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Effect of Acute Administration of loganin on Spatial Memory in Diabetic Male Rats

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ABSTRACT

Purpose: Diabetes is associated with memory and learning disorder. The purpose of this study is to determine the effect of acute oral administration of loganin on memory in diabetic male rats. ***Methods:*** 42 male Wistar rats (250-300 g) were divided into six groups: Control, Diabetic (1 week), Diabetic (12 weeks), Loganin, Diabetic (1 week) + Loganin, Diabetic (12 weeks) + Loganin. Diabetes was induced by IP injection of Streptozotocin (60 mg/kg). Loganin (40 mg/kg, po) was administrated 1 hour before test. Then, spatial memory was compared between groups with Morris Water Maze tests. ***Results:*** Administration of loganin during acquisition, significantly ($p<0.05$) decreased both escape latency and traveled distance to find hidden platform in 1 and 12 weeks diabetic rats. In evaluation of recall phase of memory, loganin significantly ($p<0.05$) increased time and distance spent in the target quadrant in 1 and 12 weeks diabetic rats. ***Conclusion:*** Acute administration of loganin could improve spatial memory in diabetic rats.

Introduction

Diabetes mellitus is a very common metabolic disorder characterized by hyperglycemia and insufficiency of secretion or action of endogenous insulin.[1] Diabetes causes complications affecting the retina, kidney, muscle and blood vessels, and the nervous system.[2]

Many studies show that changes in cerebral structure and function in diabetes are related to hyperglycemia-induced end organ damage, macrovascular disease, hypoglycemia, insulin resistance, and amyloid lesions.[3] On the one hand, diabetes induces cytochrome c release from mitochondria into cytoplasm that may play a role in apoptosis of the CA1 pyramidal neurons.[4] On the other hand, diabetes causes a reduction in neurogenesis.[5]

There are also electrophysiological and structural abnormalities of the brain in diabetic patients providing good reasons to believe that cognitive functions may be impaired in diabetes mellitus.[6] Moreover, oxidative stress could contribute to learning and memory deficits in diabetes.[7]

Loganin as an iridoid glycoside first was found in Flos lonicerae, Fruit cornus, and Strychonos nux vomica.[8] It has been used as a traditional medicine in Japan and China.[9] According to one study, loganin has a plasma glucose lowering action in normal rats and regulates immune function and has anti-inflammatory, neuroprotective and anti-shock effects.[8,9]

In an Alzheimer's model of study, Kwon and colleagues proved that loganin could have anti-amnesic and anti acetylcholinesterase activity in the hippocampus and frontal cortex.[10] Furthermore, our recent studies showed that acute administration of loganin improves memory in passive avoidance tests and chronic application of it exhibits protective effect on spatial learning and memory in diabetic rats.[11,12]

In this study, we evaluated the effect of acute oral administration of loganin on learning and memory deficits in one and 12 weeks diabetic rats in the Morris water maze tasks.

Materials and Methods

Streptozotocin (STZ) was purchased from Tocris Bioscience (Bristol, UK) and dissolved in normal saline immediately before use. Loganin was purchased from Extrasynthese (France) and dissolved in normal saline.

Animals

Male Wistar rats, weighing (250–300) g, were used in the present experiment. All animals were maintained at a constant temperature (20±1) and on a 12 h light: 12 h dark cycle. They had free access to water and food ad libitum. The Regional Ethics Committee of Tabriz University of Medical Sciences approved all experimental procedures.

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Experimental Design

Male Wistar rats (n = 42) were divided into six groups (n = 7 each): control, diabetic (1 week), diabetic (12 week), loganin, diabetic (1 week) + loganin, diabetics (12 week) + loganin. Experimental diabetes was induced by a single dose of STZ (60 mg/kg, intraperitoneal (ip)). Three days after STZ injection, fasting blood glucose levels were determined. Animals were considered diabetic if plasma glucose levels exceeded 300 mg/dl.[13] Loganin (40 mg/kg, po) was administrated once after confirming diabetes. Animals were tested for spatial memory 1 h after loganin treatment.[10]

Morris Water Maze Test

The Morris water maze was black circular pool (136 cm in diameter and 100 cm in height). The pool was filled to a depth of 60 cm with water (20±1 °C) and divided into four quadrants of equal area (NE, SE, SW and NW). A platform (10 cm in diameter) was centered in one of the four quadrants of the pool and submerged 1 cm below the water surface so that it was invisible at water level. The swimming was monitored by a video camera, which was positioned directly above the center of the pool. The pool was located in a test room, which contained various prominent visual cues.[14]

One week after surgery, the rats were trained in the water maze. The single training session consisted of eight trials (in two blocks) with four different starting positions that were equally distributed around the perimeter of the maze. The task requires rats to swim to the hidden platform guided by distal spatial cues. After mounting the platform, the rats were allowed to remain there for 20 s, and then were placed in a holding cage for 30 s until the start of the next trial. Rats were given a maximum of 60 s to find the platform and if it failed to find the platform in 60 s, it was placed on the platform and allowed to rest for 20 s. Latency to platform and distance traveled were collected and analyzed later. After completion of the training, the animals were returned to their home cages until retention testing 24 h later. The probe trial consisted of 60 s free swim period without a platform and the time swum in the target quadrant was recorded.

