine hydroxylase (TH), ERS related proteins, Wnt/β-catenin signalling pathway, GSK3β in midbrain tissue, the content of Irisin in serum. To investigate whether SAE could alleviate the damage of ERS in PD rats midbrain tissue, change the expression of FNDC5, reduce the loss of dopamine neurons and improve motor function in PD rats through the pathway of Wnt/β-catenin.

Methods

Experimental reagents

L-ascorbic acid (Sigma), immunohistochemical staining kit (Zhongshan Jinqiao), DAB Chromogenic kit (Maixin Bio), RIPA lysate, protease inhibitor (Boster), 6-OHDA (Meilun Bio), apmorphine, SDS-PAGE Gel preparation Kit, BCA protein quantification kit (Sigma), rabbit anti-mouse GAPDH, Bip/Grp78, TH, Wnt, CHOP, anti-GSK3β antibody, anti β-catenin antibody, anti-alpha-synuclein antibody, anti-FNDC5, Irisin ELISA kit (Bioss), Rabbit Anti-GSK3β (Phospho-Ser9) polyclonal antibody, Rabbit Anti-GSK3β (Phospho-Tyr216) polyclonal antibody (Shanghai sangon).

Establishment of rat model of Parkinson's disease

60 SPF male SD rats weighting 180~220 g and aging about 8 weeks were purchased from the Laboratory animal center of Xinjiang Medical University. Five rats were fed in a cage. The animals were maintained in an air-conditioned room (23±3, relative humidity 40-70%) on a 12-h light/dark cycle with free access to water and food. The animals were randomly divided into four groups (sham operation group, model group, sham operation+SAE group, model+SAE group), with 15 rats in each group.

Before the surgery the rats were given intraperitoneal anaesthesia with 0.15 mL/100 g chloral hydrate (10% solution). Sterile operation was strictly executed during the surgery. The model group received slowly injection of 5 μL of 6-OHDA (dissolved with normal saline containing 1% ascorbic acid, concentration of 2 μg/μL) for each point into the right SNC (substantia nigra, compact part) and VTA (ventral tegmental area) on the rat stereolocator. After pinhole pressing to stop bleeding, the scalp was sutured and disinfected with iodine; the rats were injected with penicillin of 50,000 units intraperitoneally to prevent infection.

Sham operation group received injection of 5 μL normal saline containing 1% ascorbic acidin each point of the right SNC and VTA. Sham operation+SAE group and model+SAE group received skilled aerobic exercise two weeks after the surgery.

Animal care was executed according to the experimental animal ethics standards and has been approved by the Animal Care and Use Committee of the first affiliated hospital of the Xinjiang medical University, China before the experiment. The approval number was IACUC20200930-11.

Skilled aerobic exercise

The training started from the third week after modeling, the sham operation+SAE group and model+SAE group received SAE, which was training running on wheels with irregular spacing steps of OOOOXOX pattern (Figure 1), O represented steps and X represented missing steps with interval of 1.3 cm. At beginning of the training, rats were placed on regular running wheels (Figure 2), Rats were trained at initial speed of 2 m/min, then increased the speed by 1 or 2 m/min daily until the speed reached 8 m/min. In the second week, the rats of SAE groups were trained on irregular running wheels, and the initial speed was still 2 m/min, and the speed of the wheels was gradually increased for 8 m/min without tension of rats, defecation and urination were monitored as signs of acute stress response. The sham operation group and the model group received training on normal wheels with free speed. The training lasted 20 min a day, 5 days a week, for 4 weeks. The wheels diameters were 34.4 cm and the width of each step was 0.3 cm.

Behavior test of experimental animals

Cylinder experiment: Rats were placed in a transparent resin-glass bucket (20 cm of diameter and 30 cm of height) on day 7, 14 and 28 after modeling injury. The contact times of rats left forelimbs on cylinders in 3 min were observed and counted, and the ratio of left forelimbs contacting with cylinders was calculated with the formula of =(a+c×0.5)/(a+b+d)×100%, a means the times of rats left forelimb contacting with cylinders; b means the times of rats bilateral forelimbs alternately contacting with the cylinders; c means the times of rats both forelimbs simultaneously contacting with the cylinder; d means the times of rats right forelimbs contacting with the cylinder.

Figure 1. The running wheel with irregular steps.

Figure 2. The running wheel with regular steps.

