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RESEARCH ARTICLE

Effect of coenzyme Q10 on depression paradigms in male Wistar rats and Swiss albino mice

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ABSTRACT

Background: Depression is a major public health concern. Inflammation and oxidative stress have emerged as major contributors to the neuroprogression of depression. There is evidence that there are reduced antioxidant (AOX) defenses in depression. Hence, this study is aimed at evaluating the antidepressant activity of coenzyme Q10 (CoQ10) which is an AOX. **Aims and Objective:** The aim and objective of the study is to evaluate the effect of CoQ10 on depression using behavioral models of depression namely forced swim test (FST) in male Wistar rats and tail suspension test (TST) in male Swiss albino mice. **Materials and Methods:** The antidepressant activity of CoQ10 was evaluated using two behavioral models of depression namely FST and TST in male Wistar rats and male Swiss albino mice, respectively. The standard antidepressant used was amitriptyline. **Results:** There was statistically significant difference in the duration of immobility with amitriptyline and CoQ10 treated groups, when compared to that of control group in both behavioral models of depression. It was also found that there was no statistically significant difference between amitriptyline and CoQ10, indicating comparable antidepressant activity. **Conclusion:** Based on the findings of this study, it can be concluded that, CoQ10 has significant antidepressant activity. Taking into consideration the fact that, inflammation and oxidative stress have a major role to play in the pathophysiology of depression, CoQ10 appears to be a promising agent for the treatment of depression.

KEY WORDS: Coenzyme Q10; Depression; Amitriptyline

INTRODUCTION

Depression is a major public health concern affecting about 350 million people across the globe. It is a disabling disease causing a person to function ineffectively both at home as well as in the workplace. The worst consequence of depression is suicide. These suicides translate into loss of 1 million lives every year which is equivalent to about 3000 deaths every day. Hence, there is an urgent need to curb depression and treat it effectively.[1]

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Unfortunately, though antidepressants are so widely prescribed, it has been found that 30% of depressed patients do not respond at all and the 70% of patients who are left over do not achieve complete remission. Besides, antidepressants are known to have a variety of adverse effects. Hence, there arises a need for exploring the antidepressant effects of agents acting through mechanisms which differ from those of the existing drugs.[2]

Inflammation and oxidative stress have emerged as major contributors to the neuroprogression of major depressive disorder (MDD). Neuroprogression is a process of progressive neurodegeneration which involves various pathological

processes, namely, apoptosis, reduced neurogenesis, reduced neuronal plasticity, and increased autoimmune responses. All these can be recognized at clinical, structural and biochemical levels in MDD. Patients with the disorder have shown increased inflammatory and oxidative stress biomarkers. "Oxidative stress is the result of the biological imbalance between reactive oxygen species (ROS) and antioxidants (AOXs) which subsequently would lead to the alteration of biomolecules and the loss of control of the intracellular redox-related signaling pathways."[3]

About two decades have been spent in researching the role of altered immune regulation in the etiology and course of depression. To highlight the role of these pathophysiological factors various theories with different terminologies have been put forward, for instance, the monocyte-T-lymphocyte hypothesis of depression, the cytokine hypothesis of depression and the inflammatory hypothesis of depression. The most recent terminology has been termed as the immuno-inflammation and oxidative and nitrosativa stress model of depression.[4]

Evidence also points out that, there are reduced AOX defenses in depression as indicated by lowered levels of key AOXs and AOX enzymes which include reduced levels of coenzyme Q10 (CoQ10), serum zinc, vitamin E, glutathione and glutathione peroxidase (GPX). CoQ10 offers resistance to oxidative and nitrosative stress (O and NS) induced damage to mitochondria and is a key player in the electron transport chain (ETC) that is required in the generation of adenosine triphosphate (ATP).[5] Hence, this study aims to evaluate the effect of CoQ10 on depression.

