Neurochemical Research (2022) 47:1280–1289
https://doi.org/10.1007/s11064-021-03522-8

ORIGINAL PAPER

Potential Protective Effect of Coenzyme Q10 on Doxorubicin-Induced Neurotoxicity and Behavioral Disturbances in Rats

Nilsel Okudan[1] · Muaz Belviranlı[1] · Tuğba Sezer[1]

Received: 18 August 2021 / Revised: 27 December 2021 / Accepted: 28 December 2021 / Published online: 3 January 2022

Abstract

The aim of this study was to investigate the potential neuroprotective efficacy of coenzyme Q10 (CoQ10) against doxorubicin (DOX) -induced behavioral disturbances in rats. Female rats were randomly assigned into 4 groups as control, CoQ10, DOX, and DOX plus CoQ10. The CoQ10 groups received CoQ10 (200 mg kg^{-1}) for 21 days, and the DOX groups received DOX (4 mg kg^{-1}) on days 7 and 14 of the study. The open field (OF) and elevated plus maze (EPM) tests were performed to assess locomotor activity and anxiety levels. Additionally, malondialdehyde (MDA), and protein carbonyl (PC) levels and acetylcholinesterase (AChE), and glutathione peroxidase (GPx) activities and total antioxidant capacity (TAC) were quantified in brain tissue. DOX administration caused alterations in locomotor activity, and anxiety-like behaviors. Moreover, DOX produced significant elevation in AChE activity . PC level and GPx activity tended to alter with DOX administration. Co-treatment with CoQ10 significantly attenuated DOX-induced behavioral alterations via improving AChE activity in the brain tissue of rats. CoQ10 treatment may be potential for the alleviation of DOX-induced behavioral disturbances. This improvement might be due to the inhibition of AChE activity.

Keywords Doxorubicin · Anxiety · Coenzyme Q10 · Oxidative stress · Acetylcholinesterase · Rat

Abbreviations

CoQ10	Coenzyme Q10
DOX	Doxorubicin
OF	Open field
EPM	Elevated plus maze
MDA	Malondialdehyde
PC	Protein carbonyl
GPx	Glutathione peroxidase
TAC	Total antioxidant capacity
AChE	Acetylcholinesterase

Introduction

Although chemotherapy is one of the most common and successful treatment methods used in cancer treatment, side effects of agents such as doxorubicin (DOX, Adriamycin) are an important problem. Approximately 70% of cancer survivors undergoing chemotherapy experience cognitive impairment during or after treatment, characterized by cognitive deficits and depressive and anxiety-like symptoms [1, 2] and this phenomenon is known as chemobrain or chemo-fog [3]. DOX, one of the anti-cancer medications commonly used in the treatment of several types of cancer, is a member of the anthracycline family. It exerts its cytotoxic effects in the brain and other parts of the body by disrupting topoisomerase-II mediated DNA repair and increasing the production of reactive oxygen/nitrogen species that damage cellular membranes, DNA, and proteins [4, 5].

Although brain tissue is sensitive to the effects of DOX, it cannot pass the blood–brain barrier (BBB). Instead, it causes inflammation in peripheral tissues, and this inflammatory response crosses the BBB, leading to neuroinflammation in the brain. Ultimately, it causes oxidative/nitrosative damage to molecules such as lipids, proteins, and nucleic acids, mitochondrial dysfunction, and neuron death [6, 7]. DOX administration also causes impaired hippocampal cell proliferation and neurogenesis [8]. These factors may be responsible for DOX-induced depressive- and anxiety-like symptoms.

Treatment with anti-oxidative agents is thought to prevent oxidative damage induced by DOX [9, 10]. Therefore, interest in studying the protective effects of various antioxidants

✉ Muaz Belviranlı
mbelviranli@yahoo.com; mbelviranli@selcuk.edu.tr

[1] Division of Sports Physiology, Department of Physiology, Faculty of Medicine, Selçuk University, Konya 42131, Turkey

such as coenzyme Q10, astaxanthin, phenethyl ester caffeic acid, and catechins against DOX-induced organ toxicity has been growing in recent years [11–15]. Additionally, studies have shown that co-administration of DOX with antioxidants that can pass BBB results in improved behavioral disturbances [16].

