Chronic Oral Pelargonidin Alleviates Learning and Memory Disturbances in Streptozotocin Diabetic Rats

Mohammadali Mirshekar, Mehrdad Roghani*, Mohsen Khalili and Tourandokht Baluchnejadmojarad

Abstract

Diabetes mellitus is accompanied with disturbances in learning, memory, and cognitive skills in the humans and experimental animals. Due to the anti-diabetic and antioxidant activity of pelargonidin (PG), this research study was conducted to evaluate the efficacy of chronic oral PG on alleviating learning and memory disturbance in streptozotocin-diabetic rats. Male Wistar rats were divided into control, diabetic, PG-treated control and PG (single-and/or multiple-dose)-treated diabetic groups. PG was administered p.o. once at a dose of 10 mg/kg and/or multiple doses on alternate days for 8 weeks. For induction of diabetes, streptozotocin (STZ) was injected IP in a single dose of 60 mg/kg. For the evaluation of learning and memory, initial latency (IL) and step-through latency (STL) were determined at the end of study using a passive avoidance test. Meanwhile, spatial memory was assessed in a Y-maze task. It was found that the alternation score of the diabetic rats was lower than the control (p < 0.05) and that single dose PG-treated diabetic rats (p < 0.05) showed a higher alternation score in comparison with the diabetic group. Regarding initial latency, there was no significant difference among the groups. In addition, diabetic and single-dose PG-treated diabetic rats developed a significant impairment in retention and recall in the passive avoidance test (p < 0.01), as was evident by a lower STL. Furthermore, the retention and recall of multiple-dose PG-treated diabetic rats was significantly higher in comparison with diabetic rats (p < 0.05). Therefore, it can be concluded that single-dose oral PG may attenuate spatial memory in the Y maze paradigm and multiple-dose chronic PG could improve retention and recall capability in the passive avoidance test in STZ-diabetic rats.

Keywords: Pelargonidin; Learning and memory; Spatial memory; Cognition; Diabetic rat; Oral Pelargonidin.
Animal models have been widely used to study the pathophysiology of diabetes, particularly in the context of its cognitive and neurological complications. Diabetes mellitus, a chronic metabolic disorder characterized by hyperglycemia, affects not only the glucose metabolism but also various other systems, including the central nervous system. The hippocampus, a brain region crucial for memory function, has been shown to be particularly vulnerable to the effects of diabetes.

The hippocampus is known for its role in the consolidation of short-term into long-term memory, and it is affected by diabetes in multiple ways. Hyperglycemia, a hallmark of diabetes, can lead to oxidative stress, which in turn damages neural tissue and impairs memory function. Additionally, diabetes can affect neurotransmission, electrophysiological disorders, and alterations in hippocampal synaptic plasticity, including LTP (long-term potentiation) and LTD (long-term depression), which are fundamental mechanisms underlying learning and memory.

To study these effects, researchers have employed a variety of experimental models. One such model involves the use of diabetic rat models. Diabetes is induced through protocols like the administration of streptozotocin (STZ) to rats, which leads to the destruction of pancreatic beta cells and hyperglycemia. Other models include the use of T1D (type 1 diabetes) rat models and T2D (type 2 diabetes) models, which can be induced through dietary means or genetic modifications.

In these models, researchers often compare diabetic animals with control groups to assess the impact of diabetes on cognitive and neurological functions. Behavioral tests are commonly used to evaluate memory and learning abilities, such as the Y-maze task, the Morris water maze, and the passive avoidance test. These tests assess various aspects of memory, including spatial learning, recognition memory, and mnemonic consolidation.

Recent studies have focused on the role of antioxidants, such as flavonoids, in managing the cognitive and neurological complications of diabetes. Flavonoids are a class of natural compounds found in various plants and possess antioxidant and anti-inflammatory properties. They are known to protect neurons from oxidative stress and reduce inflammation, potentially improving cognitive function in diabetic patients.

In one study, the effects of flavonoids on memory function in diabetic rats were investigated. Rats were divided into four groups: normal, diabetic, diabetic treated with flavonoids, and diabetic treated with a control. Diabetic rats treated with flavonoids showed improved spatial memory performance compared to untreated diabetic rats, as measured by reduced escape latency in the Y-maze task.

In conclusion, animal models provide a valuable tool for understanding the mechanisms underlying the cognitive and neurological complications of diabetes and for testing potential therapeutic interventions. Further research is needed to translate these findings into clinical applications for the benefit of diabetic patients.
Results

General considerations

After 8 weeks, the weight of the vehicle-treated diabetic rats was found to have significantly decreased in comparison to the control rats (p < 0.01) and PG treatment (single and multiple doses) caused a less significant decrease in diabetic rats as compared to non-diabetics (p < 0.05-0.01). In this respect, PG administration for 8 weeks (multiple doses) was more effective in preventing weight loss than a singular dose. In addition, diabetic rats also had an elevated serum glucose level than those of control rats (p < 0.001) and treatment of diabetic rats with PG (single and multiple doses) caused a significant decrease in their serum glucose (p < 0.01-0.005) relative to vehicle-treated diabetics. Again, PG administration for 8 weeks was more effective in reducing serum glucose than a singular dose. Meanwhile, PG treatment in control rats did not produce any significant change with regards to serum glucose levels (Figure 1).