Objective

The objective of the study is to evaluate the effect of CoQ10 on depression using behavioral models of depression namely forced swim test (FST) in male Wistar rats and tail suspension test (TST) in male Swiss albino mice.

MATERIALS AND METHODS

Animals

Adult male Wistar rats weighing 150±25 g and adult male Swiss albino mice weighing 25±5 g were obtained from the Central Animal House of the Institution. They were acclimatized to 12:12 h light-dark cycle for 10 days before the starting of experimentation. They were maintained on standard chow pellets and water *ad libitum*. The study was approved by the Institutional Animal Ethics Committee constituted as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals, New Delhi.

For the FST, rats were divided into three groups of six animals each, amounting to a total of 18 animals. Control group received 0.5 ml of 1% gum acacia suspension. The standard group received amitriptyline in 1% gum acacia suspension. Test group received CoQ10 in 1% gum acacia suspension. All drugs were administered orally.

For the TST, mice were divided into three groups of six animals each, amounting to a total of 18 animals. Control group received 0.5 ml of 1% gum acacia suspension. Standard group received amitriptyline in 1% gum acacia suspension. Test group received CoQ10 in 1% gum acacia suspension. All drugs were administered orally.

Drugs and Doses

Considering the therapeutic doses of amitriptyline and CoQ10, equivalent doses for rats and mice were calculated with the help of converting table devised by Paget and Barnes.[6,7] Amitriptyline tablets manufactured by Inta's Pharmaceutics Ltd. and CoQ10 tablets manufactured by Elder Pharmaceuticals Ltd. were used in this study. Standard groups received amitriptyline (27 mg/kg body weight of rat and 39 mg/kg body weight of mice) equivalent to 300 mg of clinical dose orally.[6,7] Test groups received CoQ10 (18 mg/kg body weight of rat and 26 mg/kg body weight of mice) equivalent to 200 mg of clinical dose orally.[6,7] Antidepressant activity was assessed with the help of following paradigms.

FST

Principle

When a rat is forced to swim in an environment from which there is no escape, after an initial period of vigorous activity, it ultimately ceases to move altogether making only those movements necessary to keep its head above the water. This immobility indicates a state of despair from which escape is not possible, and the rat resigns itself to the experimental conditions. Such behavior is supposed to be equivalent to clinical depression. Therefore, drugs that decrease this immobility would have to possess antidepressant activity. Rats are preferred over mice in this test because the rat version is said to be more selective for this experiment, i.e., fewer false positives.[8-10]

Procedure

A vertical plexiglass cylinder measuring 21 cm in height, 12 cm in diameter, containing a 15 cm water column maintained at 25°C was used. FST has two swim sessions. The first session is called "Pre-test" which consists of 15 min session conducted before drug administration. This prior habituation session ensures a stable and high duration of immobility during the 6 min test session, usually performed 24 h later. Adult male Wistar rats weighing 150 ± 25g were subjected to swimming for 15 min. The immobility time was measured only when the rat ceased to struggle and remained floating motionless in the water making only those movements necessary to keep its

head above the water. The rats were removed, dried, and the first dose of the drug was given orally, and they were returned to their cages, where food and water were provided. The water in the cylinder was changed for every rat before subjecting it to swimming. These rats were subjected to the test session on the next day 24 h after the pretest session.

On the day of the test session, the rats were given the second dose of the drug orally - 4 h before test and third dose of drug orally - 1 h before test. Then, they were subjected to FST and the duration of immobility (in seconds) was recorded for 6 min.[8-10]

TST

Principle

Basic principle of this test is the behavioral despair paradigm. When mice are hung by their tails, they are subjected to inescapable stress. After an initial period of vigorous activity, the mice attain immobility. Any drug that decreases the time spent in immobility is supposed to possess antidepressant activity.[8,9]