Rotation experiment induced by APO: Rats of four groups were intraperitoneally injected with apmorphine of 0.05 mg/kg respectively on day 7, 14 and 28 after modeling injury, to induce the unilateral levorotation, and the rotation number of rats was recorded within 30 min.

To detect the expression of Tyrosine Hydroxylase (TH) in the substantia nigra with immunohistochemistry

After fixation, embedding, and section, the substansubstania nigra tissues were soaked in xylene for dewaxing, hydration, and antigen repair. The endogenous peroxidase was soaked in 3%H2O2 deionized water to remove endogenous peroxidase. The diluted primary antibody (TH 1:170) was soaked overnight in a refrigerator at 4, and the horseradish peroxidase labelled secondary antibody was dropped and incubated at room temperature for 20 min. DAB for 3-10 min, tap water stops for colour, hematoxylin is redyed for 3 min, dehydrated, transparent and neutral gum seals, and films are observed and taken under a microscope.

The expression levels of Bip/Grp78 and CHOP protein in the substantia nigra and FNDC5 protein in the quadriceps femoris of the rats left hind limbs were detected by WB

After grinding with liquid nitrogen, about 100 mg of the samples were added into a precooled 1.5 ml centrifuge tube, and then 400 μL RIPA lysis solution (RIPA: PMSF: Broad-spectrum phosphatase inhibitor=100:1:1) was added, fully mixed, and placed at 4 for 60 min. Supernatant was collected at 12000 RPM and centrifuged at 4 for 15 min. Protein concentration was determined by BCA method. The samples were loaded with 5×SDS-Page loading buffer (containing β-mercaptoethanol), heated with boiling water at 100 for 5 min, and the proteins were fully denaturated before being stored in a refrigerator at -80. According to the formula, 15%, 12%, 8% separated glue and 5% concentrated glue. Adding sample: Marker 9 L of pre-dyed protein, 50 g of sample protein per well. Electrophoresis: at a constant pressure of 80 V, bromophenol blue was transferred to the separation glue, and at a constant pressure of 100 V for 90 min, the electrophoresis was stopped when bromophenol blue reached the bottom. After sdS-PAGE

electrophoresis, the PVDF membrane was soaked in methanol for 10 s and rinsed in distilled water for 1 min. Then the polyacrylamide gel, filter paper and the treated PVDF membrane were soaked in the Transfer Buffer for 10 min to prepare the "sandwich" of membrane Transfer. Bip/Grp78 and Actin were treated with 0.45 μm PVDF membrane, CHOP, FNDC5 and β-actin were treated with 0.22 μm PVDF membranes, and the membrane transfer time of CHOP, FNDC5 and β-actin was 60 min, and Bip/Grp78 was 80 min. After membrane transfer, the PVDF membrane was washed with water for 3 times, 5 min/time. Use sealing solution containing 5% skim milk powder to seal the transfer film for 1 h, and then wash it with TBST 3 times, 5 min/time. TBST diluted primary antibody, β-actin (1:1000), CHOP (1:500), Bip/Grp78 (1:500), FNDC5 (1:500) were added. Incubate overnight at 4 in a shaker. Rinse 1×TBST for 3 times, 5 min/time. Suitably diluted secondary antibody (1:5000) was added and incubated at room temperature for 1 h. Rinse 1×TBST for 3 times, 5 min/time. DAB chromogenic solution A and B were mixed and 2 mL of DAB chromogenic solution was added to the membrane. ChemiScope Mini chemiluminescence instrument was used for detection and photography. Image J Image analysis software was used for analysis. Each experiment was repeated three times.

Irisin in serum was detected with ELISA kit

After the rats were anesthetized by intraperitoneal injection of chloral hydrate, the abdominal wall was cut open and the abdominal aorta was revealed, then 3 ml of blood was extracted from the abdominal aorta into the anticoagulant tube. Put it on ice and centrifuge it at 5000 rpm for 10 min as soon as possible. Then the serum was sucked out. The detection was executed following the instructions of Irisin ELISA kit strictly. There were 6 rats in each group and 3 multiple holes for each rat. There were blank holes, standard holes and sample holes. Each well in the working plate was added with sample of 100 μL, and then incubated in an incubator at 37 for 90 min; the holes were filled with biotinylated antibody working solution, and then incubated for 1 h at a constant temperature again. Then enzyme conjugate working solution of 100 μL was added into each well after the plate was washed sufficiently, incubated for 30 min at a constant temperature. Substrate solution of 90 μL was added, and incubated for 15 min avoid light. Stop solution of 50 μL was added to each well, and then the blue colour quickly changed to different shade of yellow. When the reaction stopped, the absorbance (OD) of wave length at 450 nm was measured by a microplate reader. The concentration of each sample was calculated by standard curve.

