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ORIGINAL ARTICLE

Effect of coenzyme Q10 supplementation on diabetes induced memory deficits in rats

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Abstract

The main objective of current work was to determine the effects of low and high dose supplementation with coenzyme Q10 (CoQ10) on spatial learning and memory in rats with streptozotocin (STZ)-induced diabetes. Male Wistar rats (weighing 220 ± 10) were randomly divided into six groups: (i) Control (Con, $n = 8$); (ii) Control+ Low dose of CoQ10 (100 mg/kg) (CLD, $n = 10$); (iii) Control+ high dose of CoQ10 (600 mg/kg) (CHD, $n = 10$); (iv) Diabetic (D, n = 10); (v) Diabetic + Low dose of CoQ10 (100 mg/kg) (DLD, n = 10); (vi) Diabetic + high dose of CoQ10 (600 mg/kg) (DHD, n = 10). Diabetes was induced by a single intraperitoneal injection of 50 mg/kg STZ. CoQ10 was administered intragastrically by gavage once a day for 90 days. After 90 days, Morris water maze (MWM) task was used to evaluate the spatial learning and memory in rats. Diabetic animals showed a slower rate of acquisition with respect to the control animals [$F(1, 51) = 92.81$, $P < 0.0001$, two-way ANOVA]. High dose (but no low dose) supplementation with CoQ10 could attenuate deteriorative effect of diabetes on memory acquisition. Diabetic animals which received CoQ10 (600 mg/kg) show a considerable decrease in escape latency and traveled distance compared to diabetic animals ($p < 0.05$, two-way ANOVA,). The present study has shown that low dose supplementation with CoQ10 in diabetic rats failed to improve deficits in cognitive function but high dose supplementation with CoQ10 reversed diabetes-related declines in spatial learning.

Keywords Diabetes mellitus · Coenzyme Q10 (CoQ10) · Learning and memory · Wistar rats

Introduction

Diabetes mellitus (DM) is a group of heterogeneous metabolic disorders characterized by high blood sugar levels that result from insufficient and defective insulin secretion, insulin resistance, or both (Association 2016). There is a great deal of evidence that DM exerts harmful effects on the central nervous system. In addition to being a risk factor for cardiovascular and metabolic diseases, DM in humans has been implicated in cognitive decline and is a risk factor for the development of Alzheimer's disease and dementia (Ristow 2004; Brismar et al. 2007). Cognitive impairments also occur in rats with streptozotocin (STZ)-induced diabetes; these effects have been correlated with structural and functional deficits in brain areas such as the hippocampus and cerebral cortex (Baydas et al. 2003; Kucukatay et al. 2007; Tiwari et al. 2009). DM leading to oxidative damage of cellular components by rising free radical formation and decreasing antioxidant capacity (Bashan et al. 2009). Despite the recent advances in DM treatment and drug discovery, the prevalence of diabetes has risen dramatically.

Insulin resistance and/or impaired insulin secretion in DM resulting in hyperglycemia. Persistent hyperglycemia induces overproduction of reactive oxygen species (ROS), the formation of advanced glycation end products (AGEs), secretion of the pro-inflammatory cytokines and cellular death, and consequently diabetic complications (Volpe et al. 2018). Deficiency of antioxidant capacity affects numerous brain functions

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including memory (Fukui et al. 2001). Oxidative stress caused by free radical generation and lipid peroxidation plays a significant role in pathogenesis of cognitive decline (Berr et al. 2000).

Since oxidative damage leads to neurological problems, use of antioxidants in the prevention and treatment of various types of neurodegenerative disorders has increased (Aksenov et al. 2001; Ahmad et al. 2005; Niedzielska et al. 2016). Coenzyme Q10 (CoQ10) (Fig. 1), a vitamin-like lipophilic antioxidant compound has shown protective effects in animal models of Parkinson's and Alzheimer's disease (Beal 2004a). It has been reported that administration of CoQ10 improves learning in aged mice (McDonald et al. 2005). In the mitochondrial inner membrane, CoQ10 plays a major role in the electron transport chain by contributing to energy production via carrying electrons (Turunen et al. 2004).

