On the Functional Recovery Mechanism of the Cerebral Nervous System in Diabetic State under the Combination Effect of Exercise and Medication

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ABSTRACT

This paper studies the effects of moderate exercise and epigallocatechin gallate (EGCG) on the recovery of mitochondrial injuries in the cerebral nervous system under diabetic state through experiment, and analyses the improvement mechanism of mitochondria in energy synthesis, biosynthesis, anti-oxidation, integration and division under the combination of exercise and EGCG medication, hoping to provide some theoretical reference for the protection of cerebral nervous system under diabetic state. The study concludes that diabetes has great impacts on the normal functioning of mitochondria and that its energy synthesis and biosynthesis are controlled by a variety of enzymes. When a rat has diabetes, the protein levels of NRF1, NRF2, TFAM and HO1 in mitochondria are significantly decreased, and the pathways of SIRT1 and PGC-1α proteins are also reduced accordingly. After diabetic rats were treated with the combination of exercise and EGCG for 3 months, the pathways of SIRT1 and PGC-1α proteins were effectively increased, the energy synthesis and biosynthesis of mitochondria were enhanced, and the activity of related enzymes was also improved. In this way, the cerebral nervous system diseases of the rats were mitigated. The combination of exercise and EGCG has better effect than either of them alone. The fusion protein expression in diabetic rats decreased significantly compared with that in normal rats, whereas the split protein expression significantly increased in diabetic rats compared with normal rats, indicating that with diabetes, the division and fusion of mitochondria are unstable. Treating diabetes with both exercise and EGCG medication can effectively improve the expression of fusion protein and reduce the level of split protein. Compared with those in the normal group, the autophagy protein levels in diabetic rats were significantly decreased while the expression of Parkin protein increased. The combination of exercise and EGCG can enhance the autophagic ability of mitochondria, thereby changing the ischemic injury of the cerebral nervous system. The EGCG medication can obviously enhance the activity of related enzymes in mitochondria and promote the metabolism of mitochondria.

Key Words: Diabetes, Cerebral Nervous System Injury, Functional Recovery of Mitochondria, Exercise, EGCG

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Introduction

Diabetes is one of the most widely reported and hardest-to-treat conditions in the world. According to the forecast, the number of diabetic patients in the world will rise to 600 million by 2030. At present, diabetes is mainly divided into Type I and II. Those with Type II diabetes account for over 60% of the total diabetic patients.

Damages in the cerebral nervous system caused by diabetes mainly include central

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nervous system, peripheral nerve and peripheral nerve damages (Sakaguchi *et al*., 2012; Umpierre *et al*., 2011; Balducci *et al*., 2006; Hun *et al*., 2009; Dixit *et al*., 2014; Kruse *et al*., 2010; Otterman *et al*., 2011; Colberg *et al*., 2010; Kluding *et al*., 2015; Khaodhiar *et al.,* 2009). Central nervous system damage is the main form of nerve injury in diabetic patients (Bittel *et al*., 2015; Tuttle *et al*., 2011; Unick *et al*., 2011). External manifestations include disorder of consciousness, sleepiness, chronic confusion; numbness, muscle atrophy, skin swelling pain and loss of skin tactile sense (Sigal *et al.,* 2007; Angelis *et al*., 2009; Visser *et al*., 2014; Popbusui *et al*., 2013;).

Mitochondrion is the most important component of a nerve cell. Many functions of neurons need the energy supplied by mitochondria. When mitochondria have problems in energy supply or are poisoned or contain apoptosis inducing agents, nerve cells will suffer from degeneration, diseases or insulin production disorders. Therefore, it is of great practical significance to conduct research on inhibiting the pathogenesis of mitochondria in the cerebral nervous system by means of exercise and nutrition improvement (Kwon *et al*., 2011; Erken *et al*., 2013; Udina *et al*., 2011).