Procedure

It consists of 2 metallic rods 35 cm apart connected with a horizontal rod to suspend a nylon thread from its center. A mouse pretreated with a drug or vehicle was suspended from the hook hanging at the center of the horizontal rod by an adhesive tape stuck 1 cm proximal to the tail tip. The mouse was said to be immobile when it stopped moving and hung motionless. Immobility time in seconds was recorded over a period of 6 min.[8,9]

Statistical Analysis

The results are represented here are the means ± standard error of mean of 6 mice/6 rats in each group. The results were analyzed using one-way analysis of variance followed by Bonferroni's multiple comparison test. $P < 0.05$ was considered statistically significant.[11] All data were analyzed using the statistical software GraphPad Prism (Graph Pad Software, Inc. La Jolla, California, USA).

RESULTS

In this study, CoQ10 was evaluated for its antidepressant activity using two animal models of depression namely FST in rats and TST in mice. Amitriptyline as a standard antidepressant was used for comparison.

FST

The duration of immobility in seconds was noted over a period of 6 min. The mean duration of immobility time in the control group was 156 ± 1.5 while it was 74 ± 1.6 and 56 ± 1.9 in the amitriptyline and CoQ10groups, respectively. There was statistically significant difference ($P < 0.0001$) in the duration of immobility in amitriptyline and CoQ10 treated groups when compared to that of the control group. There was comparable antidepressant activity between amitriptyline and CoQ10 (Table 1 and Graph 1).

TST

The duration of immobility in seconds was noted over a period of 6 min. The mean duration of immobility in the control group was 190 ± 3.2 while it was 82 ± 2 and 80 ± 1.8 in the amitriptyline and CoQ10 groups, respectively. There was statistically significant difference ($P < 0.0001$) in the duration of immobility with amitriptyline and CoQ10 treated groups when compared to that of control groups. There was comparable antidepressant activity between amitriptyline and CoQ10 (Table 2 and Graph 2).

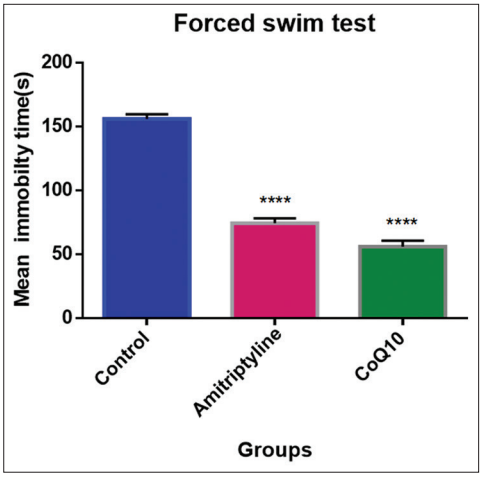
DISCUSSION

In this study, CoQ10 was evaluated for its antidepressant activity using two animal models of depression, namely, FST in rats and TST in mice. The findings of this study indicate that CoQ10 has significant antidepressant activity comparable to that of amitriptyline.

Table 1: Effect of various treatments on duration of immobility in FST

Groups	Control	Amitriptyline	CoQ10	ANOVA
Mean±SEM	156±1.5	74±1.6****	56±1.9****	*P*<0.0001

Post-hoc analysis by Bonferroni's test: ****$P<0.0001$;
SEM: Standard error of mean, ANOVA: One-way analysis of variance, FST: Forced swim test, CoQ10: Coenzyme Q10

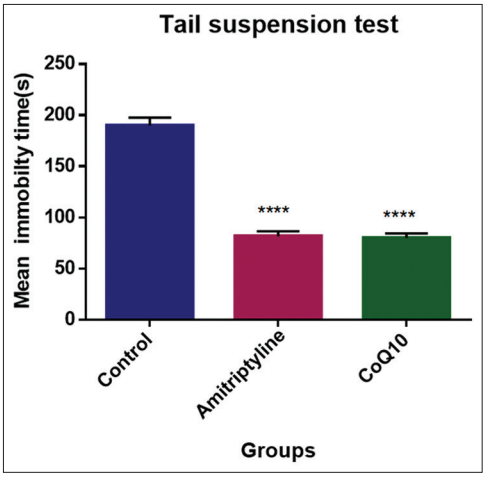


Graph 1: Effect of various treatments on duration of immobility in forced swim test. Data has been expressed as mean ± standard error of mean. ANOVA followed by Bonferroni's multiple comparison test. ****$P < 0.0001$