CoQ10 is an essential cofactor of the electron transport chain in mitochondrial membranes and has a central role in the chemoosmotic production of adenosine triphosphate (ATP) (Ernster and Dallner 1995; Rauchova et al. 1995; Crane 2001). CoQ10 act as a mobile redox agent shuttling electrons and protons in the electron transport chain (Bhagavan and Chopra 2006). CoQ10 is also known as ubiquinone. CoQ10, in its reduced form (ubiquinol) acts like a chain breaking antioxidant, acts as a potent free radical scavenger in lipid membranes, and reduces oxidative stress in subjects with diabetes (Kwong et al. 2002; Somayajulu et al. 2005; Quinzii et al. 2010). Also, CoQ10 treatment ameliorates cognitive deficits by modulating mitochondrial functions in surgically induced menopause (Sandhir et al. 2014).

Based on above-mentioned complications and our knowledge, CoQ10 may has a therapeutic role via its antioxidant potential and modulation of energy generating properties in many conditions. Therefore, this study was undertaken to evaluate the post-treatment effects of CoQ10 therapy on cognitive dysfunction in rats with streptozotocin (STZ)-induced diabetes.

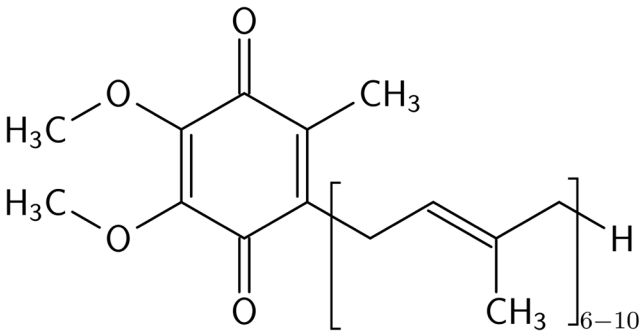

Fig. 1 The chemical formula of coenzyme Q10

Materials and methods

Ethics statement

All experimental procedures using rats were conducted in accordance with the animal care and use guidelines approved by the institutional ethics committee at Hamadan University of Medical Sciences and were performed in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Care et al. 1985). All efforts were made to minimize suffering. The operations that could cause pain and distress were performed in another room in the absence of other animals.

Animals and experimental design

Adult male Wistar rats weighing 220 ± 10 g obtained from Pasteur Institute of Tehran, Iran. The animals were housed in an air-conditioned room at 22 ± 2 °C with a 12-h light/dark cycle. The animals were kept in Plexiglas cages (40 × 25 × 15 cm) with 2–3 rats in each cage. Standard animal chow and water were freely available. After one week of adaptation, subjects were randomly divided into six groups: (i) Control (Con, $n = 8$); (ii) Control+ Low dose of CoQ10 (100 mg/kg) (CLD, $n = 10$); (iii) Control+ high dose of CoQ10 (600 mg/kg) (CHD, n = 10); (iv) Diabetic (D, n = 10); (v) Diabetic + Low dose of CoQ10 (100 mg/kg) (DLD, n = 10); (vi) Diabetic + high dose of CoQ10 (600 mg/kg) (DHD, n = 10). CoQ10 was administered intragastrically by gavage once a day for 3 months. After 90 days, Morris water maze (MWM) task was used to evaluate the spatial learning and memory in rats. Experimental design and schedule of MWM test is shown in Fig. 2.

Induction of diabetes

We monitored the blood glucose levels before STZ injection in all animals and in different experimental groups. Diabetes was induced by intraperitoneal injection of 50 mg/kg STZ (Sigma, St. Louis, MO, USA), which was dissolved in freshly prepared 0.05 M citrate buffer, pH 4.5, immediately before injection (Moradkhani et al. 2015). Injections were performed 90 days prior to the experiment in order to allow the development of a severe diabetic state. Blood glucose concentrations were monitored once per week. A minimum blood glucose level greater than 250 mg/dl and the presence of urinary glucose were used as criteria for identification of diabetic rats. Age-matched, vehicle-treated rats were used as controls.

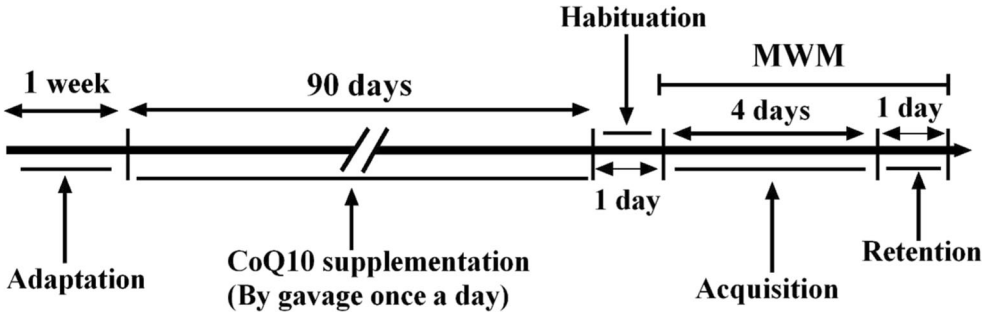

Fig. 2 Experimental design and schedule of MWM test. After one week of adaptation, CoQ10 was administered intragastrically by gavage once a day for 90 days. After 90 days, Morris water maze (MWM) task was used to evaluate the spatial learning and memory in rats

