

RESEARCH ARTICLE

Learning and memory enhancing properties of coenzyme Q10 in amnesic albino Wistar rats

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ABSTRACT

Background: The brain is the important part of the nervous system in all vertebrates. The hippocampus in the humans serves as a major component of the brain. It is a part of the limbic system and plays major roles in acquiring long-term memory and spatial navigation. Among all dementia, Alzheimer's dementia is most common. The affected person experiences inability to learn new information, has nominal and comprehensive aphasia, apraxia, agnosia, and impairment in execution of functioning. Coenzyme Q10 (Co-Q10) is a lipophilic molecule found, especially in high concentration in the mitochondrial inner membrane. The importance of Co-Q10 in mitochondrial function and its role as an antioxidant have led to therapeutic applications and clinical trials in degenerative diseases. **Aim and Objective:** This study aims to evaluate the learning and memory enhancing properties of Co-Q10 in albino Wistar rats. **Materials and Methods:** Eighteen healthy rats were selected for the study, which were divided into three groups. Scopolamine was used as amnesic agent, elevated plus maze (EPM), pole climbing test, and novel object recognition (NOR) tests were used for testing the learning and memory processes. **Results:** Co-Q10 at higher doses (400 mg/kg) showed significant activity in EPM, pole climbing test, and NOR test for assessing the learning and memory skills when compared to the control group. **Conclusion:** The present study results revealed that Co-Q10 high doses potentiated the process of learning and memory skills when tested using EPM, pole climbing test, and NOR test which are considered as standard paradigms of learning and memory screening models. The results of this study need to be further evaluated by comprehensive experimental studies and further validated by clinical trials.

KEY WORDS: Coenzyme Q10; Elevated Plus Maze; Learning and Memory; Novel Object Recognition; Pole Climbing Test; Scopolamine

ABBREVIATIONS: Alzheimer's dementia, Co-Q10: Coenzyme Q10, EPM: Elevated Plus Maze, NOR: Novel Object Recognition


INTRODUCTION

It has been stated that 47 million people around the globe were getting affected by dementia and making it 135 million people across the world by 2050.^[1]

Dementia is progressive and irreversible decline in cognition best characterized as a syndrome rather than a particular disease.

Dementia is a neurodegenerative disease which has variable prognosis. There is acquired deterioration of cognitive abilities and decline in performance which affects the person's independence in doing activities of daily living.^[2]

There are several types of neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease (AD), and Huntington disease, wherein dementia is associated with AD, vascular dementia, and prion disease. Among all dementia,

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Alzheimer's dementia is most common. The affected person experiences inability to learn new information, has nominal and comprehensive aphasia, apraxia, agnosia, and impairment in execution of functioning.^[3]

The production of free radicals requires more amount of energy and supply of oxygen to the brain cells. The process of high energy and oxygen requirement makes brain cells susceptible for oxidative damage and stress leading to the onset of age related neurodegenerative disorders. Several study reports suggests that brain cells are sensitive to reactive oxygen species (ROS). This neuronal cell death leads to neurodegenerative diseases.^[4]

The pathophysiology of Alzheimer's dementia involves microglial activation, excessive release of pro-inflammatory cytokines, formation of neurofibrillary tangles due to accumulation of Tau which is a microtubule associated protein, also disrupted mitochondrial function accompanied by overproduction of ROS, and oxidized molecules.

The current therapy for Alzheimer's includes cholinesterase inhibitors, anticholinergic, atypical antipsychotics, and anti-amyloid therapy which remains still unfavorable in slowing down completely the AD progression and also has many untoward effects. Therefore, new treatment strategies are still necessary to improve AD patient care.^[5]

The main cause for pro-inflammation is excessive production of ROS that contributes directly and indirectly to the pathogenesis of AD. Mitochondrial dysfunction has been associated with the onset and/or development of neurodegenerative diseases.

Few preclinical studies have shown that coenzyme Q10 (Co-Q10) may protect against neuronal damage caused by ischemia, atherosclerosis, and toxic injury.^[6] Also that during process of aging and aging related diseases, there is a significant reduction in the rate of Co-Q10 biosynthesis. In clinical studies, patients with Parkinson's disease reported lower levels of CoQ10.^[7] Furthermore, there are many studies which have shown direct association with longevity and mitochondrial levels of Co-Q10.

