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Effects of Treadmill Exercise on Memory and Hippocampal BDNF Expression in Streptozotocin-induced Diabetic Rats

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Diabetes mellitus is a chronic metabolic disorder, leading to many complications including cognitive deficit. Regular exercise has often been recommended as a therapeutic maneuver to the diabetic patients for the prevention of secondary complications. In the present study, the effects of treadmill exercise on memory and brain-derived neurotrophic factor (BDNF) in the hippocampus of streptozotocin (STZ)-induced diabetic rats were investigated. Male SD rats, aged 6 weeks, were randomly assigned to the following three groups: control group(n=8), STZ-induced diabetic group(n=8), and STZ-induced diabetes and exercise group(n=8). Diabetes was induced by a single injection of STZ (50 mg/kg body weight). Treadmill running was conducted with duration and frequency of 30 minutes and 5 times per week, respectively, for 8 weeks. Memories were tested in the Morris water maze. Western blotting was performed to detect BDNF expression in the hippocampus. In this study, we found that compared to the control group, the STZ-induced diabetes group had a significantly impaired cognitive performance along with suppressed BDNF expression in the hippocampus and the exercise group had a higher cognitive function in diabetic rats. Therefore, the current findings of the study show that a treadmill running exercise can improve diabetes-induced impairment of cognitive function. And the improved cognitive function appears to be related to an alleviation in diabetes-induced BDNF expression in hippocampus.

Key words : Diabetes, treadmill running, hippocampus, brain-derived neurotrophic factor, memory

Introduction

Diabetes mellitus (DM) is a common and serious metabolic disease characterized by disturbed glucose metabolism due to the absolute or relative insulin deficiency. In addition to the diabetic condition itself, long-term diabetes has been associated with numerous secondary complications. As these complications appear to be prevented incompletely by control of blood glucose level, additional therapeutic interventions are warranted in the case of long-term diabetes. The brain has recently known as a vulnerable organ to be damaged by diabetes [40]. In human, diabetes is associated with impaired cognitive function, including learning and memory [6]. Longitudinal population-based studies show that the rate of cognitive decline is accelerated both in Type I DM [11] and Type II DM [3]. Recent pathological studies have suggested that diabetes is one of the risk factors for senile dementia of Alzheimer type [5,44]. Impairment of cognitive function has also been demonstrated in streptozotocin (STZ)-induced diabetic rats [10,23,38].

The positive effect of exercise on the control of blood glucose levels in diabetes is widely endorsed. It has been reported that physical exercise increases blood flow [13] and enhances glucose uptake in muscles, which results in increasing insulin sensitivity in type 2 diabetes [25]. In addition, the potential of exercise to protect against neurological damage of diabetes is well recognized. For example, exercise decreased hemorrhagic injury in diabetic rats [36]. Treadmill exercise alleviated diabetes-induced decrease in hippocampal cell proliferation [32]. Shin et al.[48] reported that exercise suppresses a diabetes-induced increase of neuropeptide Y expression in the hypothalamus, inhibiting diabetes-induced increment of the desire for food. On the other hand, an epidemiological study indicates that regular exercise can decrease cognitive decay associated to diabetes [16].

Brain derived neurotrophic factor (BDNF) is a member of the neurotrophic factor family, which plays a key role in regulating survival, growth, and maintenance of neurons in many areas of the brain [39]. In the hippocampus, a major hub for learning and memory formation, BDNF is synthesized predominantly by neurons intimately asso-

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ciated with the processing of cognitive function [52]. Therefore, BDNF plays a central role in learning and memory in the hippocampus. It has been suggested that the reduction in BDNF synthesis is a pathogenetic factor to dementia [51]. In fact, Connor et al. [14] demonstrated the suppression of BDNF expression in the hippocampus of dementia patients. Recently, Krabbe et al. [35] showed that an output of BDNF from the human brain with diabetes was decreased, and Nitta et al. [42] reported that in the diabetic brains, both protein and mRNA levels of BDNF were severely reduced. These results all suggest that the suppression of hippocampal BDNF expression be the important factor for cognitive dysfunction in diabetes, and thus measures to stimulate BDNF expression in the hippocampus may be potential preventive strategies against diabetes-induced cognitive dysfunction.

Regular physical exercise has frequently been recommended as a therapeutic modality for the treatment of diabetic patients, targeted toward the prevention of secondary complications. However, no study has been made to the effect of treadmill exercise on memory ability in relation to BDNF in the hippocampus of diabetic rats. In the present study, the effects of treadmill exercise on memory function and BDNF expression in the hippocampus of STZ-induced diabetic rats were investigated.