Coenzyme Q10 (CoQ10) is a vitamin-like fat-soluble quinone that is present in nearly all cell membranes and acts as a mitochondrial mobile electron carrier [17–19], and it has multiple effects such as anti-inflammatory, anti-oxidant, anti-hyperlipidemic and anti-hyperglycemic [20]. Moreover, many reports have shown that CoQ10 can pass through BBB and CoQ10 supplementation can improve neuronal and locomotor functions thanks to its powerful neuroprotective effect, which improves the antioxidant system and attenuates inflammatory markers [21, 22]. CoQ10 has also been reported to effectively inhibit acetylcholinesterase (AChE) activity, which is an indicator of brain toxicity [23]. In addition, it has been shown that adriamycin treatment caused a reduction in CoQ10 concentrations in the liver and heart mitochondria of rats [24]. CoQ10 has been shown to have a protective role against DOX-induced cardiac, hepatic, renal and testicular toxicity [12, 13, 25, 26]. However, to our knowledge, there are no studies examining the impact of CoQ10 on DOX-induced brain toxicity and its relationship with behavioral parameters and oxidative stress levels in the brain tissue of rats.

In this study, it was hypothesized that CoQ10 supplementation could improve behavioral disorders and neurotoxicity caused by DOX treatment. This research therefore aimed to establish whether locomotor function and anxiety-like behaviors are affected by DOX, whether supplementation with CoQ10 may prevent these impairments. In addition, DOX-induced brain toxicity and the potential effect of CoQ10 were also evaluated by measuring AChE activity in the brain tissue.

Materials and Methods

Animals

This research included adult female Wistar rats, approximately 8 months of age, weighing 300–350 g. Female rats were used in this study because females have been shown to be more vulnerable than males to the behavior-impairing effects of DOX [9, 27]. The rats were housed in standard cages in a temperature (23 ± 2 °C) and humidity (50 ± 5%) controlled room at a 12 h:12 h light–dark cycle, and were fed ad libitum with standard rat chow and tap water.

This study was evaluated and approved by the local ethical committee of the Selcuk University (Protocol no # 2016-15), and all study procedures were performed in accordance with the National Institutes of Health (NIH) laboratory animal care guidelines.

Experimental Design

A total of 32 rats were randomly divided into four groups and subjected to the following treatment and supplementation for 21 days.

In the first group (CON, n = 6) defined as the control group, corn oil (1 mL kg^{-1}) was administered via gastric gavage for 21 days, while physiological saline (1 mL kg^{-1}) was injected intraperitoneally on days 7 and 14 of the study.

The second group acted as the CoQ10-supplemented group (CoQ10, n = 6) and received 200 mg kg^{-1} CoQ10 dissolved in corn oil by gastric gavage for 21 days, and physiological saline (1 mL kg^{-1}) was injected intraperitoneally on days 7 and 14 of the study. CoQ10 was kindly donated by Kaneka Corporation (Osaka, Japan), and dosage and duration were determined according to the previous studies [28, 29].

The third group was defined as the DOX-treated group (DOX, n = 10), and on days 7 and 14 of the study, 4 mg kg^{-1} DOX (Adrimisin®, Saba Pharmaceuticals, İstanbul, Turkey) dissolved in physiological saline was injected intraperitoneally (total 8 mg kg^{-1}). Additionally, corn oil (1 mL kg^{-1}) was given by gastric gavage for 21 days. The DOX dosage and duration were chosen based on previous studies that have been shown to cause behavioral disturbances [8, 30, 31].

The fourth group served as the treatment group (DOX/CoQ10, n = 10) and 200 mg kg^{-1} CoQ10 was administered by gastric gavage for 21 days and 4 mg kg^{-1} DOX (total 8 mg kg^{-1}) was injected intraperitoneally on days 7 and 14 of the study.

The open field (OF) and elevated plus maze (EPM) tests were performed on day 22 and 23, respectively. Figure 1 shows experimental design and time points of DOX and CoQ10 administration and behavioral tests.

Behavioral Assessment

In order to investigate the effect of DOX and/or CoQ10 administration on locomotor activity and anxiety-like behavior OF and EPM tests were performed. The OF and EPM tests were performed in a quiet and isolated room. All behavioral tests were videotaped, tracked and analyzed with the EthoVision XT 10.0 system (Noldus Information Technology, Wageningen, The Netherlands). The inside of the mazes was cleaned with 70% ethanol before and after each use and allowed to dry.