Co-Q10 (CoQ10; 2, 3-dimethoxy-5-methyl-6-decaprenyl benzoquinone), or ubiquinone, is a lipid-soluble quinone compound containing a redox active quinone ring and hydrophobic tail.^[8]

Co-Q10 being a component in the electron transport chain during mitochondrial oxidative respiration, generates adenosine triphosphate. The major contributors to cognitive decline and the pathogenesis of a number of neurodegenerative diseases are mitochondrial dysfunction and oxidative stress.^[9] It has been postulated that improved mitochondrial functioning leads to reductions in oxidative damage and thus reductions in age-related cognitive dysfunction.^[10]

Few animal studies have also proved that Co-Q10 supplementation helps in reduction of oxidative damage, also improves mitochondrial function, and reduces Adenosine triphosphate depletion.

Ubiquinol-10 will be the main antioxidant to react if the plasma is exposed to any of the oxidants despite having in low concentrations. Co-Q10 also maintains membrane stability and can modulate neuronal signaling, genetic expression, and maintenance of cell growth; hence, Co-Q10 may prove beneficial in prevention and treatment of neurodegenerative diseases.^[11]

Therefore, these research findings suggest that Co-Q10 has the potential to play a therapeutic role in the treatment of dementia and to explore this potential the present study was conducted.

MATERIALS AND METHODS

Ethics Committee Approval

An *in vivo* experimental study was conducted after taking the approval from the Institutional Animal Ethics Committee SDMIAEC: 001:2019. The study has been conducted in the Department of pharmacology, SDM College of Medical Sciences and Hospital, Dharwad, and the experiment was conducted in accordance with the CPCSEA guidelines.

Equipment's Used

Feeding tube, digital weighing machine, elevated plus maze (EPM) apparatus, and pole climbing apparatus were used.

Chemicals Used

Normal saline, Co-Q10 (Perennial Lifesciences Pvt. Ltd., New Delhi), scopolamine injection vials (Nicholas Piramal India Ltd., Mumbai), and carboxymethyl cellulose as a vehicle were used.

Selection of the Animal

Eighteen albino Wistar healthy rats were selected for the study. The animals weighed 150 g–250 g and the animals were kept in the sterile room with normal room temperature. Each rat was placed in a separate cage and given free access to standard food and water.

Animal Grouping and Dosing

Eighteen healthy Wistar rats were selected and divided into three groups (six rats in each group) and trained for the learning and memory screening models.

The animals will be trained for 7 days and drugs will be administered orally using feeding tube for a period of 10

days. After the dosing of test drug, animals will be screened using the same models. Rats were injected with 3 mg/kg scopolamine intraperitoneally for elicitation of amnesia 45 min before subjecting to the behavioral tests [Table 1].

Statistical Data Analysis

The results were tabulated and analyzed using SPSS 21 software. One-way ANOVA followed by *post hoc* Tukey's test is applied and the statistical value was set to $P > 0.05$ at a confidence interval of 95%. The results expressed are in mean \pm standard error.

Animal Screening Models for Learning and Memory

EPM

The EPM was employed as the exteroceptive behavioral model (wherein the stimulus exists outside the body) to evaluate the learning and memory in rats. The apparatus consisted of two covered arms and two open arms, the arms extended from a central platform and the maze was elevated to a height from the floor. On the 1st day of training, each rat was placed at the end of open arm, facing away from the central platform. Transfer latency (TL) was noted as the time taken by the rat to move into any one of the covered arms with all its four legs. TL was recorded on the 1st day. If the rat fails to enter into one of the covered arms within 90 s, then it was gently pushed in any one of the one of the covered arms and the TL was recorded as 90 s. The rat was set free to explore the maze for at least 10 s. Memory retention was examined again after 24 h of test trial.^[12]