Materials and methods

Animals and treatments

Male Sprague-Dawley rats (starting weight ~235g, 6 weeks of age) were used in this experiment. The experimental animals were housed under controlled temperature (20 ± 2°C) and were maintained on a photocycle of 12 hr of light and 12 hr of darkness (lights on from 07:00 to 19:00), with food and water being made available ad libitum. The animals were divided into three groups (n = 8 in each group): the control group; the STZ-induced diabetes group, and the STZ-induced diabetes and exercise group.

Induction of diabetes

Diabetes was induced by a single intraperitoneal injection of 50 mg/kg streptozotocin (STZ) (Sigma chemical Co., St. Louis, MO, USA) in saline. Control animals were injected with equivalent dose of normal saline. Blood glucose levels were determined 2 days after STZ injection using a blood glucose tester (Arkray, Kyoto, Japan). Animals with the blood glucose level 300 mg/dl or higher were used as the diabetes groups.

Exercise protocol

The exercise regimen for the treadmill running consisted of running on a motorized treadmill for 30 min five times per week for 8 weeks. Rats in all groups, including the controls, were run for 5 m/min, 0° slope, 5 min/session, 3 daily sessions for a week to adapt running before the experiment. Electric shocks were used sparingly to motivate the animals to run. The workload for the exercise consisted of running at a speed of 2 m/min for the first 5 min, 5 m/min for the next 5 min, and then 8 m/min for the last 20 min, with 0° slope, which has been considered as a light-intensity exercise [33]. Kim et al. [33] demonstrated that a light-intensity exercise is more effective than moderate-and severe-intensity exercises in enhancing hippocampal synaptic plasticity in rats. Rats in the non-exercise groups were left in the treadmill without running for the same period as the exercise groups.

Morris water maze

One day after the last exercise session, animals were subjected to Morris water maze tests. Published methods were followed [54]. The Morris Water Maze consisted of a circular tank 200 cm in diameter containing water (28 ± 1°C) made opaque with nontoxic black paint. Briefly, spatial learning and memory was tested using a hidden platform or place test, where a platform 11.5 cm in diameter was submerged 1 cm below the surface in the center of one of four quadrants. Each of the four surrounding walls located 2 feet beyond the edge of the tank had different shaped symbols that served as cues to locate the submerged invisible platform. Rats were placed randomly in one quadrant, against the side of the tank, and were allowed up to 120 sec swimming time to locate the platform. Rats that had located the platform, or had failed and were placed on the platform, were allowed to remain there for 30 sec to permit spatial orientation. Thereafter, rats were removed and placed under a heat lamp between trials. Rats were subjected to 3 daily trials, with a 60-sec interval between trials, for 5 consecutive days. A video camera was mounted above the tank and swim paths were analyzed with a Video Tracking System (Panlab). Both latency times and distances swum to reach the platform were computed. On the final day of the training rats were tested in the wa-

ter maze with a new location. The test with the visible platform does not require spatial orientation and was used to show possible deficits in sensorimotor processes. Rats were allowed to swim for 60 sec.

Western blotting analysis

Western blot for the detection of the BDNF proteins was performed as previously described [12]. One day after the completion of the Morris water maze, animals were deeply anesthetized with Zoletil 50® (10 mg/kg, i.p.; Vibac Laboratories, Carros, France) and then underwent rapid decapitation. Brains were quickly removed and dissected on a Petri dish over ice. After tissue dissection, samples were stored at -80°C until analysis. In preparation for Western blotting, tissue from hippocampus were placed in 350-800 ul of lysis buffer containing 50 mM Tris-HCl (pH 7.5), 150 mM NaCl, 0.5% deoxycholic acid, 1% NP40, 0.1% SDS, 1 mM PMSF, 100 g/ml leupeptin. Samples were sonicated for 10 s at 30 mV. The lysates were centrifuged at 13,000 r.p.m. for 30 min at 4°C. The supernatants were aliquoted and frozen at -80°C. Protein concentration was measured using a Bio-Rad colorimetric protein assay kit (Bio-Rad). Protein 50 g was separated on SDS-polyacrylamide gels and transferred onto a nitrocellulose membrane. Anti-BDNF (1:1000; Santa Cruz Biotech, Santa Cruz, CA, USA) were used as the primary antibody. Horseradish peroxidase-conjugated anti-mouse antibody for BDNF (Amersham Pharmacia Biothech GmbH, Freiburg, Germany) were used as the secondary antibody. The detection of band was performed using the enhanced chemiluminescence (ECL) detection system (Amersham Pharmacia Biothech GmbH).