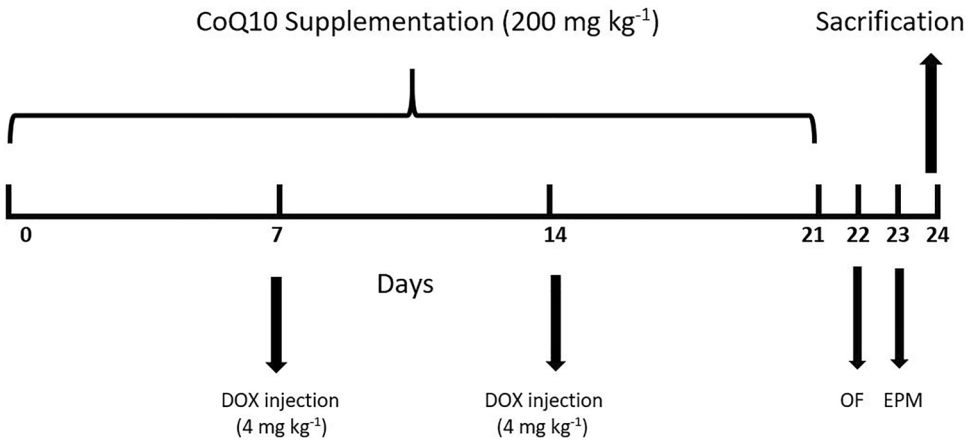

Fig. 1 Summary of study and time points of interventions. DOX: Doxorubicin, CoQ10: Coenzyme Q10, OF: Open Field, EPM: Elevated Plus Maze

Open Field Test

To determine general locomotor activity and anxiety-like behavior, the OF test was performed. Each rat was put in the center of the open field device (80 × 80 × 40 cm) and they were allowed to move freely for 5 min as described previously [32–34]. The box was separated the center and the wall parts imaginary. During the test total distance moved (cm), average velocity (cm s^{-1}), time spent as a mobile (s), number of defecations, and groomings and total time spent in the central area (s) were measured.

Elevated Plus Maze Test

The EPM test is used to evaluate anxiety-like behavior in rodents and was performed as described previously [32–34]. The EPM apparatus is a cross-shaped apparatus with two opposing open and two mutually closed arms (50 × 10 cm), which extended from the common central platform (5 × 5 cm), and it is 50 cm above the ground. At the beginning of the test, the rats were placed on the middle of the central platform faced the open arm and their behaviors were recorded for 5 min. During the test total distance moved (cm), the number of entries into the open and closed arms and the total time spent in the open arms (s) were measured.

Biochemical Analysis

Brain Tissue Collection

Twenty-four hours after the behavioral evaluation, the animals were anesthetized by short-term narcosis, induced by ether, and then decapitated. Samples of total brain tissue were removed rapidly and washed using cold saline. The specimens were then frozen in liquid nitrogen and preserved until analysis at − 80 °C.

Prior to biochemical analysis, tissue samples were diluted 1:20 with freshly prepared cold phosphate buffered saline (E404; Amresco, Solon, OH, USA) and homogenized (Wise Mix Hg-15; Daihan Scientific, Seoul, Korea). The resulting homogenates were centrifuged at 4 °C at 12,000×*g* for 30 min, then the supernatants were used for biochemical analysis.

Colorimetric Assays

AChE Activity

AChE activity in brain tissue was determined using the commercially available rat AChE ELISA kit (201-11-0725; Sunred Biological Technology, Shanghai, People's Republic of China) according to the manufacturer's instructions. AChE activity was expressed as ng mg^{-1} of protein.

Levels of Oxidative Stress Biomarkers

In order to evaluate oxidative stress and antioxidant defense biomarkers in the brain tissue of rats; malondialdehyde (MDA), protein carbonyl (PC), glutathione peroxidase (GPx), and total antioxidant capacity (TAC) were measured using commercially available kits (MDA: 10,009,055, PC: 10,005,020, GPx: 703,102, TAC: 709,001, Cayman Chemical, Ann Arbor, MI, USA). All procedures were performed according to kits' instructions and the absorbance was measured using an automated reader (Power Wave XS, Biotek Instruments Inc., Winooski, VT, USA). The protein concentrations of the samples were measured by the methods of Lowry et al. [35].

Statistical Analysis

All statistics were carried out using the SPSS v.22.0 (Chicago, IL, USA) computer program. Data are expressed as mean ± standard deviation. Parameters obtained in OF and EPM tests, and biochemical markers were initially submitted Shapiro–Wilk test of normality. To evaluate the main effects

of DOX and CoQ10 and potential interactions between these variables, a two-way variance analysis (ANOVA) was performed. If a main effect was observed, the Tukey HSD test with Bonferroni correction was used to allow a post hoc comparison. Significance level was accepted as $p < 0.05$.

Results

General Appearance of the Animals

The general appearance of the animals in all groups was observed throughout the study. At the end of the experiment, the rats in the DOX group appeared sick, weak, and lethargic. These rats also had red exudates around the eyes and nose, and an enlarged abdomen. These symptoms were less severe in the DOX + CoQ10 group. There were no observable changes in CoQ10 and control groups. No death was observed in any group.