Morris water maze (MWM) task

Apparatus

MWM task is a hippocampal-dependent test of spatial learning for rodents (Karimi et al. 2017; Hajisoltani et al. 2019). The water maze apparatus consisted of a black-painted circular pool, (155 cm diameter, 60 cm height), filled to a depth of 35 cm with water (22 ± 1 °C). The pool was divided into four equal quadrants. A hidden platform (10 cm in diameter), made of Plexiglas, was located 2 cm under the water surface in the center of the eastern quadrant (target quadrant). A video-computer tracking system (CCD camera, Panasonic Inc., Japan) was used to record the rats' swim path for later analysis (EthoVision software XT7, Netherland). Large posters on the wall of the room served as visual cues.

Habituation

Twenty-four hours before starting the hidden platform training, rats were given a 60 s swim in the tank without platform for adaptation to the environment.

Hidden platform training

The training session was done according to the previous procedure conducted in our laboratory (Karimi et al. 2017, 2019). In summary, training session was consisted of one block of 4 trials per day for four consecutive days. Each trial was started by placing the animal in one of the four quadrants. Animals were allowed to swim the in pool during a period of 90 s to find the hidden platform that was kept in the middle of one of the four quadrants (Zarrinkalam et al. 2016; Karimi et al. 2019). If an animal did not find the platform within this period, it was manually guided to the platform by the investigator. The rats rested 10 min between the two consecutive trials.

The escape latency (i.e., time to reach the platform) and swimming distance were used to assess acquisition of the water maze task.

Retention and visual test

Twenty-four hours after the 4th session the spatial probe test (retention) was given. In the spatial probe test, the platform was removed, and rats were allowed to swim for 60 s before they were removed (Asadbegi et al. 2017). Animals were released in the water in a location that was exactly opposite from where the platform was placed. Behavior was recorded with a video tracking system. Escape latencies and swim speeds were recorded for subsequent analysis. Duration in target quadrant was used to assess how the rats remember the location of the platform (i.e. retention of memory) (Rezvani-Kamran et al. 2017). Thirty minutes after the probe trial, the platform was elevated above the water surface; covered by bright color aluminum foil, and placed in a different zone and rats were allowed to swim and find the visible platform during 60 s in order to test their visual ability (Zarrinkalam et al. 2018). All experiments were conducted between 10:00 and 12:00.

Statistical analysis

Data were presented as mean ± SEM and processed by commercially available software GraphPad Prism® 6.0. In behavioral study, the data of the training trials were analyzed using a two-way analysis of variance (ANOVA) with days as repeated measures factor and treatments as between subjects' factor. For statistical analyses of probe and visibility trial data, one way ANOVA was used. Two-way and one-way ANOVA were followed by post hoc analysis (Bonferroni and Tukey's tests, respectively).

Results

High dose supplementation with CoQ10 could attenuate deteriorative effect of diabetes on memory acquisition

All animals except diabetic animals learned the location of the hidden platform after 4 days of training. Escape latency

decreased significantly (control rats: F (3, 31) = 33.45, $P < 0.0001$; CLD rats: F (3, 35) = 7.771, $P = 0.0004$; CHD rats: F (3, 23) = 9.190, $P = 0.0003$; DLD rats: F (3, 24) = 5.783, $P = 0.0040$; DHD rats: F (3, 20) = 3.973, $P = 0.0226$, one-way ANOVA) after 4 days when compared to the first day (Fig. 3a). In diabetic animals escape latency decreased after 4 days of training but it was not significant (F (3, 20) = 1.780, $P = 0.1834$). Swimming distance also decreased during training in experimental group except diabetic animals ($p < 0.05$, (Fig. 2b)).

There were considerable differences between experimental groups with respect to escape latency (F (5, 153) = 36.17, $P < 0.0001$, two-way ANOVA) and swimming distance (F (5, 153) = 10.95, $P < 0.0001$, two-way ANOVA). Swimming speed was used to assess the motor activity of the rats. Swimming speed did not reveal remarkable change during training ($p > 0.05$, data not shown).

