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Coenzyme-Q10 Reverses Metronidazole-induced Cognitive Dysfunction in Rats

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ABSTRACT

Objective: Metronidazole, an essential component in surgical prophylaxis and treatment of several infections is faced with an increase in reports of neurotoxic outcomes. The search for means of resolving or abolishing the occurrence of metronidazole-induced neurotoxicity is necessary. The objective therefore is to evaluate the effects of coenzyme-Q10 on metronidazole-induced cognitive dysfunction in adult rats. **Methods:** Eighty adult rats were allotted to 4 groups (n=20). Group 1 was given 5 mL/kg 0.5% Tween-80®, group 2 was treated with 50 mg/kg metronidazole, group 3 was given 10 mg/kg coenzyme-Q10, group 4 was treated with metronidazole 50 mg/kg + 10 mg/kg coenzyme-Q10. All drug administrations were done daily for 28 days using the oral route. On the 28th day the rats were exposed to tests that evaluated cognitive function like the hole-board, Morris's water maze and Y-maze test. Thereafter the animals were euthanized with halothane and the brains excised for oxidative stress tests. One-way ANOVA followed by Dunnet's post hoc test for multiple comparison. Statistical differences were considered significant at $p<0.05$. **Results:** Metronidazole distorted memory acquisition and learning, and decreased reference memory index (RMI) on the hole board, prolonged the time to find the escape platform in the Moris water maze, reduced percentage alternation and spatial recognition memory in the Y-maze ($p<0.01$). Co-administration of coenzyme-Q10 with metronidazole reversed all the cognitive deficits induced by metronidazole in the various tests. Coenzyme-Q10 also reversed metronidazole-induced oxidative stress by increasing *superoxide dismutase* activity and reducing lipid peroxidation. **Conclusion:** In conclusion, we suggest that oxidative stress is a contributing factor to metronidazole-induced cognitive dysfunction and coenzyme-Q10 improves cognitive function, hence, could be explored to alleviate the occurrence of metronidazole-induced neurotoxicity.

Keywords: *Neurotoxicity, Memory and learning, metronidazole, cognitive dysfunction, oxidative stress.*

INTRODUCTION

Metronidazole is an old war horse in surgical prophylaxis and treatment of several infections especially in the developing world due to its effectiveness and low cost. Neurotoxicity arising from the use of metronidazole is still a subject of major concern in therapy of clinical infections. Unraveling the mechanism of metronidazole-induced neurotoxicity and seeking ways of mitigating it is necessary to prevent injury and maximize patient outcomes.

Metronidazole is a prodrug which undergoes reductive activation mediated by pyruvate:ferrodoxin oxidoreductase (PFOR) whose expression is positively

regulated by iron[1]. Reductive activation of metronidazole leads to formation of reactive intermediates including the nitro anion radical, hydrogen peroxide and the superoxide anion which are toxic to susceptible organisms in anerobic conditions[2,3]. Several other reports have mentioned that neurotoxicity associated with metronidazole is linked to interference with oxidative processes in the nervous system[2,4,5,3].

Free radicals produce deleterious effects on mitochondria and several subcellular organelles via oxidation of nucleic acids, proteins, and lipids thereby inducing decline of several cognitive functions including attention, decision-making, sensory perception, as well as learning and memory[6,7]. Due to their antioxidant properties, naturally occurring bioactive compounds are reported to efficiently scavenge or neutralize free radical-induced oxidative stress in both animal models and clinical trial studies thereby improving underlying conditions such as neurodegeneration and cognitive decline[8,9].

Coenzyme-Q10 (CoQ10) is a natural product which is produced via the mevalonate pathway[10]. It is found in mammals, fish, nuts, and some oils[11]. It has endogenous antioxidant properties, and is an important component of the mitochondrial respiratory chain known to reduce reactive oxygen species (ROS) production[12]. it has also been shown to prevent lipid peroxidation *in vivo* and *in vitro* [13,14]. We hypothesize that CoQ10 may be a potential intervention to alleviate symptoms of metronidazole-induced neurotoxicity hence we investigated CoQ10 for its protective potential against metronidazole-induced learning and memory impairment.

MATERIALS AND METHODS

Metronidazole and CoQ10 (Sigma, St. Louis, MO, USA) were bought from Merck chemicals and reagents, Lagos, Nigeria, other reagents and chemicals used for the study were from reputable companies.