The Effects of DOX and/or CoQ10 on Locomotor Activity

In the OF test, the total distance moved was 38% lower in the DOX group compared to the CON group, and 25% higher in the DOX/CoQ10 group than in the DOX group ($F_{3,28} = 5.801$; $P = 0.003$) (Fig. 2A). Total distance moved in the EPM test was not different between groups ($F_{3,28} = 0.569$; $P = 0.640$) (Fig. 3A). Although the average speed ($F_{3,28} = 0.888$; $P = 0.459$) (Fig. 2B) and time spent mobile ($F_{3,28} = 1.521$; $P = 0.231$) (Fig. 2C) in the OF test were affected by DOX, there was no difference between the groups according to the post-hoc analysis result. These findings suggest that with DOX therapy, locomotor activity is decreased and may improve with CoQ10 supplementation.

The Effects of DOX and/or CoQ10 Anxiety-Like Behavior

In the OF test, the number of defecations was 48% lower in the DOX/CoQ10 group than in the DOX group ($F_{3,28} = 6.850$; $P = 0.001$) (Fig. 2D). However, there was no difference between the groups in terms of number of groomings ($F_{3,28} = 0.083$; $P = 0.969$) (Fig. 2E) and time spent in the central zone of the maze ($F_{3,28} = 0.695$; $P = 0.563$) (Fig. 2F).

In the EPM test, the number of entries ($F_{3,28} = 8.710$; $P = 0.000$) (Fig. 3B) and time spent ($F_{3,28} = 4.495$; $P = 0.011$) (Fig. 3D) in the open arms were 74% and 68% lower in the DOX group compared to the CON group, and 62% and 82% higher in the DOX/CoQ10 group compared to the DOX group, respectively. The number of entries to closed arms was not different between the groups ($F_{3,28} = 2.505$; $P = 0.080$) (Fig. 3C). These findings suggest that DOX treatment induces anxiety-like behavior that can be improved with CoQ10 supplementation.

The Impacts of DOX and/or CoQ10 on AChE Activity

Figure 4 shows the brain tissue AChE activity in each of the study groups. AChE activity was 86% higher in DOX group than CON group, and 48% lower in DOX/CoQ10 group than DOX group ($F_{3,28} = 8.116$; $P = 0.001$). These findings suggest that DOX treatment causes toxicity in brain tissue, and CoQ10 supplementation can improve this toxicity.

The Effects of DOX and/or CoQ10 on Oxidative Stress and Antioxidant Defense

According to the results of two-way ANOVA analysis, there was no difference between the groups in terms of MDA level ($F_{3,28} = 1.470$; $P = 0.245$) (Fig. 5A) and TAC ($F_{3,28} = 1.785$; $P = 0.177$) (Fig. 5D). Although PC level was affected by DOX and DOX x CoQ10 and GPx activity was affected by DOX x CoQ10, there was no difference between groups according to the post-hoc analysis result. However, although not statistically significant, the PC level was higher in the DOX and DOX/CoQ10 groups ($F_{3,28} = 1.470$; $P = 0.245$) (Fig. 5B), and GPx activity tended to increase in the DOX/CoQ10 group while it was lower in the DOX group ($F_{3,28} = 2.623$; $P = 0.077$) (Fig. 5C). These findings indicate that DOX treatment and/or CoQ10 supplementation has a limited effect on oxidative stress and antioxidant defense in brain tissue.

Discussion

This study investigated the effect of DOX and/or CoQ10 treatment on locomotor activity, anxiety level, and biomarker of the brain toxicity and oxidative stress in rats. The primary finding is that DOX treatment causes a deterioration in locomotor activity and anxiety-like behavior, and CoQ10 supplementation reverses this impairment. The second important finding is that CoQ10 supplementation improves AChE activity, a marker of brain toxicity, without affecting oxidative stress in brain tissue in rats treated with DOX. The neuroprotective effect of CoQ10 supplementation against sevoflurane-induced neuroinflammation [36, 37], Alzheimer's disease [38] and neurotoxicity induced by propionic acid [39], lead acetate [40] and arsenic [41] has been demonstrated.

In this study, locomotor activity decreased following DOX administration, especially in OF test. Previous reports [15, 42–45] on the effect of DOX on locomotion in rodents are inconsistent. As in this study, Rodynskii et al. [44] and Salas-Ramirez et al. [45] showed that locomotion reduced

