Exercise Training Alleviates Cognitive Functions in Diabetic Rats through the Hmgb1/Rage/Nf-Kb Pathway

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Abstract

Objective: To observe the effect of exercise training on cognitive functions of a diabetic rat model.

Methods: Male SD rats were given a high fat and high sugar diet, except for the control group. Afte rfour weeks, 35 mg /kg STZ has intraperitoneally injected to establish type 2 diabetes model rats. After successful modelling, rats were randomly divided into the model group, model + exercise group. Animals performed five days of consecutive treadmill exercise (60 min/day) with 22 m/min speeds for 60 days. After 60 days, Morris water maze task was used in the behavior test. Then rats were weighed, and blood samples were obtained to detect blood glucose. Some animals are sacrificed to prepare serum to detect glycosylated hemoglobin. Brain tissues were taken to detect the protein expressions of HMGB1-/RAGE-/NF-κB signal pathway. The brains of other animals were perfused and taken for RAGE and NF-κB immunohistochemical staining.

Results: Compared with the control group, escape latency and probe distance in the model group are significantly prolonged, the swimming time of the target quadrant is obviously shortened, and the number of platform crossing has been significantly reduced. The average grey values of NF-κB and RAGE has been significantly decreased. Expressions of HMGB1, RAGE,p-NF-κBp65 and p-IκBα were significantly up-regulated($P<0.05$ or $P<0.01$). Compared with the model group, escape latency and probe distance are significantly shortened, swimming time in the target quadrant was prolonged and increased the number of crossing platform, it also reduced the fasting blood glucose, increased body weights, reduced the level of glycated hemoglobin, and significantly increased the mean gray values of NF-κB and RAGE. The protein expressions of HMGB1, RAGE, p-NF-κBp65 and p-IκBα are decreased in model + exercise group.

Conclusion: Exercise training can ameliorate the cognitive dysfunction of diabetic rats, its mechanism may be related to lower blood glucose, lower the level of glycated hemoglobin and improvement of the HMGB1 /RAGE/NF-κB pathway in the brain tissue.

Keywords: Exercise training • Diabetic Cognitive Function • HMGB1/RAGE/NF-κB pathway

Introduction

Type 2 diabetes is one of the risk factors for dementia, which has a significant impairment on the brain cognition since its early stage [1,2]. In recent years, the incidence of diabetes has increased year by year, and many studies have shown that diabetes is an independent high-risk factor for cognitive impairment [3,4].The probability of cognitive impairment in patients with diabetes is significantly higher than that in ordinary people [5]. With the prolongation of the course of the disease, the risk of cognitive decline increases, which seriously reduces the quality of life of patients [6,7]. Many researchers believe that the cognitive impairment of diabetes can be called type 3 diabetes, so the early treatment of type 2 diabetes is incredibly important [8].

Some studies have shown that exercise intervention plays a particular role in preventing cognitive decline in the elderly, and the incidence of cognitive decline in the elderly who exercise regularly for a long time is relatively low [9]. Exercise can promote limb vasodilation, promote the improvement of hemodynamics, correct neurophysiological abnormalities, improve the adaptive changes of the central nervous system, and then improve cognitive dysfunction. According to whether the muscle contraction energy comes from aerobic metabolism or anaerobic metabolism during exercise, exercise is subdivided into aerobic exercise and anaerobic exercise. At present, there are plenty of intervention studies on the effects of aerobic training on patients with cognitive impairment. Aerobic exercise, also known as aerobic training or endurance training, refers to the physical training carried out by the human body under the condition of an adequate supply of oxygen, in which the main large muscle groups of the whole body participate in continuous, rhythmic and lasting exercise for a long time. Aerobics is a low-cost, low-risk, simple and feasible physical activity. The joint aerobic exercises include brisk walking, power car, swimming, aerobics and yoga. Previous studies have suggested that aerobic exercise can ameliorate the cognitive function of patients with mild cognitive impairment, including memory, executive ability et al [10-12]. Anaerobic exercise, also known as resistance exercise or strength training, is a kind of anaerobic exercise that overcomes external resistance through continuous muscle contraction. It mainly includes free weight (dumbbells and barbells), push-ups, isometric exercises, elastic bands and strength training equipment [13]. Best et al. carried out 2-year follow-up study on 155 ageing women who participated in resistance training or balance adjustment [14]. The results showed that resistance training could improve the executive function and memory of older women, and reduce cerebral cortex and white matter atrophy. The purpose of this study is to evaluate the effect of exercise training on diabetic cognitive impairment and its mechanism.