Experimental Animals

For this study, albino rats with an average weight of 132.5 g were housed in 20 different cages, with separate cages for males and females (maximum of 5 rats per cage) to avoid overcrowding. The animals were maintained on normal rodent feed (Topfeeds, Calabar, Nigeria) and had free access to drinking water. Ethical approval was obtained from the institutional animal and ethics committee. All animals were handled in accordance with standard protocols[15] and ARRIVE 2.0 guidelines for handling of animals (https://arriveguidelines.org/arrive-guidelines/sample-size).

METHODS

Effect of metronidazole on memory and learning

Adult rats were allotted to groups (n=20). Group 1 was given 5 mL/kg 0.5% Tween-80®, group 2 was treated with 50 mg/kg metronidazole, group 3 was given 10 mg/kg CoQ10, group 4 was treated with 10 mg/kg CoQ10 + 50 mg/kg metronidazole. Drug administrations were done daily for 28 days using the oral route. From day 25, the groups that required training on the apparatus were exposed to training sessions after treatment while all the rats were exposed to final tests like the hole-board, Morris water maze and Y-maze test on the 28th day that evaluated cognitive function. The animals were there after sacrificed via halothane inhalation in a glass chamber, the brains were then excised for antioxidant assessment.

Hole board test (modified)

The hole-board test was carried out with some refining to assess spatial reference memory[16] using a wooden board (60 cm x 60 cm x 45 cm) with 16 symmetrically spaced holes (5 cm diameter) at a height of 60 cm from the floor. Spatial reference memory was measured using objects placed permanently as spatial cues with 4 holes of the board baited with food pellets. The position of baited holes was fixed for the whole test duration. The food pellets were placed beneath the board to remove olfactory orientation bias. The rats were trained for three days (2 trials per day) from day 25 and a final test on the 28th day, each session beginning 30 minutes post treatment. Every trial was 20 minutes apart and lasted for 120 s. The apparatus was swabbed with 70% alcohol betwixt trials. Visits to baited holes and food pellet removals were noted for each trial. Reference Memory Index (RMI) was computed as (total visits of baited holes)/ total visits of all holes[16]

Morris water maze test

The Morris water maze[17] was utilized to assess the effect of metronidazole treatment on spatial learning in rats using a cylindrical vessel, measuring 100 cm by 45 cm and an elevated platform (6 cm diameter, 29 cm height) placed in the center of a quadrant of the pool. The pool was filled with water made opaque with starch to a depth of 1 cm below the water surface and visual clues fixed on the walls of the room throughout the test period and served as visual cues. Thirty (30) minutes post-treatment, each rat was placed in the water and subjected to two training sessions daily which were 20 minutes apart, for 4 days (the fourth day being day-28) and timing was after they had found the elevated platform. The cut-off time was 120 seconds. The change in escape latency for the first test represents long-term memory while difference in escape latency between the first and second test was recorded as an index of working or short-term memory.

Y-maze test for spatial memory evaluation

The Y-Maze with three arms (40 x 8 x 15 cm) inclined at an angle 120° to each other was used to evaluate short term memory[18]. The arms were labeled A, B and C. Thirty (30) minutes post-treatment, each rat was allowed to explore for a period of five (5) minutes after being placed in the middle of arm A facing away from the center of the maze. The number and sequence of arm entries (ABC, BCA, CAB, CBA, BAC or ACB) were recorded. Percentage alternation was calculated as using the formula below

$$Percentage\ Alternations = \left({}^{NA}/_{TAE-2}\right) \times 100$$

Where NA is the number of alternations and TAE is the total arm entries.

Spatial recognition memory on the Y-Maze

Spatial recognition memory was evaluated based on the innate exploratory proclivity of rodents. Treated rats (30 minutes post-treatment) were placed into arm A (start arm) of the Y maze with arm C closed and allowed to explore the maze for 10 minutes (training trial) after which it was returned to its cage. After an hour inter-trial interval, rats were placed arm A and allowed to freely explore all arms for 3 minutes (test trial). Arm entries, dwell time (time spent in the arm) and the arm of first choice entry were recorded. Discrimination ratio which is the inclination of rats for the novel arm over the familiar other arm for arm entry and dwell time were calculated as (Novel/Novel + Other)[19].