Statistical analysis

All the results are expressed as the mean ± standard error of the mean (S.E.M.). Between group differences in body weight, blood glucose, and BDNF were analysed by one-way analysis of variance (ANOVA) followed by Duncan's post-hoc analysis. The water maze data were analyzed using ANOVA with repeated measures, with group as the between subject factor and trials/time as the within subject factor. Interaction effects were analyzed further by contrast analysis. A statistical significance was tested at $p = 0.05$.

Results

Body weight changes

The weights of the rats on the 1 day, 3 day, and 56 day from the starting of experiment are summarized in Table 1. In the diabetes group, significant weight loss was observed at 3 days after the STZ injection, in contrast, the animals in the control group showed significant weight gain. Treadmill exercise exerted no significant effect on body weight change in the diabetic rats.

Blood glucose levels

The blood glucose levels on the day 1, day 3, and day 56 from the starting of experiment are summarized in Table 2. The blood glucose level was significantly increased at 3 days after the STZ injection. Treadmill exercise exerted no significant effect on the blood glucose levels in the diabetic rats.

Effect of treadmill exercise on performance of diabetic rats in a Morris water maze task

There was a significant decrease in the latencies to escape to the hidden platform over the 5 days of the test in all three group: control, $p < 0.01$; diabetic, $p < 0.02$; diabetic + exercise, $p < 0.01$. (Fig. 1). The time course for the decrease in latency was similar between the control group and the STZ-induced diabetes and exercise group; there was a progressive decline in latencies throughout the 5 days of testing. By contrast, there was a 3-day lag before latencies began to decline in the STZ-induced diabetes group. The mean latency on 3 day, 4 day, and 5 day of the

Table 1. Body weights on Day 1, 3, and 56 of the experiment (Unit: g)

Group	Day 1	Day 3	Day 56
A	223.8±2.6	233.6±2.7	416.4±9.2
B	221.3±3.1	196.9±1.6*	154.4±2.9*
C	220.1±2.7	195.6±2.0*	161.9±2.3*

A, Control group; B, STZ-induced diabetes group; and C, STZ-induced diabetes and exercise group. Each value represents mean ± SEM. * means $P < 0.05$ compared to the control group.

Table 2. Blood glucose levels on the Day 1, 3, and 56 of the experiment (Unit: mg/dl)

Group	Day 1	Day 3	Day 56
A	103.9±1.8	100.6±2.2	98.8±2.6
B	102.0±2.2	527.0±21.2*	562.1±16.1*
C	100.3±1.6	518.8±26.1*	515.0±23.3*

Each value represents mean ± SEM. * means $P < 0.05$ compared to the control group.

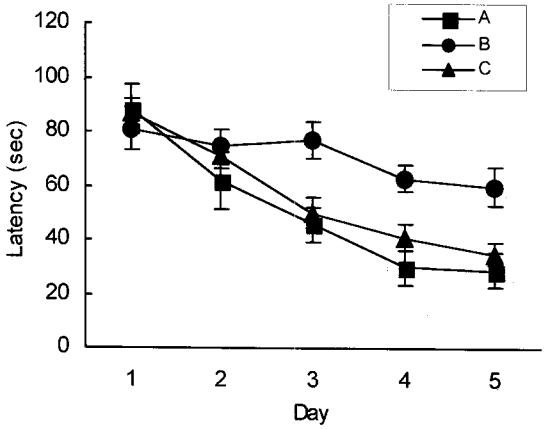

Fig. 1. Effect of treadmill exercise on the latency to the hidden platform in Morris water maze in STZ-induced diabetes rats. A, Control group; B, STZ-induced diabetes group; and C, STZ-induced diabetes and exercise group. The data are presented as the mean ± SEM.

test was significantly prolonged in diabetic rats versus control rats ($p < 0.01$),

Distances swam to find the hidden platform decreased significantly over the 5 days of the test in the control rats ($p < 0.01$) and the STZ-induced diabetes and exercise group ($p < 0.01$) (Fig. 2), demonstrating that shortening of their search path for escaping to the hidden platform was the cause of their reduced latencies. By contrast, the distance swam by diabetic rats did not change significantly over the 5 days ($p < 0.458$). The mean distances on 3 day, 4 day, and 5 day of the test were significantly higher in the STZ-induced diabetes group than both the control