In order to assess the possibility of drug interference with animal sensory and motor coordination or the animal motivation, the capability of rats to escape to a visible platform was tested in this study. The trained rats were given four trials for visuo-motor coordination on the visible platform.[15]

Statistics

SPSS 13.0 software was used for statistical comparisons of data, and data expressed as the means ± SEM. For comparisons between Block 1 and Block 2 in each group, a paired-sample T test was used. The statistical analysis of the data between groups was carried out by one-way ANOVA followed by Tukey test. In all comparisons, P<0.05 was the criterion for statistical significance.

Results

In comparison of block 1 and block 2, diabetes increased escape latency and traveled distance (Figures 1, 2) in 1 and 12 weeks diabetic rats during acquisition phase. Loganin (40 mg/kg) significantly decreased latency time (P<0.05) and traveled distance (P<0.05) in 1 and 12 weeks diabetic rats.

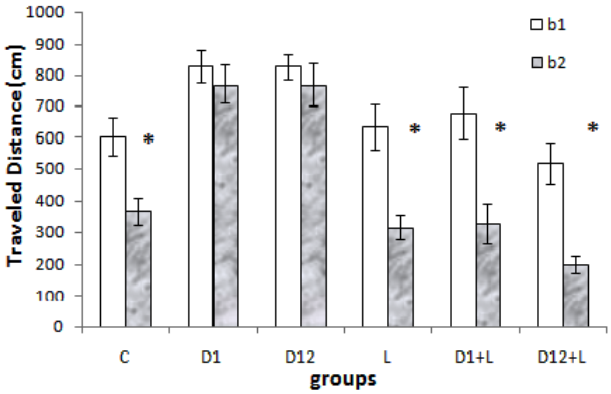

Figure 1. Effect of loganin on the traveled distance to find hidden platform in two consecutive blocks (b1 and b2). In the diabetic rats, loganin (40 mg/kg, po) were administered 60 min before the tests. Data represent means ± S.E.M. (n=7). *P<0.05, significantly different when compared with the b_1 same group.

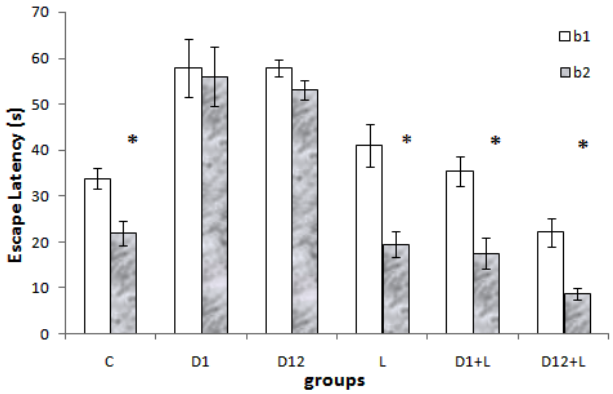

Figure 2. Effect of loganin on the escape latency to find hidden platform in two consecutive blocks (b1 and b2). In the diabetic rats, loganin (40 mg/kg, po) were administered 60 min before the tests. Data represent means ± S.E.M. (n=7). *P<0.05, significantly different when compared with the b_1 same group.

Probe test data were compared between groups. One-way ANOVA of the distance traveled in the target quadrant revealed significant differences (P<0.05) between groups. Loganin (40 mg/kg) increased the time and distance in the target quadrant after the platform was removed (Figures 3, 4). No treatments significantly changed swimming speed in the target quadrant (Figure 5). Loganin gavage 60 min before visual trial (visible platform) also showed no difference in escape latency and traveled distance to find the visible platform, compared to the control group (data are not shown).

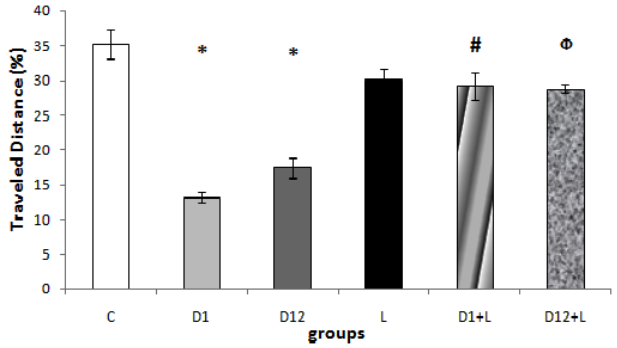

Figure 3. Effect of loganin on the traveled distance in trial sessions of the Morris water maze test. Data represent means± S.E.M. (n=7).
*P<0.05 significantly different when compared with the control group.
#P<0.05 significantly different when compared with the 1 week diabetic group.
ΦP<0.05 significantly different when compared with the 12 weeks diabetic group.