Materials and Methods

Animals

30 Male Sprague Dawley rats (250 g–280 g)has used in this study. The rats are maintained at an ambient temperature of 22°C–24°C and 50%–60% humidity, under a 12 h light: 12 h dark cycle with food and water available ad libitum... The animals were randomly divided into three groups:

(1) regular control group,
(2) STZ injection group, and
(3) STZ injection plus treadmill exercise group. The study has approved by the institutional ethics committee and complied with the Declaration of Helsinki.

Reagents and instruments

RAGE antibody (Cell Signaling Technology); HMGB1, NF-κB-p65 antibody (American Santa Cruz Biotechnology Co., Ltd.) HMGB1, NF-κB-p65 antibody, IκBα, GAPDH antibody, immunohistochemical kit, glycosylated hemoglobin kit, PBS phosphate buffer, 4% paraformaldehyde (Nanjing Jiancheng Biology Co., Ltd.), streptozotocin (Sigma Co., Ltd.); Before streptozocin injection , the solution has been prepared with 0.1mol/L citric acid buffer (0℃-4℃, pH=4.2) at the ratio of 1 to 100. Morris water maze (Shanghai Jiliang Software Technology Co., Ltd.); Eon full-wavelength enzyme labelling instrument of Shanghai Jisun Software Technology Co., Ltd. (BioTek); Sanolian Blood glucose Meter (SanNuo Biosensor Co., Ltd.); BI-2000 medical image analysis system (Chengdu Tai Meng Software Co., Ltd.).

Induction of diabetes

Induced diabetes, Four weeks after high-fat diet (Basic feed 59%, sucrose 20%, lard 18%, egg yolk 3%), a single intraperitoneal injection of STZ (35 mg/kg, dissolved in 0.01-M citrate buffer at pH 4.5; Sigma Chemical Co.) is given to each animal, as the previously described method [15].One week later, rats fasted for 10 hours, hen blood glucose levels were measured by a glucometer (Roche, Germany). The rats whose blood glucose exceeded 12 mmol/L had diabetes and were utilized for the following study. A total of 10 rats were observed after the exclusion of rats with subnormal blood glucose levels. Morris water maze is analyzing to detect whether the rat model had cognitive impairment (compared with the blank control group, whether the platform could be found in the shortest time) [16].

Exercise protocol

Before beginning the formal 60-day exercise protocol, animals have familiarized to treadmill running (5 min/day-20 min/day) for five consecutive days. After this period of habituation, the exercised animals performed five days of consecutive treadmill exercise (60 min/day) with 22 m/min speeds [17]. At the beginning of the 60-minute exercises, to warm up the rats, treadmill speed had been set at 5 m/min and progressively increased to 22 m/min. At the final of the 60-minute exercises, the speed progressively decreased to 5 m/min to cool down. The mild electrical shock was accustomed to the negligible amount to motivate animals to run. Control animals did not carry out treadmill exercise but were put on a nonmoving treadmill for 60 min/day for five days a week. Exercised animals were studied 24 h after their last exercise session.

Morris Water Maze task

The Morris water maze task is used to evaluate memory function according to a previously described method [16]. Four marked points has identified in the middle of the four quadrants of the maze, and a black platform has set in the water. The Morris water maze test was performed 1 hour after the last exercise. Each marked point was trained once in the morning, once in the afternoon, each training interval was more than 30 min for four consecutive days. On the 5th day, the platform was removed, and the rat was thrown into the water from the marked point of the toward the pool wall. The target rat's swimming time in the target quadrant and crossing the virtual platform has been recorded within 90 seconds.

Sampling and specimen handling

After the Morris water maze task, all rats fasted for 12 hours and recorded their weight and fasting blood glucose.The blood have been obtained from the orbital venous plexus of 8 rats in each group and centrifuged with 3500r/min for 10 minutes. according to the instructions of the kit, the serum can be used to determine glycosylated hemoglobin After blood samples were collected, four rats were randomly selected from each group for anaesthesia (10% chloral hydrate 3 ml/kg), fully fixed with PBS intracardiac perfusion, and the tissue of coronary artery from 3mm to 4mm has removed by craniotomy. Hippocampus DG area), placed in 4% paraformaldehyde, fixed at 4℃ for seven days, routine paraffin embedding and coronal sectioning, RAGE and NF-κB immunohistochemical staining, the remaining brain tissues were frozen with liquid nitrogen for using [18,19].