In recent years, the treatment and prevention of diabetes have been transformed from drug treatment alone into a combined treatment with both drugs and non-drugs (exercise, diet control and lifestyle improvement, etc.). At present, most of the treatments use the combination of exercise and drug therapy (Chen *et al*., 2012; Yardley *et al*., 2013; Chamnan *et al*., 2011; Zimmet *et al*., 2001; Rathmann *et al*., 2000; Kim *et al*., 2009; Rönnemaa *et al*., 2008; Mcnay and Recknagel, 2011). Exercise therapy mainly includes aerobic exercise, anaerobic exercise and resistance exercise, the main purpose of which is to increase the patients' muscle endurance, fibre vitality, vascular resistance to shear stress. In drug therapy, epigallocatechin gallate (EGCG) is a new type of drug used to treat diabetes, but the effect of the combined treatment with both exercise and the drug still needs further research.

This paper studies the effects of moderate exercise and epigallocatechin gallate (EGCG) on the recovery of mitochondrial injuries in the cerebral nervous system under diabetic state through experiment, and analyses the improvement mechanism of mitochondria in energy synthesis, biosynthesis, anti-oxidation, integration and division under the combination of exercise and EGCG medication, hoping to provide some theoretical reference for the protection of cerebral nervous system under diabetic state.

Related description

Studies have shown that more than 93% of diabetes is Type II. The effects of diabetes on the human cerebral nervous system are mainly manifested in behavioural disorders, memory loss, and, in severe cases, dementia. The intrinsic mechanism of neuropathy caused by diabetes is mainly formed by such factors as vascular variation, neuronal cell impairment, insulin signalling failure and intracellular metabolic disorders.

Mitochondrion is the most important component of a nerve cell. Many functions of neurons need the energy supplied by mitochondria. When mitochondria have problems in energy supply or are poisoned or contain apoptosis inducing agents, nerve cells will suffer from degeneration, diseases or insulin production disorders. Therefore, it is of great practical significance to conduct research on inhibiting the pathogenesis of mitochondria in the cerebral nervous system by means of exercise and nutrition improvement.

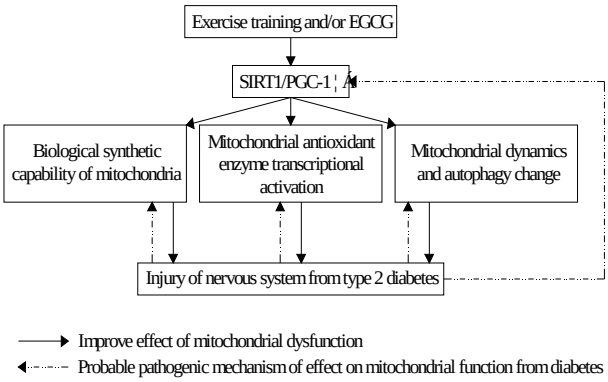

Figure1. Diabetes-II mitochondrial functions improved with exercise and EGCG.

Epigallocatechin gallate (EGCG) has been proved to be effective in treating central cerebral nervous system diseases caused by diabetes such as epilepsy, memory loss, and Alzheimer's disease (AD). However, at present, few researches has been conducted on the combination of EGCG and appropriate exercise for the treatment of diabetes. Fig.1 is a flow chart of increasing the abilities of diabetic patients to resist cerebral nervous system injuries by enhanced exercise training and EGCG medication. This combined treatment

reduces the neurological injuries of Type II diabetic patients by enhancing the biosynthetic capacity of mitochondria and transcription of antioxidant enzymes and inhibiting autophagy changes

Test results and analysis

Test materials and process

The test subjects were 2-month-old male rats weighing 170-200g. They were kept in separate cages at room temperature, with daily light exposure from 9 am to 4 pm. Changes in daily body weight, feed, excretion, and exercise of the rats were recorded. The high-sugar diet for rats included lard, protein powder, sodium cholate, sucrose and other high-fat feeds; test drugs and reagents mainly included STZ, citric acid, EDTA, ethanol, buffer, coenzyme, potassium chloride and sucrose, etc.; and test equipment mainly included GHB and GSP detectors, blood glucose detectors, mitochondrial protein extractor, mitochondrial respiratory chain complex activity tester, detector of ions like Ca^{2+} and Na^{+}, weighing balance, incubator, humidifier and so on.

The author studied the activity and metabolism of mitochondria in diabetic rats and normal ones after the combined treatment of exercise and EGCG medication within different culture cycles (1 month, 2 months and 3 months), so as to explore the effects of mitochondria on the cerebral nervous system.