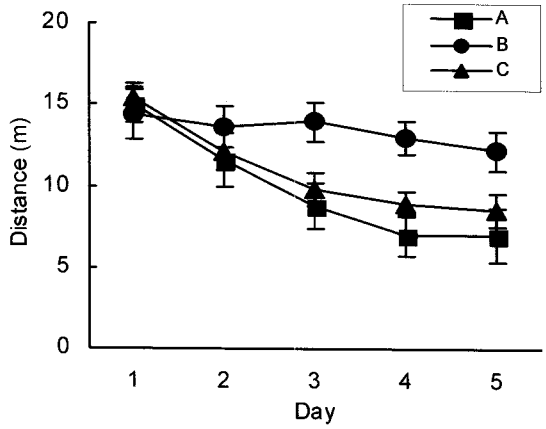

Fig. 2. Effect of treadmill exercise on the distance to the hidden platform in Morris water maze in STZ-induced diabetes rats. A, Control group; B, STZ-induced diabetes group; and C, STZ-induced diabetes and exercise group. The data are presented as the mean ± SEM.

group and the STZ-induced diabetes and exercise group ($p < 0.01$). All groups were submitted to a test of their ability to escape to a visible platform. The performance of all the groups of rats in the trial with the visible platform was not significantly different.

Effect of treadmill exercise on hippocampal BDNF expression in STZ-induced diabetes rats

The levels of BDNF protein in the control group was designated at 100. The levels of BDNF protein was found to have significantly decreased in the STZ-induced diabetes group to 57.72 ± 1.24. On the other hand, treadmill exercise significantly increased the levels of BDNF protein in the STZ-induced diabetic rats from 57.72 ± 1.24 to 89.33 ± 2.51 (Fig. 3). Actin levels did not differ significantly among any of the groups. In the present results, treadmill exercise significantly alleviated diabetes-induced suppression on BDNF protein expression in the hippocampus.

Discussion

STZ-induced diabetes is a well-documented model of experimental diabetes. A single high dose of STZ is toxic to insulin-producing β cells, and it produces irreversible

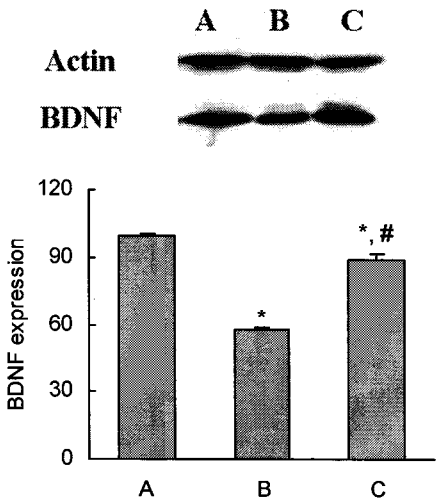

Fig. 3. Upper: Representive expressions of the protein level of BDNF and actin in the hippocampus. A, Control group; B, STZ-induced diabetes group; and STZ-induced diabetes and running group. Lower: Relative BDNF expression in the hippocampus. Molecular weights of BDNF = 15 kDa; Actin = 42 kDa. The data are presented as the mean ± SEM. * means $P < 0.05$ compared to the control group. # means $P < 0.05$ compared to the STZ-induced diabetes group.

damage to those cells [55]. Many studies have shown that STZ-induced diabetic rats produces clinically similar conditions to diabetes mellitus, resulting in many complications such as alterations in neurotransmission, electrophysiological abnormalities, and structural changes [9,10, 17]. Long-term diabetes is associated with the impairment in learning ability and memory formation and hinders cognitive processing of new information through disruption of hippocampal functions [9,30]. Longitudinal study show a two-fold increased incidence of developing Alzheimer's disease or vascular dementia [15].

In the present study, STZ-induced diabetes induced the learning and memory impairments, as accessed by the Morris water maze task. The results of the behavioral study demonstrated that diabetic rats spent more time to find the hidden platform compared to the control group. These observations are consistent with previous reports, which displayed performance deficits in the Morris water maze following the induction of diabetes [10,30,31]. Spatial learning and memory in the Morris water maze is known to involve multiple cognitive components such as problem solving, enhanced selective attention, formation of internal representations of the external world, and storage and retrieval of relevant information [54]. Deficits in learning and memory in diabetic rats were earlier shown to be paralleled by alterations in hippocampal synaptic plasticity [7,23].

Recently, it has become clear that physical exercise have beneficial effects on brain plasticity [43]. Exercise appears to maintain cerebrovascular integrity [18], increase capillary growth [50], increase dendritic connections [46], and enhance the efficiency of processing functions of the central nervous system [27]. Our present results demonstrated that treadmill exercise in diabetic rats had shorter escape latency than diabetic rats at third and fourth, and fifth days of learning trials, indicating better learning and memory performance than diabetic rats. It has been reported that learning and memory can be influenced by exercise. Animal studies on rats and mice reported better cognitive performance as a result of increased physical activities [4,22]. Regular exercise also reduced age-related decline in memory and cognition in aging humans [19]. Clinical evidence has shown that exercise decreases risk for cognitive impairment associated to diabetes [16]. It has been suggested that physical exercise modulates cognitive functions through various signaling mechanisms that lead to BDNF up-regulation in the adult hippocampus [24,53]. BDNF is known to induce the expression of long-term potentiation in the rat hippocampus [34]. In diabetic rats, the impairment of long-term potentiation has been related to the severity of cognitive deficit [29]. Farmer et al. [21] reported that exercise enhances the expression of long-term potentiation by increasing BDNF expression in the hippocampus.