Diabetic animals showed a slower rate of acquisition with respect to the control animals [F (1, 51) = 92.81, $P < 0.0001$, two-way ANOVA, Fig. 2a]. Further analysis using Bonferroni's post-test disclosed a significant increase in the escape latency in the second, third and fourth day $P < 0.01$ in diabetic group compared to control one. In addition, Diabetic animals swam long distances at the fourth day of training compared to control one [F (1, 51) = 9.492, $P = 0.0033$, two-way ANOVA, Fig. 3b].

A two-way ANOVA showed that CoQ10 supplementation has significant influence on spatial learning (Fig. 3a). It is evident that high dose supplementation with CoQ10 attenuated deteriorative effect of diabetes on memory acquisition. Diabetic animals which received CoQ10 (600 mg/kg) show a considerable decrease in escape latency and traveled distance compared to diabetic animals ($p < 0.05$, two-way ANOVA, Fig. 3a and b).

High dose supplementation with CoQ10 improved diabetes induced reference memory impairment

To assess reference memory at the end of learning, a probe trial was conducted 24 h after the last training trial on day 5. During this test, the platform was removed and time spent in each quadrant of the MWM was recorded. As shown in Fig. 4, animals in DHD group spent more time in target zone (control rats: 16 ± 3 s, $n = 9$, CLD: 18 ± 2 s $n = 7$, CHD: 27 ± 5 s n = 7, D: 10 ± 2 s $n = 6$, DLD: 18 ± 3 s n = 7, DHD: 21 ± 4 s n = 6, F (5, 36) = 2.622, $P = 0.0403$, One-way ANOVA).

Escape latencies to find the visible platform during visual discrimination task were the same in all experimental groups (data not shown, $p > 0.05$, one-way ANOVA), indicating no visual impairment in the animals.

Discussion

The present study on the neuroprotective effect of CoQ10 on cognitive in diabetic male rats, has shown that: (i) DM significantly decelerated the rate of spatial memory acquisition and impaired its retention; (ii) Supplementation with the lower dose of CoQ10 (100 mg/kg/day) in diabetic rats for a period of 90 days failed to improve deficits in cognitive function; (iii) Supplementation with highest-dose of CoQ10 (600 mg/kg/day) can mitigate the adverse effects of STZ -induced diabetes on spatial learning and memory in rats. High dose supplementation with CoQ10 could attenuate deteriorative effect of diabetes on learning and memory in male rats. CoQ10 increased the rate of memory acquisition and its retention, which has been slowed in diabetic animals. Because female rats are less sensitive to STZ as an islet-cell toxin, most STZ-induced diabetic studies are conducted on male animals (Furman 2015).

Supplementation with a high dose of CoQ10 improved learning. Furthermore, the high dose of CoQ10 diet did not

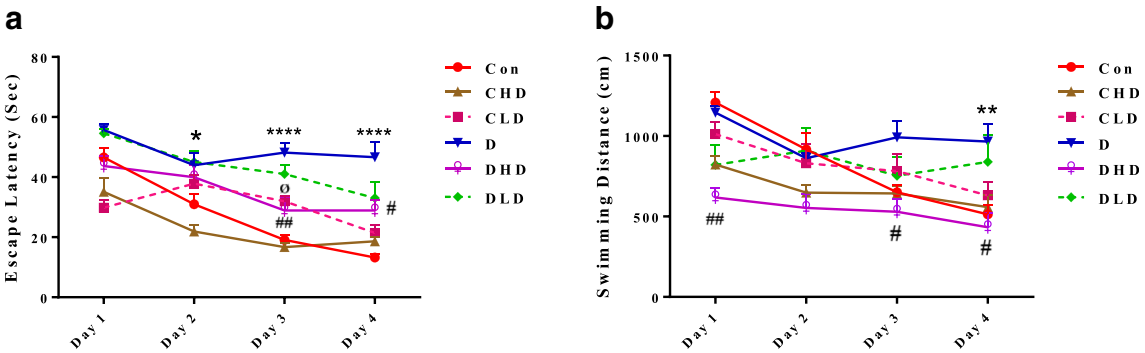

Fig. 3 CoQ10 could attenuate deteriorative effect of diabetes on memory acquisition. Diabetes increased the mean values of latency to find hidden platform (**a**) and swimming distance (**b**) vs. training days. Notice a significant decrease in latency and distances due to high dose supplementation with CoQ10 (600 mg/kg). Data presented as mean ± S.E.M. * $p < 0.05$, **** $p < 0.0001$ Diabetes vs. Control animals; # $p < 0.05$ D vs. DHD animals