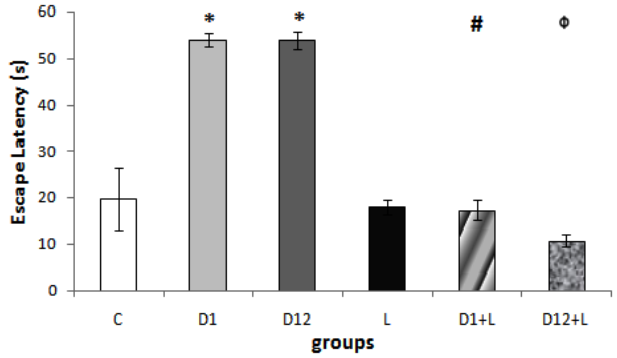

Figure 4. Effect of loganin on the escape latency in trial sessions of the Morris water maze test. Data represent means± S.E.M. (n=7).
*P<0.05 significantly different when compared with the control group.
#P<0.05 significantly different when compared with the 1 week diabetic group.
ΦP<0.05 significantly different when compared with the 12 weeks diabetic group.

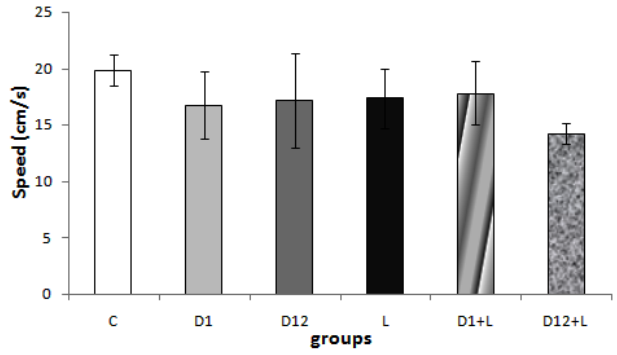

Figure 5. Effect of loganin on the swimming speed in trial sessions of the Morris water maze test. Data represent means± S.E.M. (n=7). Loganin did not change the swimming speed.

Discussion

In the present study, loganin was used for the first time in evaluating memory impairment of Streptozotocin-induced diabetes. Our results showed that diabetic (1, 12 weeks) rats had an increased escape latency time and traveled distance to find the hidden platform in a MWM task. Loganin administration with a dose of 40 mg/kg/po improved the acquisition and retrieval in diabetic rats. In addition, the results of the visible platform test suggest that loganin does not have an effect on mood or sensorimotor activity in rats; rather, it appears to shorten escape latency by enhancing memory due to the effect on brain areas involved in memory consolidation, such as the hippocampus.

Diabetes mellitus is a chronic disease characterized by widespread complications in CNS and PNS.[16] Learning and memory in animal model of diabetes are impaired.[17] Chronic hyperglycemia is associated with oxidative stress-induced neuronal and Schwann cell death and the reduction of neural size in the rat brain.[18,19] Also, learning deficits in diabetic rats have been associated with changes in hippocampal synaptic plasticity.[20]

As previously mentioned, loganin is an iridoid glycoside that is found in many traditional Chinese, Japan, and Korea herbs.[10] Loganin, is an active compound and was found to exhibit immune-regulating and anti-inflammatory activity.[21,22] It has hepato-protective, renal protective and neuroprotective effects.[8,23,24]

In addition Kwon and colleagues showed that loganin may have anti-amnesic activity in alleviating certain memory impairments observed in Alzheimer's disease.[10] Our recent study also showed that loganin improves passive avoidance learning in diabetic male rats.[11]

Although the exact mechanism of action of loganin on diabetic deficit of learning and memory is not clear, it may act by preventing oxidative stress, inhibiting acetyl cholinesterase activity in the hippocampus and inhibiting advanced glycation end product formation and NF-κB induced inflammation in the hepatic tissue.[10,25,26] Some other possible mechanisms of loganin action include inhibition of release of Cyt-c from mitochondria into cytoplasm of hippocampal pyramidal neurons and reduction of apoptosis levels and induction of neurogenesis and angiogenesis in the brain.[4,8,27]

Nevertheless, further studies are needed to increase the understanding of the physiological mechanisms leading to this memory enhancing effect of loganin.

Conclusion

In summary, our results suggested that loganin alleviates diabetes-induced memory impairments. Therefore, loganin could be used as an agent of treatment for the learning and memory-deficit cause by diabetes.

Acknowledgements

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Conflict of Interest

There is no conflict of interest in this study.

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