Effect of daily oral metronidazole treatment (28 days) on superoxide dismutase (SOD) activity in rat brain homogenates

Previously weighed brain tissues (n=5) were homogenized in ice-cold phosphate-buffered saline (PBS) and centrifuged at 3000 *g* for 15 minutes at 4°C. The resultant supernatant was used to assay the activities of superoxide dismutase (SOD)[20], and, the degree of lipid peroxidation by measuring malondialdehyde (MDA) levels[21]. Activity of SOD was determined using ab65354 (Abcam, USA) kit while MDA was colorimetrically determined using ab233471 (Abcam, USA). All assays were performed in duplicates following the manufacturer's instructions. SOD activity was calculated as percentage inhibition of xanthine oxidase which is responsible for the formazan coloration in the reaction using the following equation:

$$SOD\ Activity = \frac{(A_{Blank\ 1} - A_{Blank\ 3}) - (A_{Sample} - A_{Blank\ 2})}{A_{Blank\ 1} - A_{Blank\ 3}} \times 100$$

Where A is absorbance at 450 nm.

MDA concentration was derived from the standard curve for total MDA plotted using concentrations of 1, 2, 3, 5, 7, and 10 µM obtained from serial dilution of 10 mM MDA standard after reading the respective absorbance at 532 nm (Varian Cary 50 UV–Visible spectrophotometer).

Statistical analysis

Results are presented as mean ± standard error of mean (SEM), n is the number of rats per test group. Statistical analysis was done using one-way ANOVA followed by Dunnet's post-hoc test for multiple comparison (GraphPad prism 6, San Diego, USA). Data were considered significantly different at $p<0.05$.

RESULTS

CoQ10 abrogates metronidazole-induced learning and memory impairment in rats following 28-days co-administration.

In the hole-board experiment, daily oral treatment with metronidazole for twenty-eight days impaired memory acquisition and learning, and reduced reference memory index (RMI) compared to control ($P<0.05$). Co-administration of metronidazole with CoQ10 reversed the trend ($P<0.01$) in both the acquisition phase (day 1-3) and the test phase (day 4) as shown in **Figure 1**.

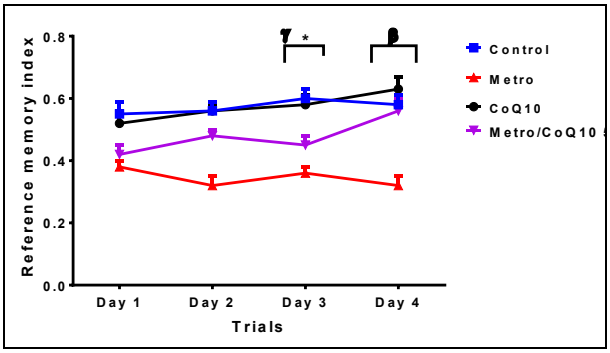

Figure 1. Performance of rats on the hole-board test for reference memory index. Assessment of Reference Memory Index (RMI) following daily oral treatment for 28 days. *$P<0.05$ metronidazole (Metro) only versus metronidazole + CoQ10; metronidazole versus control. $^{\gamma}P<0.01$ metro versus CoQ10 (day 3), $^{\beta}P<0.01$ metro compared to all groups (day 4). n=5. Control (5 ml/kg 0.5% Tween-80®), metronidazole (50 mg/kg), CoQ10 (10 mg/kg), metronidazole (50 mg/kg) + CoQ10 (10 mg/kg).

In the Morris water maze test for escape latency (**Figure 2**), the metronidazole treated group exhibited delay ($P<0.01$) to find the escape platform when compared with CoQ10 for trial 1 and trial 2 compared to other treated groups.

Percentage alternation in the Y-maze test reduced in the metronidazole group ($P<0.005$) compared to control and other treatment groups (Table1). CoQ10 alone or co-administered with metronidazole caused an increase in percentage alternation compared to the metronidazole group ($P<0.01$).

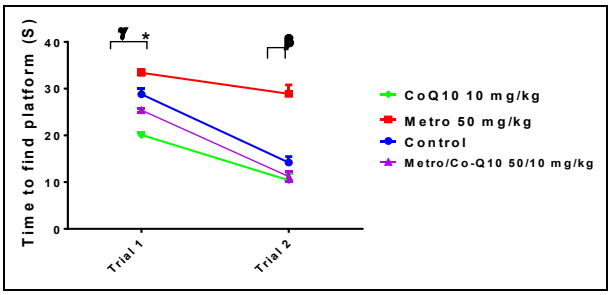

Figure 2. Evaluation of escape latency (working memory) of rats on the Morris water maze after twenty-eight days treatment with metronidazole. $^{*}P<0.05$ metronidazole (Metro) treated group versus control, $^{\gamma}P<0.01$ metro versus CoQ10 (0 min), $^{\beta}P<0.01$ metro versus all groups (20 min). Control (5 ml/kg 0.5% Tween-80®), metronidazole (50 mg/kg), CoQ10 (10 mg/kg), metronidazole (50 mg/kg) + CoQ10 (10 mg/kg).