HE staining of hippocampus DG region of brain tissue

The isolated hippocampus tissue was placed in 4% paraformaldehyde and fixed at 4℃ for 24 days. Before dehydration, fixed tissue was washed overnight with tap water. The hippocampus tissue was dehydrated in different gradients of ethanol, transparent with xylene, twice immersed in paraffin, and embedded in conventional paraffin, five μm of tissue sections were stained with HE, transparent with xylene, and sealed with gum for electron microscope observation.

Immunohistochemical detection

The isolated hippocampus tissue was placed in 4% paraformaldehyde and fixed at 4℃ for seven days, and then the coronal sections were prepared after routine paraffin embedding. According to the instructions of the immunohistochemical kit, the sections has routinely dewaxed and eliminated the activity of endogenous peroxidase. After cleaning, Antigen repair is carried out. and the sections were closed and incubated overnight with corresponding primary antibodies (target protein primary antibodies: RAGE, p-NF-κBp65) at 4℃. The blot was washed and incubated with the secondary antibody combined with the primary antibody at room temperature for two hours. The sections were stained with hematoxylin, dehydrated with ethanol, transparent with xylene and coated with neutral glue.

Western blot analysis

The frozen brain tissue was washed with PBS and incubated in lysis buffer. Phosphatase inhibitor was added, the tissue was ground with a grinding rod until completely crushed, centrifuged twice at 4°C, and using the supernatant , the brain protein concentration was quantified using the BCA protein assay kit, then mixed with the loading buffer and heated with 2-mercaptoethanol at 100 ℃ for 5 min. The extracted protein has separated by SDS-PAGE and transferred to PVDF membrane. sIn TBST, the nonspecific binding sites were blocked by 5% skimmed milk powder, and then incubated overnight at 4℃ with corresponding primary antibodies (target protein primary antibodies: HMGB1, RAGE, p-NF-κBp65, p-IκBα, internal reference protein first antibody: NF-κBp65, IκBα, GAPDH). The blot was washed and incubated with the secondary antibody combined with the primary antibody at room temperature for two hours. The ultra-sensitive ECL chemiluminescence kit and Xilinx chemiluminescence imaging system display specific bands. The grayscale analysis of WB bands was carried out by ImageJv1.8.0, and the results were introduced into Excel. GAPDH (if the target protein is phosphorylated, total protein is used) as a reference, the grey ratio of bands is used as the expression result, and SPSS is used to analyze the results of each group.

Statistical analysis

Data are presented as the mean ± standard error of the mean. SPSS software version 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. One way ANOVA was used when the normal distribution was uniform and the variance was homogeneous.The Nonparametric test was used when the normal distribution was not uniform, or the variance was not homogeneous. One way ANOVA has employed to the test results.

Results

Effect of sports training on the hidden platform of Morris water maze

On the first day of a hidden platform test, there was no significant difference in escape latency and probe distance among the three groups. However, the second day, compared with the control group, the escape latency and probe distance of the model group were significantly prolonged, while on the third day, the escape latency and probe distance of the exercise group were significantly shorter than those of the model group. On the fourth day, escape latency, and probe distance of the exercise group were significantly shortened (P < 0.01) (Table 1 and Table 2).

Table 1. The effect of exercise training on the latency time of the hidden platform test

Group	Escape latency(s)			
	First day	Second day	Third day	Forth day
A	87 ± 5	66 ± 9**	52 ± 7**	31 ± 10**
B	86 ± 7	88 ± 3	76 ± 12	54 ± 7
C	86 ± 7	78 ± 10	59 ± 5*	41 ± 6**
* P<0.05, **P<0.01 vs model group				
* A:control group; B:model group; C:model + exercise training group				

Table 2. Effect of exercise training on Hidden Platform test

Group	Probe distance / (m)			
	First day	Second day	Third day	Forth day
A	22.5 ± 5.0	13.8 ± 3.0**	9.2 ± 2.7**	5.7 ± 1.6**
B	21.5 ± 4.1	21.5 ± 2.5	19.8 ± 6.2	13.7 ± 3.3
C	23.1 ± 3.0	17.81 ± 9.1	10.6 ± 7.5*	7.1 ± 2.9*
* P<0.05, **P<0.01 vs model group				
* A:control group; B:model group; C:model + exercise training group				

Compared with the control group, the swimming time in the target quadrant of the model group was significantly shorter (P < 0.01), and the number of crossing platform was significantly reduced (P < 0.01); Compared with the model group, the swimming time in the target quadrant of the exercise group was significantly longer (P < 0.05), and the number of crossing platform in the exercise group was significantly increased (P < 0.05) (Table 3 and Figure 1).