Table 2: Effect of various treatments on duration of immobility in TST

Groups	Control	Amitriptyline	CoQ10	ANOVA
Mean±SEM	190±3.2	82±2.0****	80±1.8****	P<0.0001

Post-hoc analysis by bonferroni's test: ****P<0.0001;
SEM: Standard error of mean, ANOVA: One-way analysis of variance. TST: Tail suspension test, CoQ10: Coenzyme Q10



Graph 2: Effect of various treatments on duration of immobility in tail suspension test. Data has been expressed as mean ± standard error of mean. ANOVA followed by Bonferroni's multiple comparison tests. ****P < 0.0001

There are a few fundamental differences between FST and TST, even though both the paradigms used for antidepressant activity are based on the principle of behavioral despair. Main differences between the FST and TST are: (1) The immersion, which is necessary to produce the "behavioral despair," may induce hypothermia in animals. This is avoided in TST, (2) the recording of an objective measure in the TST might be more precise than the appreciation of immobility in the FST, i.e., there is a clear differentiation between the immobile and mobile phases in TST, (3) TST is more sensitive to lower doses of the drug and provides a clearer dose-effect relationship. FST and TST were used to study the antidepressant activity because both these tests are easy to perform, rapid and require a minimum of apparatus.[8,9,12]

New insights into the pathophysiology of depression have identified increased levels of proinflammatory cytokines, activation of cell-mediated immune, activation of (O and NS) pathways, decreased (AOX) defences, mitochondrial disorders, and neuroprogression (progressive neurodegeneration, apoptosis, and reduced neurogenesis and neuronal plasticity) as contributors to the pathogenesis of depression.[5]

Production of energy in the form of ATP is the vital task of the mitochondrion. ATP is generated using the ETC. The ETC is required for oxidative phosphorylation which provides the cell with the most efficient energy outcome in terms of ATP production. ATP production occurs through transport of high-energy electrons through the mitochondrial ETC. This step also serves as a source of ROS production.[13]

Although oxygen is essential for the optimum functioning of neurons, some of its products have proven to be neurotoxic. Oxidative stress is defined as "An imbalance between oxidants and anti-oxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage." ROS cause cellular dysfunction by lipid peroxidation, oxidation of protein backbone and side chain, breakage of DNA strands and modification of purine and pyrimidine bases. Cells in the brain are highly susceptible to the adverse effects of oxidative stress because of various reasons like abundant peroxidizable substrates being generated in the brain, high metabolic rate of the brain and modest (scanty) AOX levels in the brain.[3,14,15]

CoQ10 or ubiquinone is a lipid-soluble benzoquinone with a side-chain of 10 isoprenoid units endogenously synthesized from phenylalanine and mevalonic acid. The biological significance arises from the fact that it plays a role in energy transduction in the mitochondria. It accepts electrons from several donors and transfers them to the cytochrome complex system. Electron transport generates a proton gradient across the mitochondrial membrane that, in turn, drives the synthesis of ATP. Ubiquinol which is the reduced form of CoQ10 also has AOX properties and protects membrane lipids and proteins and mitochondrial DNA from oxidative damage. Intracellular synthesis forms the major source of CoQ10. A small quantity is acquired through dietary sources such as oily fish, organ meats (liver), and whole grains.[13,16]

CoQ10 has found to have clinical applications in the treatment of hypertension, cardiac failure, statin-induced myopathy, Parkinson's and Huntington's diseases, and Friedreich's ataxia.[17]

The evidence generated by this study, on the antidepressant activity of CoQ10 adds further weightage to the existing literature on the antidepressant activity of CoQ10 by testing parameters which are different from those of the remaining studies.