In the spatial recognition memory test, the metronidazole treated group exhibited a reduction in visits and time spent in the novel arm than previously visited arms of the Y-maze compared to other treatment groups and control ($P<0.01$). However, the metronidazole + CoQ10 treated rats showed an increase in discrimination ratio for both dwell-time and novel arm entry compared with the group given metronidazole alone ($P<0.05$) (**Figures 3** and **4**). A lower percentage of animals treated with metronidazole also had the novel arm as their first choice of entry compared to other treated groups (**Figure 5**).

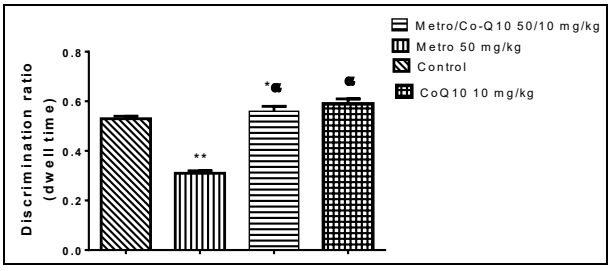

Figure 3: Effect of daily oral treatment (x 28 days) with metronidazole and CoQ10 on spatial memory performance on the Y-maze. Discrimination ratio [Preference for the Novel arm over the familiar other arm (Novel/Novel + Other)] for dwell time. $^{*}P<0.05$ versus control, $^{**}P<0.01$ versus control, $^{\alpha}P<0.01$ versus metronidazole alone. n=10. Control (5 ml/kg 0.5% Tween-80®), metronidazole (50 mg/kg), CoQ10 (10 mg/kg), metronidazole (50 mg/kg) + CoQ10 (10 mg/kg).

Metronidazole reduces superoxide dismutase activity and increased lipid peroxidation in treated rats.

Administration of metronidazole (50 mg/kg) for 28 days significantly ($P<0.01$) inhibited SOD activity (**Figure 6**). However, CoQ10 administered in combination with metronidazole or singly increased SOD activity compared to metronidazole.

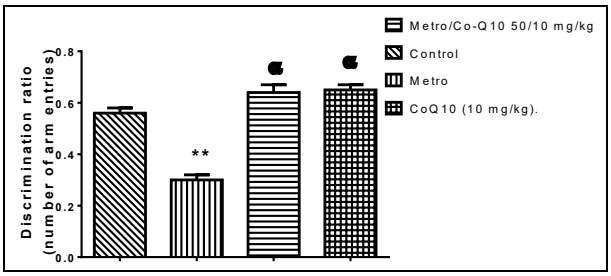

Figure 4. Effect of daily oral treatment (x 28 days) with metronidazole and CoQ10 on spatial memory performance on the Y-maze. Discrimination ratio [Preference for the Novel arm over the familiar other arm (Novel/Novel + Other)] for arm entries. $^{*}P<0.05$ versus control, $^{**}P<0.01$ versus control, $^{\alpha}P<0.01$ versus metronidazole alone. n=10. Control (5 ml/kg 0.5% Tween-80®), metronidazole (50 mg/kg), CoQ10 (10 mg/kg), metronidazole (50 mg/kg) + CoQ10 (10 mg/kg).

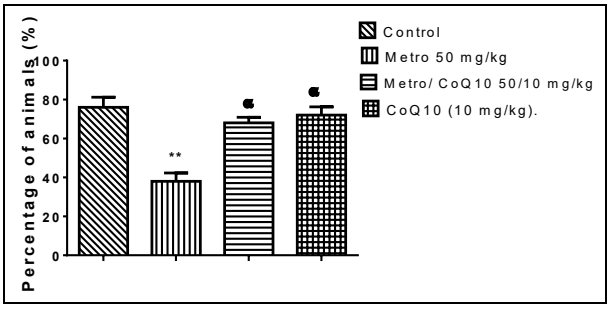

Figure 5. Effect of twenty-eight days oral treatment of rats with metronidazole and CoQ10 on the Y-maze. The percentage of animals selecting the novel arm as the first choice 1 h after the first encounter with the partially opened maze. $^{*}P<0.05$ versus control, $^{**}P<0.01$ versus control, $^{\alpha}P<0.01$ versus metronidazole. n=10. Control (5 ml/kg 0.5% Tween-80®), metronidazole (50 mg/kg), CoQ10 (10 mg/kg), metronidazole (50 mg/kg) + CoQ10 (10 mg/kg).