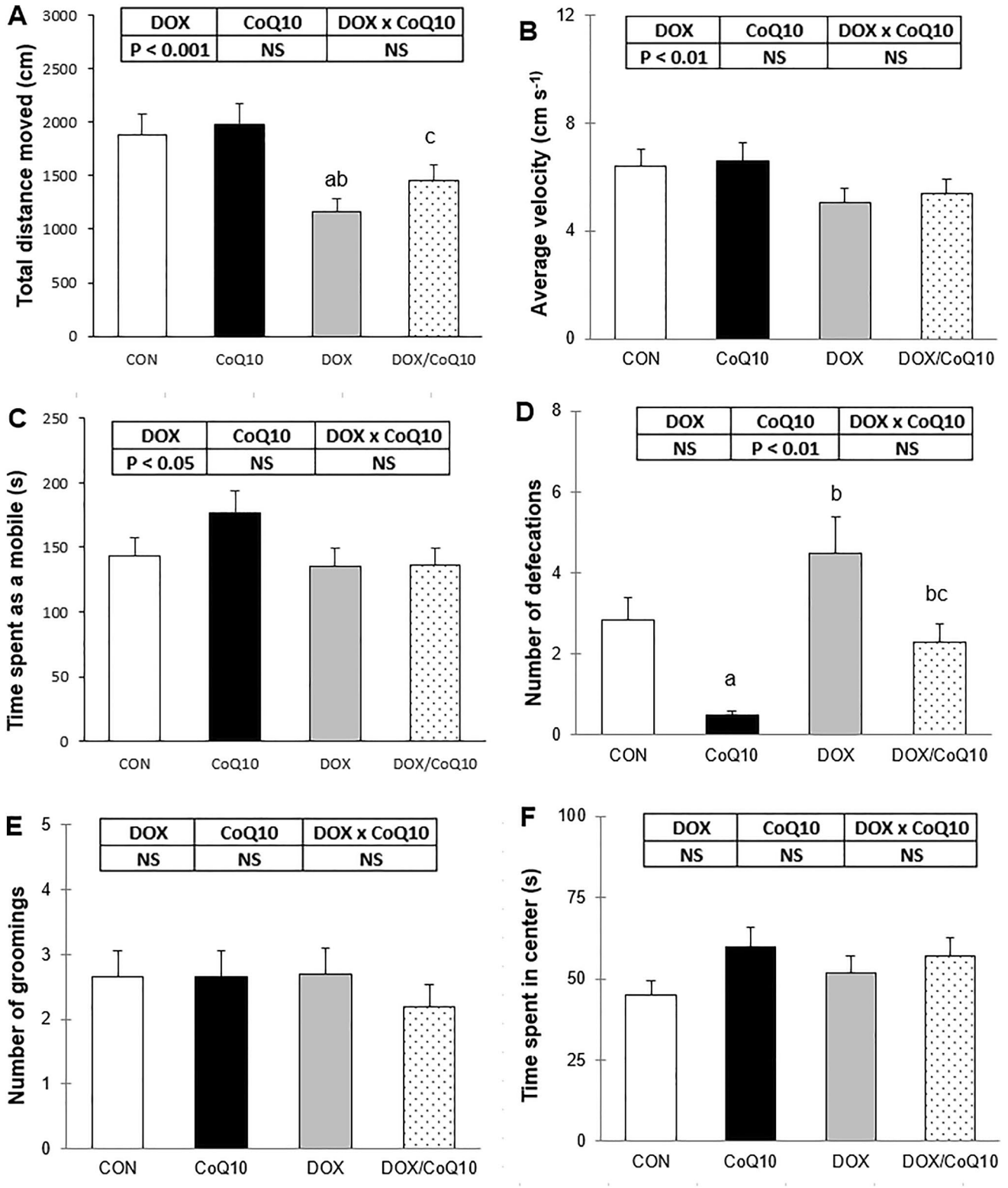

Fig. 2 Effect of DOX and CoQ10 on total distance moved (**A**), average velocity (**B**), time spent as a mobile (**C**), number of defecations (**D**), and groomings (**E**), and time spent in center zone (**F**) in Open Field test. Data are expressed as mean ± SD. [a]$P < 0.05$ compared to the CON group, [b]$P < 0.05$ compared to the CoQ10 group and [c]$P < 0.05$ compared to the DOX group. CON: Control group, CoQ10: Coenzyme Q10-supplemented group, DOX: Doxorubicin-treated group, DOX/CoQ10: Doxorubicin-treated and Coenzyme Q10-supplemented group