Table 3. Effect of sports training on swimming time in the target quadrant (the first quadrant) and crossing platform times

Group	Swimming time in quadrant I/(%)	Times of crossing platform
A	38.1 ± 5.8**	4.3 ± 2.5**
B	20.9 ± 4.3	1.3 ± 1.7
C	30.6 ± 9.4*	3.5 ± 1.7*
* P<0.05, **P<0.01 vs model group		
* A:control group; B:model group; C:model + exercise training group		

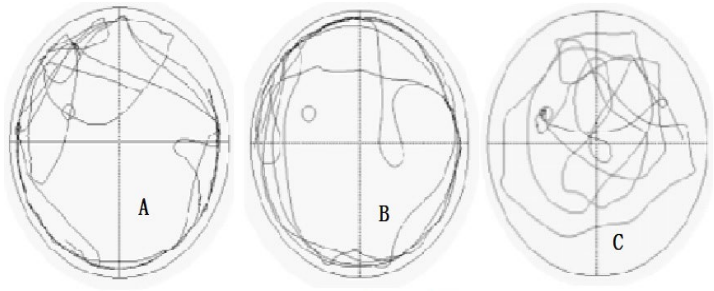

Figure 1. Effect of Exercise training on hidden platform test
A:Control Group; **B:** Model Group; **C:** Model + Exercise training group

Effects of exercise training on blood glucose, body weight and glycosylated hemoglobin

Compared with the control group, the levels of blood glucose and glycosylated hemoglobin in the model group increased significantly (P<0.01), and the bodyweight decreased significantly (P<0.01). Compared with the model group, the blood glucose in the exercise training group decreased significantly (P<0.01), the body weight in the exercise training group increased significantly (P<0.01), and the level of glycosylated hemoglobin decreased significantly (P<0.05) (See Table 4).

Table 4. Effects of exercise training on blood glucose, body weight and glycosylated hemoglobin

Group	blood sugar (mmol /L)	Weight (g)	Glycosylated hemoglobin (g /ml)
A	4.4 ± 0.4**	488.5 ± 47.0**	3.9 ± 1.0**
B	17.6 ± 2.8	247.5 ± 50.6	8.7 ± 2.2
C	13.5 ± 1.2**	370.8 ± 57.8**	6.3 ± 1.9*
* P<0.05, **P<0.01 vs model group			
* A:control group; B:model group; C:model + exercise training group			

Effect of exercise training on brain tissue

Compared with the control group, the HE staining of the hippocampus histopathological sections showed that the cells of the granular layer in the DG area of the model group were sparse and arranged irregularly. Compared with the model group, the cells in the exercise training group were dense and arranged neatly (Figure 2).

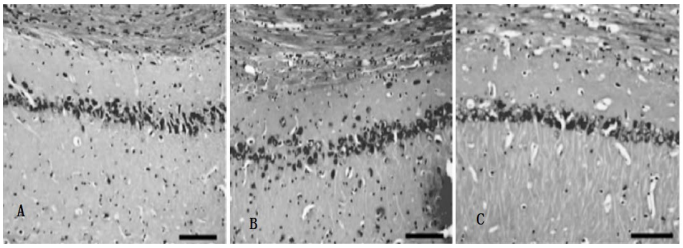

Figure 2. Effect of exercise training on histopathology of Hippocampus (HE×200); **A:** Control Group; **B:** Model Group; **C:** Model + Exercise Training Group

Effect of sports training on the hidden platform of Morris water maze

The results of immunohistochemical staining showed that compared with the control group, the number of NF-κB immunoreactive positive cells in granular cell layer and cortical neurons in the hippocampus DG region of the model group was more and deeply stained, and the grey value of NF- κB decreased significantly (P<0.01). Compared with the model group, exercise training significantly reduced the NF-κB immunoreactive positive cells in the granular cell layer and cortical neurons of the hippocampus DG area, and the average grey value of NF-κB was significantly increased (P <0.05) (Figure 3, Table 5). Immunohistochemical staining showed that compared with the control group, the number of RAGE immunopositive positive cells in the DG area of the hippocampus of the model group significantly increased, and the colouration was significantly deepened. Compared with the model group, the number of RAGE immunopositive positive cells in the hippocampus DG area of the sports training group is significantly reduced, and the colouring lighter; compared with the model group, the average grey value of RAGE in the exercise training group was significantly increased (P< 0.05) (Figure 4, Table 5). (Note: The arrows in the figure below refer to positive immunoreactive cells).