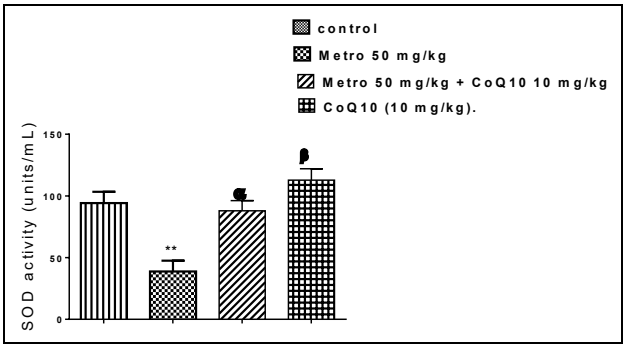

Figure 6. Superoxide dismutase (SOD) activity in rat brain homogenates following treatment with 50 mg/kg oral metronidazole or CoQ10 (28 days). $^{**}P<0.01$ compared to control, $^{\alpha}p<0.01$, $^{\beta}p<0.00$, compared to metronidazole alone, n=5.

Table 1. Evaluation of cognitive function in the Y-maze following 28-days daily oral treatment with metronidazole and CoQ10.

	Control	Metronidazole 50 mg/kg	Metronidazole 50 mg/kg + CoQ10 10 mg/kg	CoQ10 10 mg/kg
Percentage alternation (%)	50.50 ± 1.16	26.90 ± 1.03**	45.90 ± 1.20±	66. 25± 1.22β

*P<0.05, **P<0.01 compared to control; βP<0.01, ±P<0.05 when compared with metronidazole. n=5. Control (5 ml/kg 0.5% Tween-80®), metronidazole (50 mg/kg), CoQ10 (10 mg/kg), metronidazole (50 mg/kg) + CoQ10 (10 mg/kg).

The degree of lipid peroxidation as reflected in the concentration of malondialdehyde (MDA) is shown in **Figure 7**. MDA concentration increased significantly ($P<0.001$) after 28-days treatment with 50 mg/kg of metronidazole compared to control. The increase in MDA was reversed by CoQ10 administration either alone or in combination with metronidazole

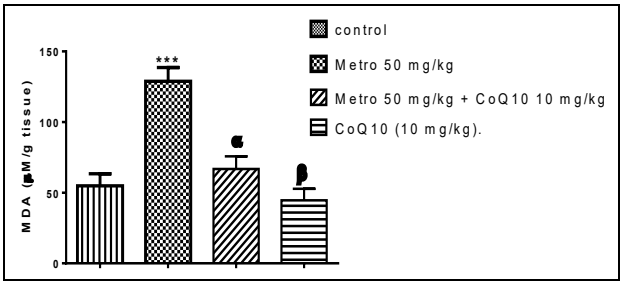

Figure 7. Metronidazole (50 mg/kg) treatment for 28 days resulted in elevated malondialdehyde (MDA) concentration in brain tissue homogenates of treated rats. ***P<0.001 *vs* control, α$P<0,01$, β$p<0.001$ compared to metronidazole, n=5.

DISCUSSION

The brain is a high energy-consuming organ and majorly depends on oxidative phosphorylation to satisfy its high energy demand arising from the sustained obligation of protein and neurotransmitter synthesis in addition to several other processes[22]. The hippocampus thought to be chiefly cognitive in function, receives multiple neuronal inputs from monoaminergic neurons, including axonal projections from the ventral tegmental area, locus coeruleus and the dorsal raphe[23]. It is known to modulate cognitive abilities such as information acquisition, retrieval of declarative memories, attention, and language skill and is prone to increased oxidative stress-induced damage[6].

Cellular ROS (95–98%) is generated as byproducts of oxidative phosphorylation, in the inner mitochondrial membrane. During mitochondrial electron transport, a fraction of electrons derived from nicotinamide adenine dinucleotide (NADH) or flavin adenine dinucleotide (FADH) directly leak out of the electron transport chain and react with oxygen or other electron acceptors to generate free radicals[24]. This oxidative phosphorylation-driven ROS generation is regulated or curtailed by an antioxidant defense mechanism that includes several antioxidant enzymes such as superoxide dismutase (SOD), catalase, superoxide reductase, glutathione peroxidase, and heat shock proteins present in the brain[22]. Several other molecules such as nicotinamide adenine dinucleotide phosphate (NADPH), thioredoxin, vitamin C and E also directly scavenge the ROS[25].