Pole climbing test

Cook's Pole Climbing Apparatus is mainly used to study the response to conditioned stimuli during learning and retention of its memory. The apparatus is a completely closed and soundproof having a chamber (30 cm \times 30 cm \times 30 cm) with the grid floor in it. The grid floor is made up of stainless steel rods to which 6 mA scrambled shock is delivered. A pole, measuring 3 cm in diameter, was placed vertically suspended inside the chamber which is connected to the upper part of the chamber. The rat was placed inside the chamber and set free to explore the chamber for 45 s. The buzzer signal known as conditioned stimulus was turned on and electric shock, that is, unconditioned stimulus was delivered after 45 s. Animal will eventually learn to connect the buzzer with the foot shock and try to avoid the foot shock by climbing the suspended pole after the buzzer signal was turned on. Avoidance to the foot shock response was defined as climbing reaction time

<10 s only; and escape response was climbing the pole after applying reaction time >10 s.

Each rat was subjected to five trials on day 1, and after 24 h, rat was subjected to relearning trials (2nd day around three trials and on 3rd day, rats were subjected only to one trial) and time is recorded to check the retention of conditioned avoidance response (CAR) and escape response. Animals who successfully demonstrated at least one escape response either on day 1 or 2 were selected for the study.^[13]

Novel object recognition (NOR) test

NOR test is a widely accepted screening tool for assessing cognitive status of rodents. NOR test can be completed quickly with a single learning phase. The principle NOR is duly based on spontaneous behavior of the animals, which does not require any reward or punishment. When rats are exposed to both familiar and novel object at a time, it is noted that rats will likely to spend more time exploring the novel than the familiar object. This apparent preference toward the novel object states that a representation of the familiar object exists in memory and it forms the main principle of the NOR task. This eliminates confusion in the interpretation of results which are derived from behavioral modifications that could potentially influence the memory performance and that are connected with drug-related changes to pain perception, stress susceptibility, thermoregulation, and anxiety.^[14]

RESULTS

EPM

The rats were subjected to various learning and memory screening models after administering the drugs for 10 days. The TL of the rats in all three groups was reduced on the test day. Both control and II low-dose 300 mg/kg group not showed any statistical significance in TL period. Group III high-dose 400 mg/kg showed significant reduction in TL period when compared with control Group I and low-dose test Group II [Table 2].

Pole Climbing Test

Cook's Pole Climbing Apparatus is mainly used to study the responses to conditioned stimuli during learning and retention of the memory. The CAR and escape response

Table 1: Animal grouping

Groups	Number
Control	6
Coenzyme Q – 300 mg/kg	6
Coenzyme Q – 400 mg/kg	6

Table 2: EPM (time in s)

Group	Results
Control	47.69 \pm 2.77
Co-Q10 – 300 mg/kg	44.14 \pm 2.16
Co-Q10 – 400 mg/kg	35.28 \pm 1.52 ^{a, b}

Values are mean \pm SEM. *Values are statistically significant with control at $P < 0.05$ using one-way ANOVA followed by Tukey's test. ^a $P < 0.05$ versus control ^b $P < 0.05$ versus Group II. Co-Q10: Coenzyme Q10. EPM: Elevated plus maze

results were statistically significant in Group III high-dose 400 mg/kg compared to control and II low-dose 300 mg/kg group. Low-dose group did not show any significant result when compared to control group [Table 3].

NOR Test

NOR is a prototype for investigating the cognitive state of the rats. The results of this test were expressed in two measures.

1. Time spent in exploring familiar or novel object
2. Total time spent in exploring novel and familiar object.

The time spent by the control group rats was almost equal in exploring familiar and novel object, whereas test Groups II and III spent less time with the familiar object (22.16 s and 17.33 s) more time for exploration of novel object (33.83 s and 24.5 s) compared to Group I [Table 4].