Data Statistics

All data were expressed as mean ± standard deviation ( ). SPSS19.0 software was used for statistical analysis. One-way anova was used for statistical analysis: P<0.05 indicated significant difference. GraphPad Prism 6.0 was used to assiste in graphing.

Results

SAE improved the motor ability of model rats

Compared with sham operation group, the motor ability of left forelimbs in model group rats were significantly decreased, and the difference was statistically significant (P<0.05). After 28 days of SAE, the motor ability of the left forelimbs of the model rats were significantly improved compared with that of the model group, and the difference was statistically significant (P<0.05), as shown in Figure 3.

Compared with the sham operation group,*P<0.05; compared with the model group, #P<0.05. In the rotation experiment of rats, compared with the sham operation group, the rotation number in the model group after induction with APO was significantly increased, and the difference was statistically significant (P<0.05). Compared with the model group, the rotation number in the model+skilled aerobic exercise group decreased significantly on the 14th and 28th days after SAE, the difference was statistically significant (P<0.05), as shown in Figure 4.

Compared with the sham operation group*P<0.05; compared with the model group, #P<0.05

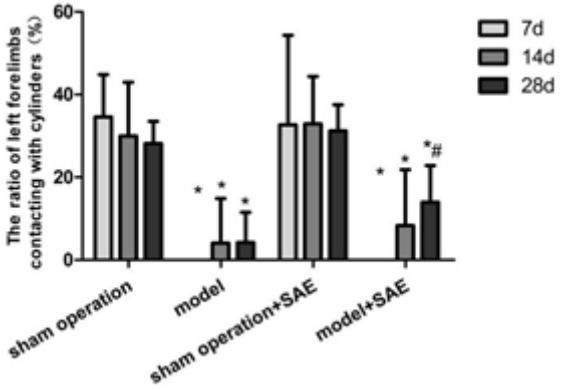

Figure 3. Comparison of the ratio of rats` left forelimbs contacting with cylinder among four groups after training of 7 days, 14 days and 28 days.

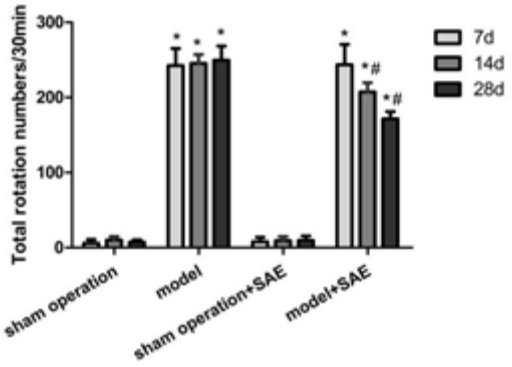

Figure 4. Comparison of the rats` rotation number per 30min in four groups after inducing with APO.

Expression of ER stress-related proteins

The expression of ER stress-related proteins Bip/Grp78 and CHOP in model group was significantly higher than that in the sham group, and the difference was statistically significant (P<0.05). After 28 days of SAE, compared with the model group, the expression of Bip/Grp78 and CHOP in midbrain of PD model rats decreased significantly, the difference was statistically significant (P<0.05), as shown in Figure 5.

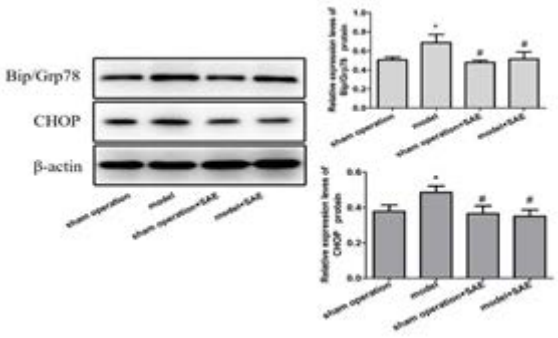

Figure 5. Expression of Bip/Grp78 and CHOP was detected by Western blot.

Compared with the sham operation group,*P<0.05; compared with the model group, #P<0.05

Expression of FNDC5 and content of Irisin

Compared with the sham operation group, the expression of FNDC5 protein in skeletal muscle and the content of Irisin in serum of model group were significantly decreased. Compared with the model group, the expression of FNDC5 protein in skeletal muscle and the content of Irisin in serum of

model+SAE group were significantly increased (Figures 6 and 7).