Neurotrophins, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and NT-4/5 have been implicated in neuronal survival, differentiation, connectivity, and plasticity [47]. Of them, BDNF is also known to exert neuroprotective effects on the hippocampus [37]. The diabetes-induced reduction of BDNF is considered as a major factor in the impairment of cognitive function [42]. Nitta et al. [42] has reported that cognitive dysfunction by diabetes was prevented by the administration of a stimulator of BDNF synthesis. In the present study, we examined the effect of treadmill exercise on BDNF expression in the hippocampus of STZ-induced diabetic rats. Here, we showed that STZ-induced diabetic rats undergo a significant reduction of BDNF expression in the hippocampus, and treadmill exercise significantly enhanced the expression of BDNF in hippocampus of diabetic rats. In STZ-induced diabetic rats, these observation is accordance with result previously reported that both protein and mRNA levels of BDNF were severely reduced in the hippocampus [42], and the diabetes-induced reduction of BDNF is considered as a major factor in the impairment of cognitive function.

In the present results, treadmill exercise increased the expression of BDNF in hippocampus of diabetic rats. BDNF plays a central role in mediating exercise-induced effects on brain plasticity [8,53]. Previous studies have consistently shown that voluntary exercise enhances both protein and mRNA levels of BDNF in the rat hippocampus [21,28] in line with studies showing a clear involvement of BDNF with synaptic transmission and neuronal plasticity, resulting in increases in learning ability and memory capability [41]. Forced running also increased BDNF mRNA and protein in the hippocampus of adult rats [49]. In addition, exercise has been reported to reverse the decrease in hippocampal BDNF under various pathological conditions such as Alzheimer's disease [56], aging [2], traumatic brain injury [26], ischemia [45], depression [20], and stress [1] with an improved behavioral outcome. In this respect, the exercise-induced enhancement of hippocampal BDNF has been tentatively implicated in brain plasticity under vari-

ous brain insults. Our data suggest that treadmill exercise ameliorate the diabetes-induced suppression of BDNF expression in the rat hippocampus.

In conclusion, we have shown that STZ-induced diabetes suppresses the expression of BDNF protein in the hippocampus and results in memory deficits in rats. However, treadmill exercise alleviates memory deficits by enhancing BDNF expression in the hippocampus of STZ-induced rats. The data from the present study suggest that treadmill exercise may be useful in the alleviation of memory dysfunction in STZ-induced diabetic rats.

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초록 : 트레드밀 운동이 당뇨흰쥐에서 기억력과 해마 BDNF 발현에 미치는 영향

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당뇨병은 만성적 대사질환으로 말초뿐만 아니라 중추신경계에서도 다양한 합병증을 유발시키는 것으로 알려져 있다. 특히, 당뇨환자는 인지기능의 손상으로 인해 치매 유병율이 높은 것으로 보고되고 있다. 규칙적인 운동은 당뇨병의 이차 합병증을 예방하기 위한 치료적 방법으로 흔히 권장된다. 이에 본 연구는 당뇨흰쥐를 대상으로 트레드밀 운동이 기억력과 해마 BDNF 발현에 미치는 효과를 조사하였다. SD계열 흰쥐를 실험동물로 하여 STZ (50 mg/kg) 투여로 유발시킨 당뇨흰쥐를 8주간 주 5회 30분씩 트레드밀에서 달리도록 하였다. 운동프로그램 종료 후, Morris water maze로 기억력을 측정하고, 해마조직을 적출하여 Western으로 brain-derived neurotrophic factor (BDNF) 발현을 정량화하였다. 본 연구결과 8주간의 당뇨는 선행연구과 유사하게 기억력 손상과 함께 해마조직의 BDNF 발현을 유의하게 감소시키는 것으로 나타났다. 하지만 트레드밀 운동은 당뇨흰쥐에서 기억력과 해마 BDNF 발현을 유의하게 향상시키는 것으로 나타났다. 이러한 결과는 당뇨동물에서 운동이 해마 BDNF 발현의 증가를 통해 인지기능의 손상을 완화시킬 수 있음을 보여주는 것이다.