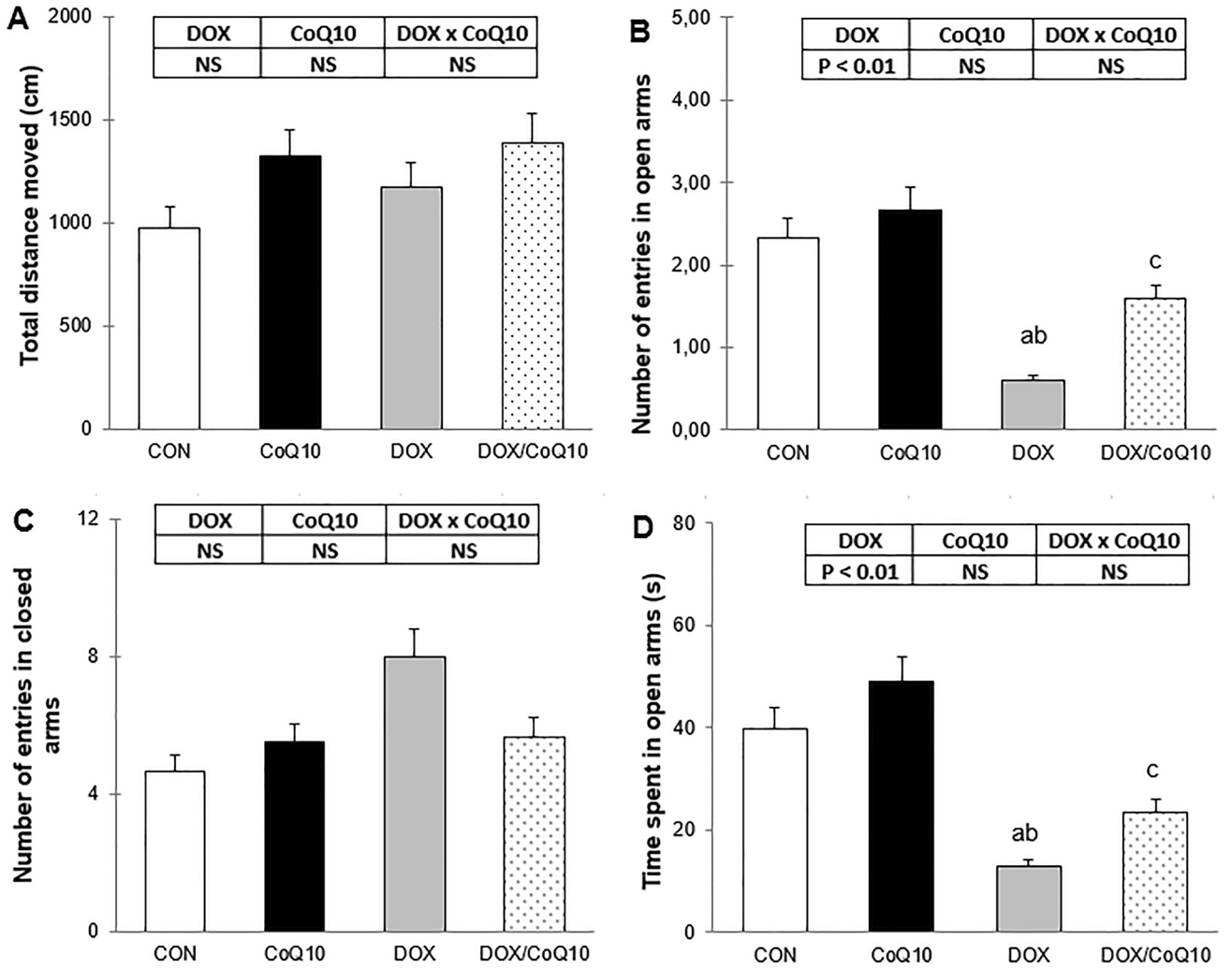

Fig. 3 Effect of DOX and CoQ10 on total distance moved (**A**), number of entries in open (**B**), and closed (**C**) arms and time spent in open arms (**D**) during the Elevated Plus Maze test. Data are expressed as mean ± SD. $^{a}P < 0.05$ compared to the CON group, $^{b}P < 0.05$ compared to the CoQ10 group and $^{c}P < 0.05$ compared to the DOX group. CON: Control group, CoQ10: Coenzyme Q10-supplemented group, DOX: Doxorubicin-treated group, DOX/CoQ10: Doxorubicin-treated and Coenzyme Q10-supplemented group

with DOX treatment, whereas Kitamura et al. [43], Aziriova et al. [42], El-Agamy et al. [15] and Ali et al. [11] reported that locomotor activity did not change with DOX treatment. In this study, the decreased locomotor activity as a result of DOX treatment can be partially explained by the pathophysiological deterioration of the locomotor and musculoskeletal systems. CoQ10 supplementation in this study appeared to increase parameters associated with locomotion, some if not significantly. Although the effect of CoQ10 supplementation on locomotor activity following treatment with DOX or other chemotherapeutic agents has not yet been investigated, CoQ10 has been showed to improve locomotion in various neurological disorders such as 6-hydroxydopamine-induced dopaminergic toxicity [29] and experimental Alzheimer's disease [46]. The improved locomotor activity with CoQ10 supplementation may be due to CoQ10's role in the electron transport chain by moving electrons from complexes I and II to complex III [17, 19].