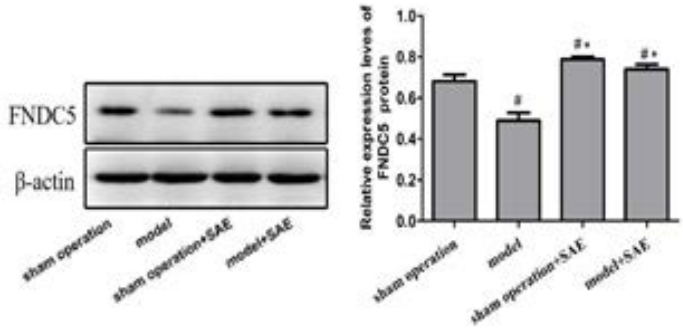

Figure 6. Comparison of the expression level of FNDC5 after training of 28 days among four groups.

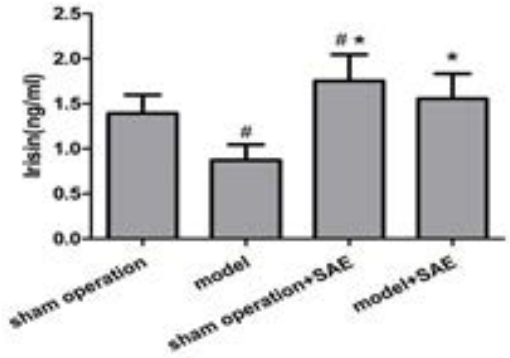

Figure 7. Comparison of the content of Irisin in serum after training of 28 days among four groups.

Compared with the sham operation group,*P<0.05; compared with the model group, #P<0.05.

Immunohistochemistry of TH protein in the substantia nigra of PD rats

Compared with sham operation group, IHC score of TH protein in the substantia nigra of PD rats decreased significantly, the difference was statistically significant (P<0.05). After 4 weeks of SAE, IHC score of TH protein in midbrain substantia nigra of rats in model group+SAE group was significantly higher than that in model group, and the difference was statistically significant (P<0.05), as shown in Figures 8 and 9.

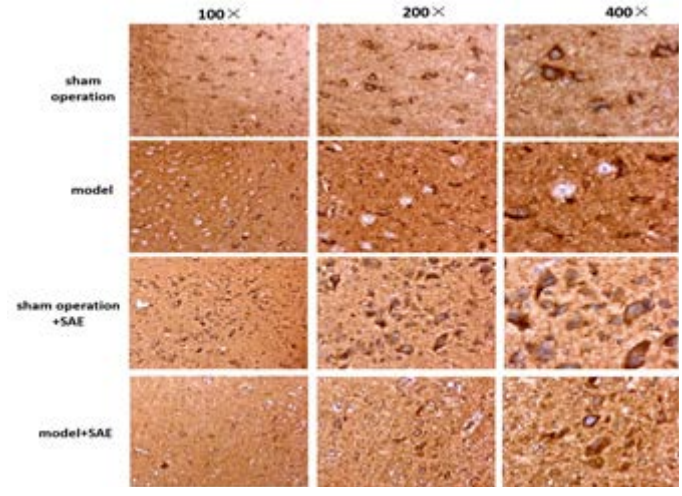

Figure 8. Comparison of expression of TH in rats` midbrain after training of 28 days among four groups (immunohistochemical staining,×100,×200,×400).

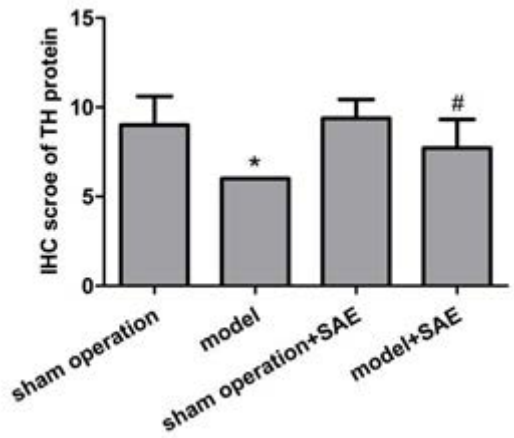

Figure 9. Comparison of expression level of TH in rats` midbrain after training of 28 days among four groups.