Alteration behavior in Y-maze

Figure 2 shows the results of the Y-maze task, in which short-term spatial memory performance can be examined. There was no significant difference in the total number of times the animal entered an arm. However, the alternation score of the diabetic rats was lower than that of the control ones at the end of 8 weeks (p < 0.05). Meanwhile, PG (single dose)-treated diabetic rats showed a higher alternation score in comparison with the untreated diabetic group (p < 0.05) at the end of the study. Meanwhile, PG treatment of control rats did not produce any significant change regarding this parameter.

To avoid the compounding effect of locomotor activity on memory processes in experimental groups, especially diabetics, the total number of arms entered was considered as an index of locomotion. In this respect, although the total number of entrances was less in diabetic animals, especially in untreated diabetic rats, this difference was not statistically significant when compared to the controls. In addition, there were also no significant differences among the groups (Figure 3).

Passive avoidance test

Figure 4 shows the performance of treated-control and diabetic rats in the passive avoidance paradigm as indicated by initial and step-through latencies. Regarding initial latency, there was no significant difference among the groups. In addition, diabetic and single dose PG-treated rats developed a significant impairment in retention and recall in the passive avoidance test (p < 0.01), as is evident by a lower STL. Furthermore, the retention and recall of multiple-dose PG-treated diabetics was higher in comparison with diabetic rats (p < 0.01). Meanwhile, PG treatment of control rats did not produce any significant change in this regard.

Discussion

The aim of this study was to determine whether chronic oral pelargonidin alleviates learning and memory disturbance in streptozotocin-diabetic rats. The results clearly demonstrated that long-term diabetes is accompanied with disturbances in animal performance in the passive avoidance and Y-maze task. In addition the results show that single-dose pelargonidin improves spatial memory performance and its administration in multiple doses could prevent retention and recall abnormality in diabetic rats.

Previous studies have reported that DM is associated with neurological complications in both the PNS and CNS. The impairment of learning and memory is also recognized as being a complication of diabetes (17). Cognitive deficits in DM can result from metabolic impairment or cerebral vascular complications (1). In animal models of DM, spatial learning impairments have also been reported. STZ-diabetic rats also display deficits in cognitive tasks, such as performance in the Morris water maze (4). Although the pathogenesis of these deficits is multi-factorial and controversial, there is strong evidence for the involvement of microvascular dysfunction and oxidative stress due to an excessive production of oxygen free radicals. In the latter case, as the mammalian hippocampus and cerebral cortex play a pivotal role in a diverse set of cognitive functions, such as novelty detection and memory, these areas are very vulnerable to oxidative damage in STZ-diabetic animals (18). In agreement with this idea, it has been reported that lipid peroxidation enhances in both regions of the brain, which in itself leads to a significant impairment in both motor and behavioral memory functions in diabetic animals (9). On the other hand, previous studies in rats have found that an induction of diabetes impairs long-term potentiation (LTP) and enhances long-term depression (LTD) induced by high frequency (HFS) and low frequency stimulations (LFS) respectively. This could indicate that diabetes acts on synaptic plasticity through mechanisms involved in metaplasticity. It is also known that LTP plays a crucial role in the consolidation of memory. In the present study, diabetic rats also showed learning impairment in the Y-maze task, which is an indicator for spontaneous alternation behavior. As was shown in Figure 4, the score of alternation behavior in diabetic rats was significantly lower than that of the control. Other tasks aimed at estimating the learning abilities of diabetic rats have previously been attempted. Such tasks request certain types of motivation, e.g., food, water, or swimming (6). Body weight, the intake of food or water, and the spontaneous motor activity of diabetic rats were significantly different from those of control rats. The Y-maze task is a moderate task that does not require such motivations. Our finding that the alternation score of diabetic rats was lower than that of control ones, is evidence of memory impairment in a diabetic animal model (19).

The beneficial effect of PG in this study may be attributed partly to its anti-hyperglycemic effect and to some extent to its attenuation of free-radical-mediated lipid peroxidation in those brain regions critical for animal performance in Y-maze and passive avoidance tests. Literature reports increased lipid peroxidation products and remarkable changes in free radical scavenger system enzymes in diabetic patients and different
Multiple-dose PG-treated diabetic animals. In addition each of both of these groups performed better in comparison to untreated diabetic rats. This could be attributed to the extent of stress felt by the animals receiving treatments through a gavage needle. It has been reported that chronic stress, as may be the case for multiple-dose PG, may improperly affect the cholinergic pathway originating from the cerebral cortex and in this way disturb some aspects of spatial memory (23, 24).

In conclusion, single-dose oral PG could attenuate the spatial memory in the Y-maze paradigm, and multiple-dose chronic PG could improve the retention and recall capability of STZ-diabetic rats in passive avoidance tests. Further studies are warranted to investigate the involved mechanisms in further detail.

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References