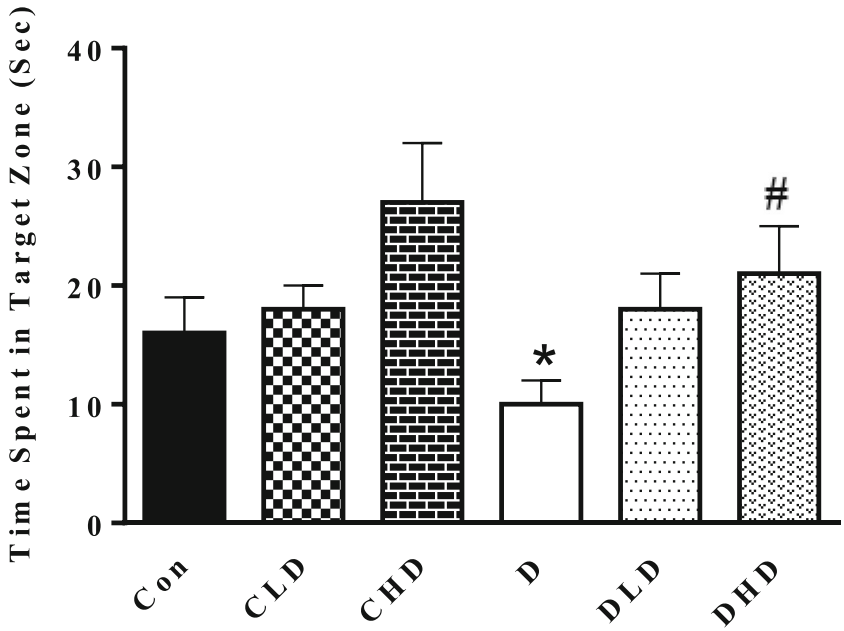

Fig. 4 Spatial reference memory was measured in a probe test. Animals in DHD group spent more time in target zone. Data presented as means ± S.E.M. * $p < 0.05$ vs. Control animals. # $p < 0.05$ vs. diabetic animals

affect swimming speed, suggesting that the spatial learning improvement is not caused by locomotion improvement. The results of the current work, suggest that the level of CoQ10 during diabetes is not sufficient. Low dose supplementation with CoQ10 in diabetic rats for a period of 90 days failed to improve deficits in cognitive function. It seems that low-CoQ10 diet cannot enhance the endogenous CoQ10 content in the brain and in brain mitochondria.

Impairment of learning and memory has been reported in both type 1 and type 2 diabetes (Saedi et al. 2016). Adverse effects of DM on cognitive system and memory disorders have been noticed for a long time (Brands et al. 2005; Vijayakumar et al. 2012; Saedi et al. 2016). In addition, DM is an important risk factor for subsequent Alzheimer's disease (Vijayakumar et al. 2012). When diabetes develops, the brain neurons may not get the large amount of glucose energy it needs especially for memory. In this condition, elevated level of blood glucose (hyperglycemia) and insulin's signal deficiency may provide a pro-oxidant milieu. Glucose reacts with oxygen and increases reactive oxygen species that induce the changes in cognitive function (Arvanitakis et al. 2006; Vijayakumar et al. 2012). In addition, oxidative stress cause mitochondrial dysfunction. Mitochondrial dysfunction is found to closely associate with DM and contributes to the pathogenesis of DM (Vijayakumar et al. 2012). Also, mitochondrial dysfunction can cause significant increase production of ROS (Shen and Pierce 2015) and triggers the neuronal degeneration and death.

CoQ10 is an essential cofactor of the electron transport chain in mitochondrial membranes. Moreover, CoQ10 acts as a potent free radical scavenger in lipid membranes (Crane 2001). It has been shown that oral administration of CoQ10 for 12-month in old rats increases brain mitochondrial concentrations and can exerts neuroprotective effects in the treatment of neurodegenerative diseases (Matthews et al. 1998).

High dose Administration of CoQ10 in rats increases endogenous CoQ10 content in the brain and in brain mitochondrial (Matthews et al. 1998; Beal 2004b). CoQ10 as an antioxidant affords protection against generation of free radicals as well as oxidative stress (Lenaz et al. 1999; Beal 2004b; Somayajulu et al. 2005) and can regenerate other potent antioxidants (Lass and Sohal 1998). It has been reported that CoQ10 up-regulates mitochondrial function (Beal et al. 1994) and improve cognitive functions (McDonald et al. 2005).