The overall process of the experiment is shown in Fig.2.

Normal rats and high-fat and high-sugar diet rats were grouped at a ratio of 1:2, with 60 in the normal group and 120 in the high-fat diet group. Rats in the high-fat and high-sugar diet group were fed for 8 weeks. 15 hours after being fed, they were injected with streptozotocin (STZ) and then fed for several weeks. The rats in this group were tested for diabetes. If the blood glucose level was over 16.8mmo/L, the rat was considered as already having diabetes.

The different groups of rats were tested for the following indicators: haemoglobin (GHb), insulin, fructosamine (GSP), blood glucose (FBG), mitochondria complex enzyme activity, mitochondrial protein concentration, Na^{+}-ATPase and Ca^{+}-ATPase activity. The data processing software was SPSS, and the final results were the averages of the statistics. $P<0.05$ and $P<0.01$ indicate significant and very significant differences, respectively.

Variation features of mitochondrial respiration enzyme activity under diabetic state

Tab.1 shows the changes in indexes like FBG, Insulin, GHb and GSP of the normal group and the diabetic group within different cycles. It can be seen that the indices of the normal group did not change significantly after 1 month, 2 months and 3 months of feeding; while the FBG, Insulin, GHb and GSP of the diabetic rats were significantly increased. From the comparison of FBG and Insulin between the diabetic group and the normal group, it is found that the diabetic rats produced in the experiment had stable blood glucose and high insulin. GHb and GSP could reflect long-term and short-term glucose levels of rats, respectively. The statistical results show that both GHB and GSP in diabetic rats increased over time.

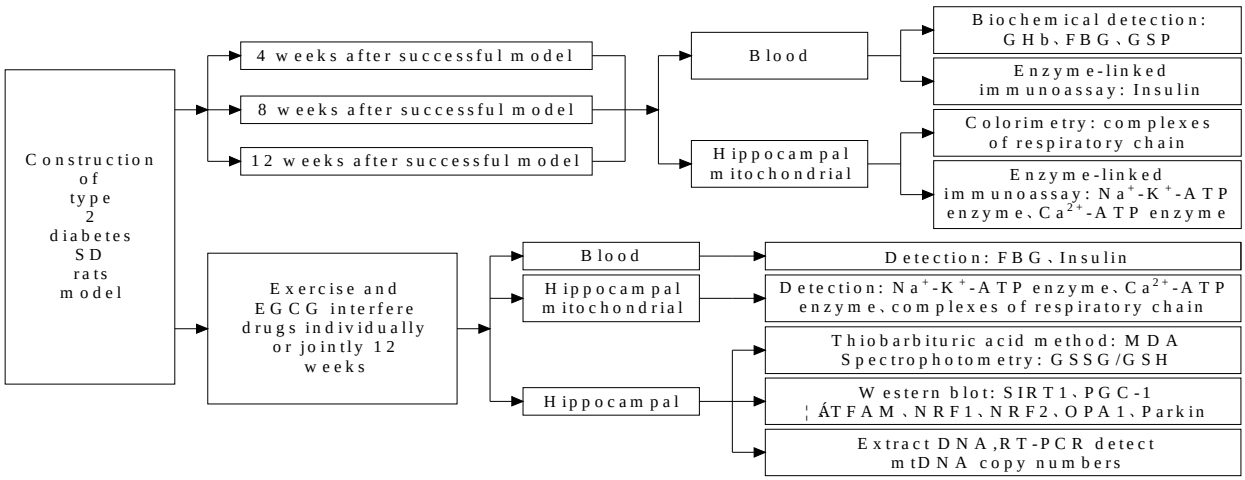

Figure 2. Structure diagram of the experimental design.