In a study, which involved the testing of the antidepressant activity of CoQ10 in chronically stressed rats, it was found that CoQ10 administration produced amelioration of chronic restraint stress (CRS) induced behavioral abnormalities in forced swimming and open field tests, elevated corticosterone level, and body weight loss. CoQ10 was found to restore the levels of various AOXs like hippocampal catalase, GPX and reduced glutathione, besides a reduction in the hippocampal malondialdehyde, nitric oxide and 8-hydroxy-2′deoxyguanosine levels. This indicates that CoQ10 does protect the hippocampus against O and NS-induced lipid peroxidation and DNA damage.[18]

In another study, it was found that chronic administration of CoQ10 dose-dependently antagonized CRS-induced behavioral aberrations by increasing sucrose preference (reversal of anhedonia), body weight and food intake and reducing adrenal gland weight. CoQ10 also enhanced the activities of mitochondrial respiratory chain complexes (I to IV) and creatine kinase (CK) in the frontal cortex and hippocampus. CK is a sensitive indicator of brain energy metabolism dysfunction.[19]

The AOX property of CoQ10 stems from two mechanisms. A direct mechanism in which CoQ10 quenches lipid peroxyl radicals directly and an indirect mechanism in which CoQ10 acts a key mediator in regeneration of α-tocopherol (an AOX) from α tocopheroxyl radicals. CoQ10 by virtue of being a membrane protective AOX confers protection to proteins in the mitochondrial membrane, unsaturated lipids in cell membranes, and low-density lipoprotein-cholesterol in blood. By doing so, it protects these entities from free radical-mediated damage. CoQ10 also plays a key role in preventing oxidative damage to phospholipids of the cell membrane and maintaining membrane fluidity.[20] Furthermore, CoQ10 supplementation has been found to enhance activities of superoxide dismutase, catalase, and GPX which are AOX enzymes.[21]

CoQ10 also exerts anti-inflammatory properties by attenuating nuclear factor (NF)-κB1-dependent gene expression and lipopolysaccharides (LPS) induced release of macrophage inflammatory protein-1 alpha (a chemokine). It also attenuates expression of LPS sensitive genes which act as regulators of signal transduction, cell proliferation pathways and transcriptional regulation. CoQ10 has also been shown to suppress the NF of activated T-cells and NF-κB signaling.[20]

In a study involving fibromyalgia patients, it was found that these patients had significantly higher levels of depression as compared to healthy controls. Platelets isolated from these patients showed significantly reduced CoQ10 and serotonin levels as compared to controls. CoQ10 deficiency was induced in platelets from healthy controls by inhibiting its endogenous synthesis by P-aminobenzoate (PABA) treatment of cultured platelets. Serotonin levels in platelets were significantly reduced by PABA treatment. Reduced serotonin levels in platelets were restored in the presence of CoQ10. It can be concluded that CoQ10 deficiency affects serotonin content in platelets and it can be presumed that this deficiency also affects the neurons of the central nervous system. Platelets are hypothesized to be good models of neuronal serotonergic cells based on the fact that, both types of cells are major sites for storage of serotonin and that serotonin levels in cerebrospinal fluid have a strong correlation with serotonin levels in platelets.[22]

CONCLUSION

Based on the findings of this study, it can be concluded that CoQ10 has significant antidepressant activity. Taking into consideration the fact that inflammation and oxidative stress have a major role to play in the pathophysiology of depression, CoQ10 appears to be a promising agent for the treatment of depression. Antidepressant activity of CoQ10 can be explained by its role in preventing oxidative damage to cell membranes, suppression of various inflammatory parameters and possible role in regulating serotonin levels.

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