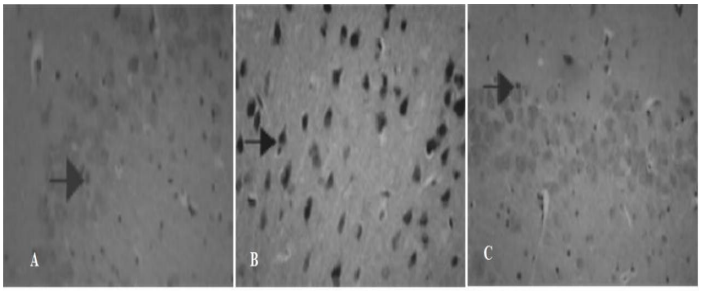

Figure 3. Effect of exercise training on expression of NF-κB protein in Hippocampus (Immunohistochemistry*400); **A:** Control Group; **B:** Model Group; **C:** Model + Exercise Training Group

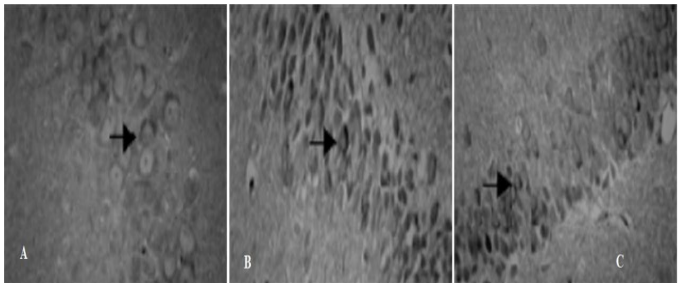

Figure 4. Effect of exercise training on RAGE protein in Hippocampus (Immunohistochemistry × 400); **A:** Control Group; **B:** Model Group; **C:** Model + Exercise Training Group

Table 5. Effect of exercise training on the average grey value of RAGE, NF- κ B in the hippocampus

Group	NF-κB average gray value	RAGE average gray value
A	127 ± 4**	130 ± 9**
B	93 ± 6	98 ± 7
C	110 ± 7*	119 ± 9**
* P<0.05, **P<0.01 vs model group		
* A:control group; B:model group; C:model + exercise training group		

Table 6. Effect of exercise training on the expression of HMGB1/RAGE/NF- κB signal pathway protein in brain tissue

Group	HMGB1 /GAPDH	RAGE /GAPDH	P-NF-κBP65 /NF-κBP65	P-IkBa /IkBa
A	0.0941 ± 0.0019**	0.0633 ± 0.0021**	0.1651 ± 0.0210**	0.348 ± 0.021**
B	0.2139 ± 0.0075	0.1728 ± 0.0057	0.4797 ± 0.0407	1.033 ± 0.069
C	0.1395 ± 0.0078**	0.0788 ± 0.0061**	0.5003 ± 0.0039**	0.598 ± 0.028*
* P<0.05, **P<0.01 vs model group				
* A:control group; B:model group; C:model + exercise training group				

Effect of exercise training on the expression of HMGB1/RAGE/NF- κ B pathway protein in brain tissue

Compared with the control group, the expression of HMGB1, RAGE, p-NF-κBp65, p-IκBα protein in the model group was significantly up-regulated (P < 0.01). Compared with the model group, the exercise training group could significantly down-regulate the expression of HMGB1, RAGE, p-NF-κB p65, p-IκBα protein (Figure 5, Table 6).