Table1. FBG, Insulin, GHb and GSP changes in rat blood within different periods

Cycle	Group	FBG(mmol/L)	Insulin(ng/mL)	GHb(10gHb)	GSP(mmol/L)
4 weeks	Normal group	5.61±0.25	1.14±0.09	11.47±1.54	2.78±0.47
	Diabetes group	14.56±1.42 * *	1.50±0.15 *	14.57±1.64 *	5.80±0.82 * *
8 weeks	Normal group	5.91±0.50	1.17±0.18	11.05±1.66	2.60±0.67
	Diabetes group	14.74±1.33 * *	1.67±0.16 * *	27.43±4.11 * *	5.71±0.88 * *
12 weeks	Normal group	5.93±0.35	1.45±0.18	16.23±0.43	2.90±0.17
	Diabetes group	14.90±0.55 * *	1.81±0.19 * *	33.27±5.44 * *	6.04±0.59 * *

Table 2. Changes in respiratory chain complexes and ATP enzyme in rat blood within different periods

Cycle	Group	Complex I	Complex II	ComplexIII	ComplexIV	Na+-K+-ATPase	Ca2+-ATPase
4 weeks	Normal group	18.05±2.54	85.89±11.42	47.90±4.79	75.47±6.50	8.51±1.62	6.98±0.80
	Diabetes group	19.06±2.35	83.43±7.66	47.13±4.98	71.13±9.89	7.50±1.91	7.12±1.05
8 weeks	Normal group	19.18±2.03	84.31±8.94	45.25±5.11	76.41±7.55	8.03±1.65	7.25±0.94
	Diabetes group	16.32±2.71 *	83.31±8.54	39.63±5.22 *	58.63±7.33 * *	5.33±1.54 * *	6.57±0.99 *
12 weeks	Normal group	17.73±2.12	87.23±7.66	49.78±5.97	74.16±8.38	8.90±1.96	6.90±0.88
	Diabetes group	11.35±2.81 * *	51.03±7.65 * *	32.07±3.58 * *	41.78±5.30 * *	4.51±1.11 * *	3.05±0.66 * *

Tab.2 shows the changes in the activity of 4 respiratory chain complexes and APT synthase of mitochondria in the normal rats and diabetic rats. It can be seen that when rats were fed for 1 month, there was no significant change in the activity of 4 respiratory chain complexes in either the normal group or the diabetic group; after 2 months of feeding, the activity of the respiratory chain complexes in Group I and III of diabetic rats was significantly reduced. In terms of ATP synthase, the activity in diabetic rats was also significantly weakened after 2 months. In the early stage of diabetes, the blood-brain barrier inhibited the destruction of mitochondria by toxic substances. But as time went by, mitochondrial synthase was damaged in many ways, and the transgene encoding was gradually exposed outside the mitochondrial matrix. Under the damage effect, gene mutation occurred, thereby affecting the normal operation of the cerebral nervous system.

Effects of moderate exercise and EGCG on the anti-oxidation and biosynthesis of nerve cells

In order to make the test results more clear, the diabetic rats were further divided into the exercise group, the medication group and the exercise and medication group to analyse the inhibitory effects of exercise and EGCG on the cerebral nervous system injuries under diabetic state. According to statistics, the body weights of diabetic rats were significantly lower than those of normal ones, while the food intakes were greater than those of normal ones. After exercise and medication, the weights of diabetic rats started to increase and the food intake decreased.

Tab.3 shows the changes in FBG, Insulin and HOMA-IR in normal rats and diabetic rats (including exercise group, medication group and exercise & medication group). ** means P<0.01 in the comparison with the normal group of rats. It can be seen from the table that, compared with those in normal rats, FBG, Insulin and HOMA-IR in diabetic rats significantly increased, but that after exercise and EGCG medication, the indices of the rats all declined to different extents. The exercise and medication combined method was the most effective in reducing the FBG, Insulin, HOMA-IR indices in the bodies of rats.

Table 3. FBG, Insulin and HOMA-IR changes with exercise and EGCG

Group	FBG(mmol/L)	Insulin(ng/mL)	HOMA-IR
Normal group	5.92±0.29	1.19±0.14	0.33±0.04
Diabetes group	14.90±0.52**	1.79±0.18**	1.16±0.10**
Diabetes drug group	11.96±1.11$^{\Delta\Delta}$	1.66±0.22$^{\Delta}$	0.90±0.07$^{\Delta}$
Diabetes exercise group	10.83±0.87$^{\Delta\Delta}$	1.64±0.23$^{\Delta}$	0.85±0.06$^{\Delta}$
Diabetes exercise and drug group	9.45±0.82$^{\Delta\Delta}$	1.48±0.20$^{\Delta\Delta}$	0.61±0.05$^{\Delta\Delta}$