In this study, DOX administration caused impairment in anxiety-like behaviors measured in OF and EPM tests. Thus, these data show that DOX administration triggers anxiety-like behaviors in rats. In accordance with our study, although it has been shown in many studies [43, 47, 48] that DOX administration causes anxiety-like behavior in OF, EPM and light–dark box tests, it has been shown that it does not affect anxiety level in a few studies [6, 31, 45]. Differences in findings may be due to differences in the timing of the test and factors such as the dose and duration of DOX treatment. It has been claimed that the anxiety-like behavior caused by DOX may be due to increased oxidative stress and decreased cycsin D1 levels in brain tissue [42, 49]. CoQ10 supplementation appeared to reduce parameters associated with

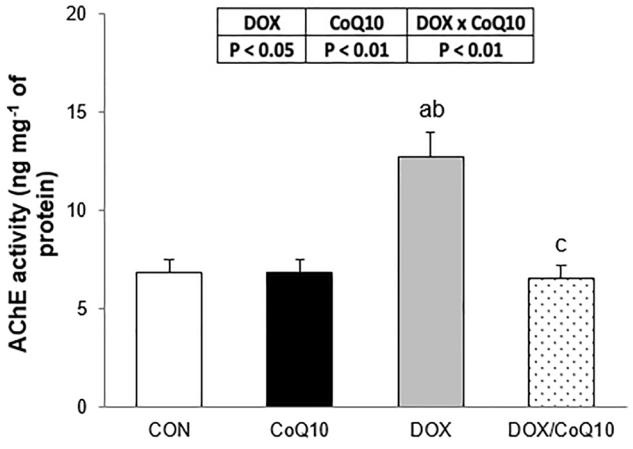

Fig. 4 Effect of DOX and CoQ10 on acetylcholinesterase (AChE) activity in the brain tissue. Data are expressed as mean ± SD. [a]P < 0.05 compared to the CON group, [b]P < 0.05 compared to the CoQ10 group and [c]P < 0.05 compared to the DOX group. CON: Control group, CoQ10: Coenzyme Q10-supplemented group, DOX: Doxorubicin-treated group, DOX/CoQ10: Doxorubicin-treated and Coenzyme Q10-supplemented group

anxiety-like behaviors in rats, some if not significantly in this study. However, although there are no studies investigating the effect of CoQ10 on anxiety-like behavior following treatment with DOX or other chemotherapeutic agents, CoQ10 supplementation has been reported to exhibit anxiolytic effects in various pathophysiological conditions such as chronic stress [50], Alzheimer's disease [46], dichlorvos poisoning [51], and Parkinson disease [52].

Although the BBB protects the brain from the harmful effects of systemically administered drugs, chemotherapeutic agents such as DOX may affect brain functions and ultimately cause behavioral disturbances [53]. AChE is an enzyme that breaks down acetylcholine into acetate and choline, ultimately stopping cholinergic transmission. Hence, increased AChE activity in the brain decreases acetylcholine levels [54]. In this study, consistent with previous studies, DOX administration caused a significant increase in AChE activity in the brain. Since AChE inhibition is a fundamental strategy for treating disorders associated with behavioral impairment [55], CoQ10 supplementation restored AChE activity in rats treated with DOX in this study as well. Consistent with our finding,