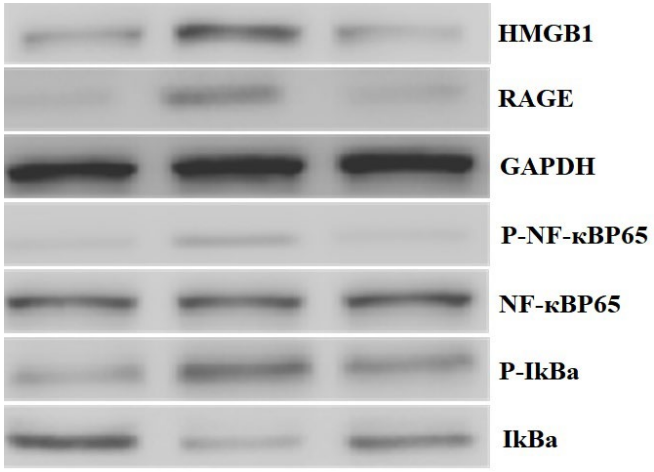

Figure 5. Effect of exercise training on expression of HMGB1, RAGE, p-NF-κB signal pathway protein in brain tissue

Discussion

Long-term hyperglycemia can increase the damage of oxygen free radicals, cause metabolic disorders, increase the level of inflammatory factors, and produce advanced glycation end products, which affect the nervous system. Cukierman-Yaffe et al. showed that for every 1% increase in glycosylated hemoglobin , the score of digital symbol learning test and mini-mental state examination scale in patients with type 2 diabetes decreased by an average of 1.75 points and 0.2 points respectively [20]. Another study confirmed that the higher the glycosylated hemoglobin , the lower the cognitive test score of type 2 diabetic patients. After three years of follow-up, the cognitive impairment of type 2 diabetic patients with high glycosylated hemoglobin is more worse [21]. The current research results show that exercise training can reduce the fasting blood glucose of diabetic rats, improve cognitive impairment caused by diabetes, and improve the learning and memory function in rats.

Studies have shown that aerobic exercise is related to cognitive function in brain structure [22]. The hippocampus in the brain is the field responsible for learning and memory, and once the structural and functional integrity of the hippocampus has destroyed, it can lead to a decline in cognitive function. Studies have shown that aerobic exercise can increase the volume of hippocampus, gray matter and white matter [23]. Studies have shown that after 6 months of aerobic exercise intervention, the left, right and all hippocampus volumes of the elderly with mild cognitive impairment increased significantly [24]. Exercise can change the adaptability of brain structure and function, and then maintain or ameliorate the cognitive function of the elderly [25]. Erickson et al. showed that after one year of aerobic exercise intervention, the left and right hippocampus capacity of the elderly increased by 2.12% and 1.97%, respectively [23]. High mobility group protein B1 (HMGB1) is an essential late inflammatory factor, which can act as an endogenous pyrogen in the central nervous system [26]. Increased levels of HMGB1 in the brain can induce memory abnormalities, which may be mediated by advanced glycation end products receptor (RAGE) [27].

The results of this study show that compared with the model group, exercise training can significantly down-regulate the protein level of HMGB1, RAGE in the brain and effectively improve the memory abnormality of model rats. Other studies have shown that (RAGE), nuclear transcription factor (NF- κB), a receptor for advanced glycation end products, plays a vital role in the pathogenesis of diabetic cognitive impairment. The combination of HMGB1 and RAGE can lead to oxidative stress in neurons and activate the expression of NF- κB. Hofmann et al confirmed the activation of NF- κB in patients with diabetes for the first time. This study showed that compared with the model group, the protein expression of p-NF-κB p65 and p-IκBα in the exercise training group was significantly down-regulated. Due to the down-regulation of the protein level of HMGB1, RAGE in the brain, the activation of downstream NF- κB pathway has inhibited. Therefore, the protein levels of p-NF-κB p65 and p-IκBα in the exercise training group were also significantly down-regulated. The results of pathological sections of hippocampus tissue showed that compared with the model group, exercise training could increase the average grey values of NF- κB and RAGE of diabetic cognitive impairment rats, and effectively improve the development of hippocampus pathological changes. Besides, the results of this study also show that exercise training can improve the cognitive ability of diabetic cognitive impairment rats, and significantly reduce the levels of blood glucose and glycosylated hemoglobin, indicating that exercise training may improve the cognitive impairment of diabetic rats by reducing blood glucose, reducing the level of glycosylated hemoglobin and improving HMGB1/RAGE/NF- κB pathway in the brain tissue of diabetic rats. It also shows that exercise training may have the effect of improving cognitive impairment mediated by RAGE.

Conclusion

Higher circulating homocysteine levels were noted in MS patients compared with controls. Physical disability was associated with HHcy in our research. No association was noticed between HHcy and cognitive impairment in MS patients.

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Conflicts of Interest

The author declared that there are no conflicts of interest.

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