Fig.3 shows the different expressions of SIRT1 and PGC-1α proteins in mitochondria in five different groups (normal group (C), diabetic group (D), medication group (DY), exercise group (DE) and exercise & medication group (DEY)). Δ means P<0.05 in the comparison with the diabetic group; ΔΔ means P<0.01 in the comparison with the diabetic group. As can be seen, compared with the normal group, the diabetic group had P<0.01, and the expression levels of the two proteins were low. After exercise and medication, the levels of proteins in the diabetes group were improved to different extents. The exercise & medication method had the best effects.

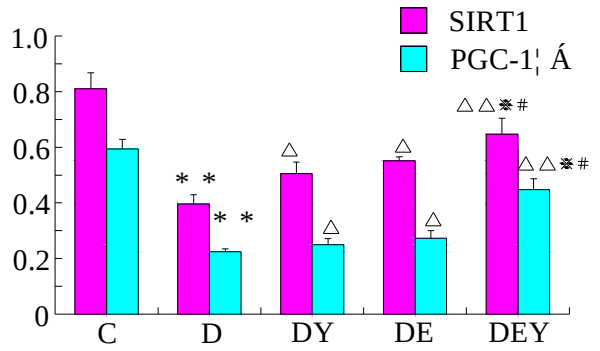

Figure 3. Effects of exercise and EGCG on SIRT1 and PGC-1α expressions in the hippocampus by rat group.

Fig.4 shows the effects of diabetes on NRF1 and TFAM proteins and Fig.5 shows the levels of NRF2 and HO1 proteins in mitochondria in the hippocampus. Similar to the SIRT1 and PGC-1α proteins, the NRF1, NRF2, HO1 and TFAM protein expressions in diabetic rats were significantly lower than those in normal rats. After medication and exercise, the expressions of NRF1 and TFAM proteins were significantly increased.

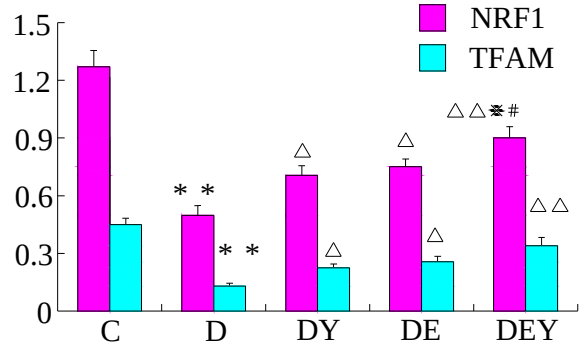

Figure 4. Effect of exercise and EGCG on NRF1 and TFAM expressions in the hippocampus by rat group.

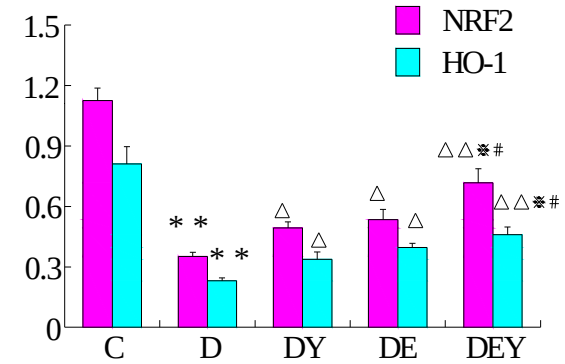

Figure 5. Effect of exercise and EGCG on NRF2 and HO-1 expressions in the hippocampus by rat group.

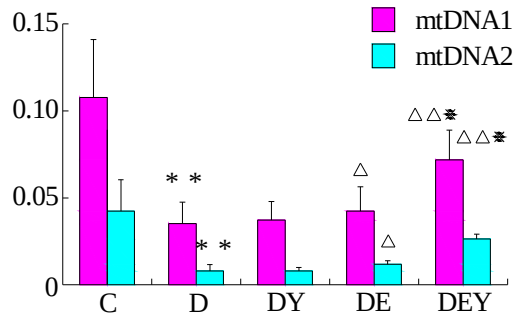

Figure 6. Effect of exercise and EGCG on mtDNA expressions in the hippocampus by rat group.