Tauheed Ishrat et al. (2006) demonstrated that CoQ10 may have a therapeutic importance in the treatment of Alzheimer's type dementia. They showed that supplementation with CoQ10 in STZ-infused rats reversed oxidative damage and a decline in the level of ATP in the hippocampus and cerebral cortex of intracerebroventricular STZ rat. In addition, they observed that CoQ10 modulates cognitive impairment against intracerebroventricular injection of streptozotocin in rats in Morris water maze and passive avoidance tests (Ishrat et al. 2006).

A significant decrease in cholineacetyltransferase (ChAT) activity and a concomitant increase in acetylcholinesterase (AChE) activity were observed in the hippocampus of ICV-STZ infused rats. And reported that CoQ10 supplementation significantly restored ChAT activity and attenuated AChE activity in ICV-STZ infused rats (Ishrat et al. 2006). It is clear that cholinergic transmission is required for learning and memory formation, and its modification is considered as one of the main causes of cognitive impairment in AD (Cummings 2000).

It has been proposed that, increased levels of plasma glucose, HbA1c and markers of oxidative stress are correlated with reduced blood CoQ10 levels (El-ghoroury et al. 2009; Zahedi et al. 2014). The safety of CoQ10 has been confirmed in a wide range of disorders and long-term use of CoQ10 had no serious adverse and known toxic effects, cannot be overdosed, and is generally well tolerated (Hosoe et al. 2007; Hidaka et al. 2008). In addition, it has been demonstrated that high dose supplementation with Coenzyme Q10 reverses age-related impairments in spatial learning and lowers protein oxidation (Shetty et al. 2013). Moreover, high-CoQ10 diet supplementation led to a decrease in oxidative damage in the brain and peripheral tissue mitochondria (Shetty et al. 2013).

Contrasting with the improvement effect of CoQ10 supplementation in our work, Nathalie et al. showed that prolonged intake of CoQ10 impairs cognitive functions in mice (Sumien et al. 2009). In their work, mice were fed a diet containing 0.68 mg/g (low dosage) or 2.6 mg/g (high dosage) CoQ10, starting at 4 month of age, and were tested for sensory, motor, and cognitive function at 7, 15, and 25 month of age. In contrast, the current study showed that high dose CoQ10 supplementation improve cognitive functions in rats. The contradictory observation between our work and Nathalie et al. may be due to differences in type of animal used (subjects), variations in study design, experiment conditions, duration and dosage of CoQ10 supplementation.

CoQ10 operates as a redox couple (ubiquinone/ ubiquinol), responsible for proton and electron transport. (Bhagavan and Chopra 2006; Littarru and Lambrechts 2011). CoQ10 is also known as ubiquinone. CoQ10, in its reduced form (ubiquinol) acts like a chain breaking antioxidant, acts as a potent free radical scavenger in lipid membranes, and reduces oxidative stress in subjects with diabetes (Kwong et al. 2002; Somayajulu et al. 2005; Quinzii et al. 2010).

Mitochondrial dysfunction due to oxidative stress contributes to the pathogenesis of DM. CoQ10 deficiency is often found among DM cases. CoQ10, as a strong antioxidant is supposed to eliminate excessive ROS and protect cells from oxidative damage. Therefore, external CoQ10 supplementation can potentially reduce oxidative stress by restoration of endogenous CoQ10 level, and ultimately lead to improvement of glucose control and cognitive functions. The presence of high concentrations of CoQ10 in all membranes provides a basis for antioxidant action either by direct reaction with radicals or by regeneration of tocopherol and ascorbate (Crane 2001).

Also it has been reported that CoQ10 acts as a potent gene regulator and affects expression of genes involved in cell signalling, metabolism, transport, transcription control, disease mutation, phosphorylation, and embryonal development in human (Groneberg et al. 2005) and some of the effects of exogenously CoQ10 administration may be due to this property.

Conclusion

Briefly, present findings indicate that STZ induced diabetes causes learning and memory deficits in rats probably by generating free radicals and depleting the ATP level by altering its synthesis. High dose supplementation with CoQ10 improves learning and memory deficits possibly by inhibiting the oxidative stress and improving the level of ATP.

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Compliance with ethical standards

Conflict of interest statement We confirm that the authors do not have any conflict of interest with this publication.

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