DISCUSSION

The present study was carried out to assess the effects of Co-Q10 on learning and memory tasks in rats with the help of different learning and memory tools such as EPM, pole climbing test, and NOR test. The equilibrium of cholinergic system is very important for learning and retention of memory. A muscarinic receptor antagonist like scopolamine can affect the cognitive functions such as learning and memory by interrupting with the integrity of cholinergic system through competitively blocking the receptors.^[15]

Several other study reports stated that oxidative stress, protein and lipid peroxidation, has a significant role in impairment of learning and memory tasks.^[16] As it is known that increase in the oxidative stress can lead to impairment of learning and memory ability of an individual with other pathological factors. Co-Q10, which is well noted for its antioxidant property, may be proved beneficial in various diseases mainly affecting the learning and memory ability.^[17] The EPM test is

mainly used to test the active memory. As a normal behavior in rats, it is observed that they generally avoid bright and open compartment and opt for closed and dark compartment. When rat is placed on well-illuminated compartment, connected with a closed compartment, rats quickly move into the closed compartment.^[18] In the EPM model, though the TL of the rats in all three groups was reduced on the test day, Group III high-dose 400 mg/kg exhibited significant results ($P < 0.05$) when compared with control and low-dose test group. Cook's Pole Climbing Apparatus used to determine the behavioral activity, mainly based on the ability of nootropic drugs to avoid the conditioned response. Group III high-dose 400 mg/kg showed the statistically significant results ($P < 0.05$) CAR and escape response compared to control and II low-dose 300 mg/kg group. No statistically significant results were noted between low-dose test drug II and control group I.

NOR test is an important tool in assessing cognitive status of rodents. The results of this test are assessed by two different measures, that is, time spent for exploring familiar or novel object and total exploration time of novel and familiar object. Both the test Groups II and III, rats depleted more time in exploration of novel entity than familiar entity compared to Group I. Group I rats took similar time in exploration of both familiar and novel object.

The present study results can be compared to the other research studies done using similar platforms of learning and memory models. A study by McDonald *et al.* assessed the beneficial effects of Co-Q10 administration on cognitive function in aged mice, researchers observed that Co-Q10 treated mice usually escaped from the electric shock by rapidly shifting to the correct arm of T maze when compared to control which suggests that Co-Q10 may help improve cognitive impairments associated with the aging process.^[19] The study done by Sandhir *et al.* stated that rats treated with Co-Q10 were more likely to locate the underneath hidden platform in the morris water maze test, suggesting an improvement in cognitive function. Moreover, on doing the brain assay of the mice, they found that Co-Q10 supplementation was able to reverse cognitive impairment by improving mitochondrial electron transport and decreasing levels of free radicals.^[20] The above-stated study results draw a conclusion which is similar to the present study that Co-Q10 is effective in enhancing learning and memory in experimental animals.

Strength and Limitation of the Study

The present study results showed that Co-Q10 has a potential effect in learning and memory process and it can be considered for a remedial role in the treatment of dementia. The study, however, is not destitute of limitations. The major limitations are the study duration. Since cognitive enhancing drugs are administered for a prolonged period, the safety and efficacy of these drugs for long-term usage becomes a major determinant in the long-term use of newer agents.

Table 3: Pole climbing test (escape response in s)

Group	Results
Control	25.60±0.33
Co-Q10 – 300 mg/kg	23.16±0.40 ^a
Co-Q10 – 400 mg/kg	19.29±0.44 ^{a, b}

Values are mean±SEM (n=6). Values are statistically significant at * $P < 0.05$ using one-way ANOVA followed by Tukey's test. ^a $P < 0.05$ versus control
^b $P < 0.05$ versus Group II. Co-Q10: Coenzyme Q10

Table 4: NOR test

Group I			Group II			Group III		
FOET	NOET	TET	FOET	NOET	TET	FOET	NOET	TET
26.83	27.66	54.83	22.16	33.83	51.16	17.33	24.5	41.66

*Time in seconds – FOET: Familiar object exploration time,
NOET: Familiar object exploration time, TOE: Total exploration time.
NOR: Novel object recognition

CONCLUSION

The present study results revealed that Co-Q10 high doses potentiated the process of learning and memory skills when tested using EPM, pole climbing test, and novel object recognition test which are considered as standard paradigms of learning and memory screening models. However, similar studies should be done to look over for other reputed properties by which Co-Q10 may exert its beneficial role in learning and memory and revalidated by clinical trials.

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