Fig.6 shows the DNA transcription in the hippocampuses of rats after exercise and medication. As can be seen, the DNA levels of hippocampuses in diabetic rats were significantly lower than those in normal rats. In the diabetic rats treated with exercise alone, the DNA levels in the hippocampuses were not significantly different from those in the diabetic rats before treatment, but after medication, the DNA levels were significantly higher than those in the diabetic rats treated with exercise and the ones not treated.

From the above test results, it can be found that diabetes has great impacts on the normal functioning of mitochondria and that its energy synthesis and biosynthesis are controlled by a variety of enzymes. When a rat has diabetes, the protein levels of NRF1, NRF2, TFAM and HO1 in mitochondria are significantly decreased, and the pathways of SIRT1 and PGC-1α proteins are also reduced accordingly. After diabetic rats were treated with the combination of exercise and EGCG for 3 months, the pathways of SIRT1 and PGC-1α proteins were effectively increased, the energy synthesis and biosynthesis of mitochondria were enhanced, and the activity of related enzymes was also improved. In this way, the cerebral nervous system diseases of the rats were mitigated. The combination of exercise and EGCG has better effect than either of them alone.

Effects of moderate exercise and EGCG on the energy metabolism and kinetics of mitochondria

Fig.7 shows the changes in the levels of fusion proteins Mfn2 and OPA1 in mitochondria after exercise and EGCG treatment. As can be seen, the expression levels of the two fusion proteins in the diabetic rats were significantly lower than those in the normal rats, whereas the Mfn2 and OPA1 protein levels in the rats treated with exercise alone were not significantly different from those

in the ones treated with EGCG alone and the ones with both exercise and EGCG (P> 0.05).

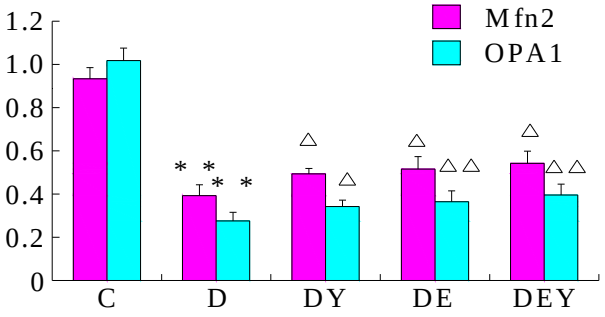

Figure 7. Effect of exercise and EGCG on mitochondrial fusion protein expression in the hippocampus by rat group.

Fig.8 shows the expressions of split proteins Drp1 and Fis1 in mitochondria under the diabetic state. After exercise and medication, the expression levels of both split proteins were lower than those in the diabetic rats not treated (P<0.05), while the expression levels in the rats treated with the exercise and EGCG combined method were not much different from those in the rats treated with medication alone (P> 0.05).

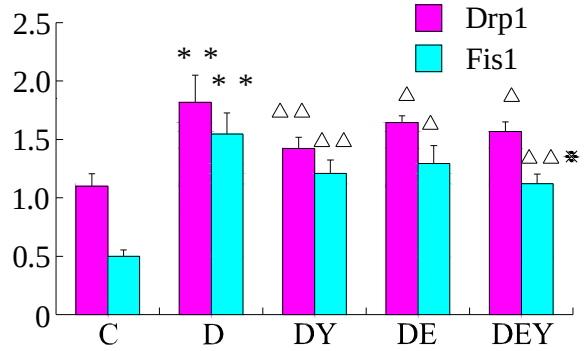

Figure 8. Effect of exercise and EGCG on mitochondrial split protein expression in the hippocampus by rat group.

NIX, BNIP3, PINK1 and Parkin are the autophagy proteins in mitochondria. The expressions of autophagy proteins were compared between diabetic rats, normal rats and those treated with exercise and EGCG, as shown in Fig.9. Compared with those in the normal rats, the autophagy protein levels of diabetic rats were much lower (P<0.05). After the combined treatment with both exercise and medication, the expressions of NLX and BNIP3 were significantly increased compared with those in the rats treated with medication alone (P<0.05).