The expression of Wnt/β-catenin pathway related proteins

Compared with sham operation group, the expression of Wnt, β-catenin, p-GSK3β (Ser9) was down-regulated, and p-GSK3 β (Tyr216) was up-regulated. Compared with the model group, the expression of Wnt, β-catenin, p-GSK3 β (Ser9) was up-regulated in the model+SAE group; the expression of P-Gsk3β (Tyr216) was down-regulated. Compared with sham operation group, the expression of Wnt, β-catenin, p-GSK3β (Ser9) was down-regulated, and p-GSK3 β (Tyr216) was up-regulated. Compared with the model group, the expression of Wnt, β-catenin, p-GSK3 β (Ser9) was up-regulated in the model+SAE group; the expression of P-Gsk3β (Tyr216) was down-regulated (Figure 10).

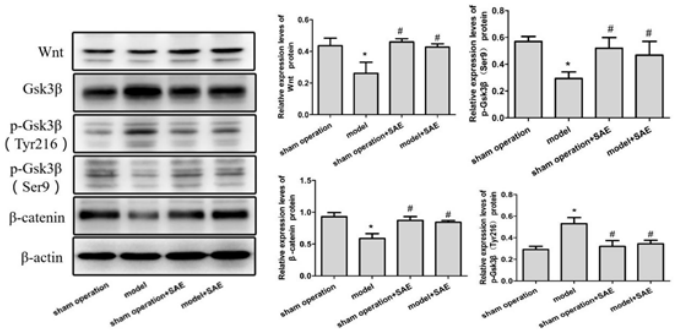

Figure 10. Comparison of the expression level of Wnt, Gsk3β, p- Gsk3β (Ser9) p-GSK3 β (Tyr216) β-catenin after training of 28days among four groups.

Compared with the sham operation group,*P<0.05; compared with the model group, #P<0.05.

Discussion

At present, the treatment means of Parkinson's disease include medication, surgery, kinesitherapy, psychological counselling and nursing care, etc. [15]. Medication is still the main treatment for PD, while rehabilitation is believed to improve multiple dysfunction and improve self-care ability of PD patients c. Aerobic training and muscle strengthening exercise, including cycling and running, may be helpful for improving the symptoms and even delaying the progression of PD [16]. There is positive evidence that clinical training techniques for balance and gait can reduce fall in patients with PD [17]. Kinetic training may increase the motor function and improve clinical symptoms of PD patients, by changing the motor circuit and neuroplasticity

of basal ganglia mainly [18-20].

Mode and complexity of exercise are key factors for the prognosis of Neurorehabilitation of PD. Exercise training (ET) includes both skilled training and aerobic exercise. Compared with simple non-skilled aerobic Exercise (NSAE), skilled aerobic exercise (SAE) animals can improve motor deficits better, through increasing cerebral blood flow in the prefrontal limbic cortex, somatosensory cortex and cerebellum regions [9]. ET is thought to synergistically improve the voluntary and involuntary parts of motor control in PD patients.

In this experiment, the expression of FNDC5 in skeletal muscle was up-regulated and the content of Irisin in serum reduced in the model group. SAE can improve the motor function of the affected forelimb and reduce the number of rotations induced by APO in PD model rats. SAE up-regulated the expression of FNDC5 in skeletal muscle and the content of Irisin in serum of PD rats. Previous studies have found the presence of Irisin in human cerebrospinal fluid by Western blot and spectrometry. It proved that Irisin can go across the blood-brain barrier. The level of FNDC5 was up-regulated during the maturation of primitive embryos of mouse, the culture of cortical neurons, or the differentiation of human embryonic neural stem cells into neurons. Over-expression of FNDC5 during neural precursor formation of mouse embryonic stem cells increases the expression of BDNF, GFAP and markers of neuronal maturation (Map2, β-tublin III and Neurocan) [21]. Over-expression of FNDC5 in primary cortical neurons up-regulated expression of BDNF, while knockdown of FNDC5 with RNAi down-regulated BDNF expression. It was confirmed that FNDC5 is an important regulator of expression of BDNF. BDNF is an important neurotrophic factor, which can enhance neuronal survival, migration and dendrite growth, regulate synaptic plasticity and cognitive function; it plays an important role in neuronal homeostasis and functional maintenance, especially neurogenesis, so it is an important regulator of the beneficial effects of exercise on the brain [22]. Rezaee Z showed that Parkinson's disease reduced levels of PGC-1α, FNDC5 and brain-derived neurotrophic factor (BDNF) and increased neurodegeneration in the striatum and the hippocampus. Treadmill running before disease attenuated 6-OHDA-induced memory deficit and elevated neuroprotection. Exercise has multiple effects on memory and biochemical factors [23].