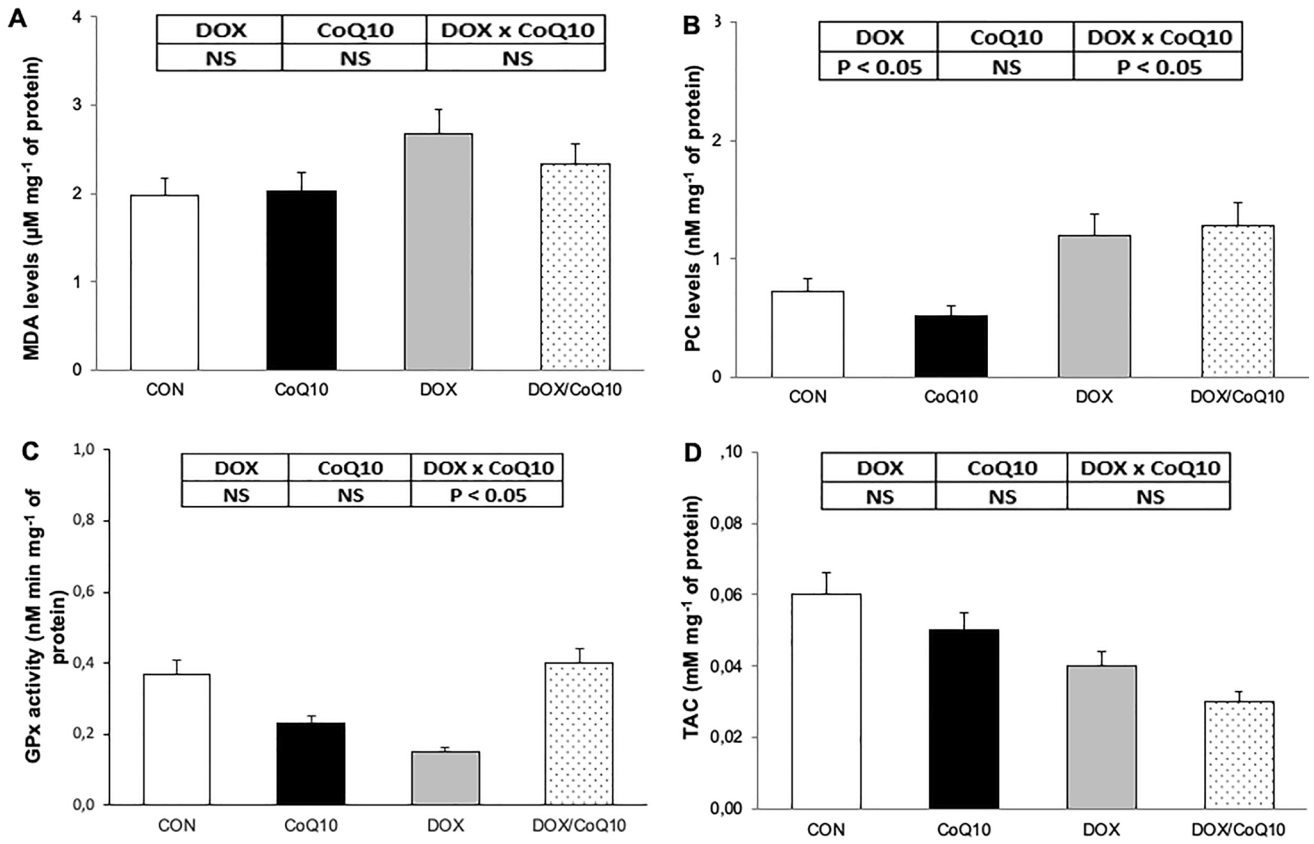

Fig. 5 Malondialdehyde (MDA) (**A**), protein carbonyl (PC) (**B**), glutathione peroxidase (GPx) (**C**) and total antioxidant capacity (TAC) (**D**) measurements in the brain tissue of the rats which were exposed to DOX and CoQ10. Data are expressed as mean ± SD. CON: Control group, CoQ10: Coenzyme Q10-supplemented group, DOX: Doxorubicin-treated group, DOX/CoQ10: Doxorubicin-treated and Coenzyme Q10-supplemented group

CoQ10 supplementation has been reported to attenuate AChE activity in various neurological disorders such as the experimental Alzheimer's disease model [23, 38, 56]. Taken together, these findings suggest that CoQ10 has a neuroprotective potential in DOX-treated rats, and this effect can be attributed to CoQ10's ability to cross the BBB [21, 57].

It has been reported that DOX administration causes oxidative damage in nerve cells and this is accompanied by anxiety and depression [58–60]. Since DOX does not pass the BBB, it has been suggested that oxidative stress plays an important role in the mechanism of DOX-induced neurotoxicity and behavioral impairment [61, 62]. In this study, neither DOX treatment nor CoQ10 supplementation did affect MDA and PC levels, and GPx and TAC activities in the brain tissue of the rats. The protective effect of CoQ10 against DOX-induced oxidative stress in various organs such as the heart [12, 13] and kidney [25], and neuroprotective effect in chronic stress [50], Alzheimer's disease [46], dichlorvos poisoning [51], and Parkinson disease [52]. In this study, the fact that no statistically significant difference was observed between the groups may depend on the CoQ10 dose, duration of treatment, sample size, or the biochemical analysis methods used.

Limitations of the Study

This study has some limitations that need to be emphasized. The first limitation is that there are no different doses of DOX and CoQ10, we had to use different dosages of DOX and CoQ10 to observe the main effects on behavioral and biochemical parameters. The second limitation is that the measurement of CoQ10 concentrations in blood and brain tissue, which is necessary to assess the bioavailability of CoQ10, cannot be made. The third limitation is the inability to measure ATP levels, amount of ROS, and cell death signal or inflammatory factors to determine the effect of DOX and CoQ10 from a mechanistic perspective.

Conclusions

In conclusion, this study provides evidence that CoQ10 can be a promising anxiolytic and neuroprotective agent that can protect against behavioral disturbances caused by DOX. In addition, this study also serves as a driving force in supporting clinical research of the neuroprotective effect of CoQ10 supplementation in cancer patients treated with DOX. However, more research is needed to identify the mechanism of action of CoQ10 in the nervous system.

Declarations

Conflict of interest There is no conflict of interest—financial or otherwise—related to the material presented herein.

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