According to the statistical results of the mitochondrial protein test on diabetic rats, the fusion protein expression in diabetic rats decreased significantly compared with that in normal rats, whereas the split protein expression significantly increased in diabetic rats compared with normal rats, indicating that, with diabetes, the division and fusion of mitochondria are unstable. Treating diabetes with both exercise and EGCG medication can effectively improve the expression of fusion protein and reduce the level of split protein.

Compared with those in the normal group, the autophagy protein levels in diabetic rats were significantly decreased while the expression of Parkin protein increased. The combination of exercise and EGCG can enhance the autophagic ability of mitochondria, thereby changing the ischemic injury of the cerebral nervous system. The EGCG medication can obviously enhance the activity of related enzymes in mitochondria and promote the metabolism of mitochondria.

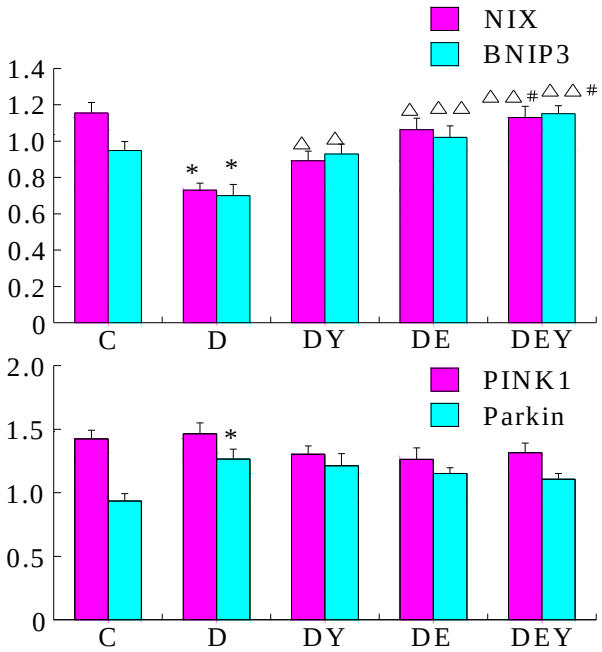

Figure 9. Effect of exercise and EGCG on mitochondrial protein expression in the hippocampus by rat group.

Conclusion

This paper studies the effects of moderate exercise and epigallocatechin gallate (EGCG) on the recovery of mitochondrial injuries in the cerebral nervous system under diabetic state through experiment, and analyses the improvement mechanism of mitochondria in energy synthesis, biosynthesis, anti-oxidation, integration and division under the combination of exercise and EGCG medication, which provides some theoretical reference for the protection of

cerebral nervous system under diabetic state. The research conclusions are as follows:

(1) Diabetes has great impacts on the normal functioning of mitochondria and that its energy synthesis and biosynthesis are controlled by a variety of enzymes. When a rat has diabetes, the protein levels of NRF1, NRF2, TFAM and HO1 in mitochondria are significantly decreased, and the pathways of SIRT1 and PGC-1α proteins are also reduced accordingly. After diabetic rats were treated with the combination of exercise and EGCG for 3 months, the pathways of SIRT1 and PGC-1α proteins were effectively increased, the energy synthesis and biosynthesis of mitochondria were enhanced, and the activity of related enzymes was also improved. In this way, the cerebral nervous system diseases of the rats were mitigated. The combination of exercise and EGCG has better effect than either of them alone.

(2) The fusion protein expression in diabetic rats decreased significantly compared with that in normal rats, whereas the split protein expression significantly increased in diabetic rats compared with normal rats, indicating that with diabetes, the division and fusion of mitochondria are unstable. Treating diabetes with both exercise and EGCG medication can effectively improve the expression of fusion protein and reduce the level of split protein. Compared with those in the normal group, the autophagy protein levels in diabetic rats were significantly decreased while the expression of Parkin protein increased. The combination of exercise and EGCG can enhance the autophagic ability of mitochondria, thereby changing the ischemic injury of the cerebral nervous system. The EGCG medication can obviously enhance the activity of related enzymes in mitochondria and promote the metabolism of mitochondria.

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