Irisin is the secreted form of FNDC5, it is a product of the physical activity Irisin is released from skeletal muscle within exercise, and it is a circulating hormone that regulates the energy metabolism in the body. It has great influence on lipid metabolism, thermogenesis, browning of white adipose tissue, neuronal differentiation from bone metabolism to brain and neuroprotection. In the nervous system, Irisin influences neurogenesis and neural differentiation in mice [24]. Study demonstrated that the Irisin induce bone marrow stem cells (BMSCs) transport into the injured area of the brain. Co-treatment of the Irisin with BMSCs increased tyrosine hydroxylasepositive neurons (TH+) and decreased the number of apoptotic cells significantly in substantia nigra (SN) and striatum of the PD mice brain. So Irisin is a neuroprotective factor.

Endoplasmic reticulum is an important organelle inner cells, it mainly involves in regulating protein synthesis and protein folding. Pathological stimuli (such as oxidative stress, lipid accumulation) may induce aggregation of unfolded or misfolded proteins in the ER, which generates endoplasmic reticulum stress (ERS), activating the unfolded protein response (UPR) to protect the cells from damage of ERS. Severe ERS may initiate the apoptosis process. Glucose regulatory protein 78 (Bip/Grp78) and C/EBP homologous protein (CHOP) are molecular markers of ER stress, and their up-regulation suggests the induction of ERS [25-26]. TH is a marker protein of dopamine neurons. In this study, the expression of TH in the midbrain tissue of PD rat model was significantly lower than that of sham operation group, and the expression of Bip/Grp78 and CHOP were up-regulated. After 4 weeks of SAE, the expression of TH in midbrain tissue of PD rats up-related significantly than that of model group, while the expression of Bip/Grp78 and CHOP down-regulated. It may be related to SAE potentially reducing the degeneration of dopaminergic neurons and inducing structural and functional adaptation (plasticity) in motor regions including motor cortex, basal ganglia, midbrain, cerebellum and red nucleus in PD model animals. Study also showed that Irisin alleviated ER stress and hepatic fibrosis, suggesting that Irisin may represent a promising therapeutic strategy for patients with liver fibrosis [27].

Wnt signalling plays an important role in the development and maturation of midbrain DN [28]. The Wnt/β-catenin signalling pathway, classical Wnt pathway, is an important signalling branch of cell survival. Activation of the Wnt/β-catenin pathway initiates Wnt protein binding to Trans membrane receptors, and stable β-catenin aggregates and is brings into the nucleus to regulate gene transcription [29]. It has been reported that toxicity induction can down-regulate the Wnt/β-catenin pathway in PD cells and animal models, and activation of the Wnt/β-catenin signalling pathway can inhibit ER stress in DN and alleviate 6-OHDA-induced DN damage [30]. In this research, for PD model rats, the expression of FNDC5 protein in skeletal muscle and the content of Irisin in serum decreased, and the expressions of ERS-related proteins were up-regulated. the activity of Wnt/β-catenin pathway was down-regulated, and the activity of GSK3β was up-regulated by dephosphorylation of GSK3β (Ser9) and phosphorylation of GSK3β (Tyr216), promoted the apoptosis of dopamine neurons in midbrain, the number of dopamine neurons in the substantia nigra reduced, the motor ability of forelimb decreased significantly. After 4 weeks of SAE, the expression of FNDC5 protein in skeletal muscle and the content of Irisin in serum increased, and the level of ERS decreased. In the medium and long term, SAE activated the Wnt/β-catenin pathway, decreased the activity of GSK3β, up-regulated the expression of FNDC5 protein, increased the content of Irisin in serum, and decreased the ERS level in midbrain, and reduced the loss of DA neurons in the substantia nigra, thus improving the motor performance of PD model rats.

Conclusion

SAE may up-regulate the expression of FNDC5 in skeletal muscle and the content of Irisin in serum, then up-regulated the activity of Wnt/β-catenin pathway, inhibit the expression of GSK3β, reduce endoplasmic reticulum stress, and reduce the apoptosis of dopamine neurons, thus improving motor function of PD rats. However, the mechanism of how Irisin acts on Wnt/β-catenin pathway of DA neurons in midbrain and reduces ERS needs to be further explored in future studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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