Reductive activation of metronidazole to its active form is reported to increase generation of free radicals which causes damage to susceptible[2,3]. We have previously reported that metronidazole induces cognitive function deficits in rats[26]. In this study, the various tests used to evaluate cognitive function demonstrate that metronidazole induces cognitive dysfunction in the treated rats. In the hole-board experiment, metronidazole induced a reduction memory acquisition, learning, and reduced reference memory index (RMI) (**Figure 1**). This is demonstrated by the low RMI values ($p<0.05$) of metronidazole treated rats in terms of memory acquisition and retention following treatment and infers an impairment in their ability to relate with objects in fixed locations. This cognitive impairment appears to be more pronounced on the fourth day ($p<0.01$) compared to other treatments. A higher escape latency in the Moris water maze for both trial 1 and 2 (**Figure 2**) in metronidazole treated rats ($p,0.05$) compared to control and ($p,0.01$) compared with other treatments is another indicator of metronidazole-induced cognitive dysfunction. This infers that metronidazole treated rats are unable to retain the position of the escape platform or find it at a much-delayed time compared to other treatments. A reduced percentage alternation ($p<0.05$; $p<0.01$) in the Y-maze (**Table1**) for metronidazole treated rats compared with other treatments is another indication of metronidazole-induced cognitive dysfunction. The treated rats exhibited a reduced drive to explore and could not maintain the sequence or arm entries as much as other treatment groups. This reduced exploratory drive resulted in a reduction in visits and time spent in the novel arm than previously visited arms

of the Y-maze compared to other treatment groups and control (P<0.01) with a consequent reduction in spatial recognition memory in terms of discrimination ratio in the metronidazole treated rats (**Figures 3** and **4**). Additionally, a lesser percentage of metronidazole treated rats chose the novel arm as their first choice of entry compared to other treated groups (**Figure 5**).

We also report that metronidazole reduced ($p<0.01$) superoxide dismutase (SOD) activity and increased ($p<0.01$) lipid peroxidation in terms of malondialdehyde (MDA) concentration in the brain homogenates of treated rats compared with other treatments (Figure 6 and 7) which can result in induction of oxidative stress. Multiple cell line based, molecular and behavioral studies implicate oxidative stress as a major culprit in the actuation and advancement of cognitive deficits and several neurodegenerative diseases[27,7]. Hence, we propose that oxidative stress induction is a contributory factor to metronidazole-induced cognitive dysfunction.

Naturally occurring bioactive molecules have been extensively used to improve or restore learning and memory as demonstrated in different animal models. Such memory-enhancing or restoring properties of bioactive compounds are thought to result from reduction of oxidative stress as well as oxidative stress-mediated mitochondrial dysfunctions and oxidation of biomolecules[25]. Moreover, antioxidant supplementation in animal models resulted in improvement of spatial learning memory, working memory, and increased memory retention capacity[28]. Coenzyme Q10 is a naturally occurring redox-active lipid, it is mainly found in the inner mitochondrial membrane of living tissues with elevated energy demands, such as the heart, skeletal muscle and neurons. In addition to mitochondria, CoQ10 is present in peroxisomes, lysosomes, and the Golgi apparatus[29]. It is an obligate component in the electron transport chain and it is associated with the process of oxidative phosphorylation[30]. CoQ10 has notable antioxidant properties like direct scavenging of free radicals, and an indirect regeneration of other antioxidants such as ascorbic acid and alpha-tocopherol, offering protection to cells against oxidative stress processes[29].

SOD is a major detoxifying enzyme in the mitochondrial respiratory chain, it inhibits mitochondrial endogenous ROS production and reduces ROS-associated increase in MDA levels[31]. MDA is the major product of lipid peroxidation[32]. In **Figure 6**, CoQ10 alone or in combination with metronidazole increased the activity of SOD ($p<0.001$) compared with the metronidazole alone treated rats which may translate into an increased free radical scavenging activity. This study also shows that CoQ10 administered alone or in combination with metronidazole reduced ($p<0.001$; $p<0.01$) MDA concentrations in brain homogenates compared with metronidazole alone treated rats (**Figure 7**). These results are in agreement with other reports[13,14,33]. Furthermore, recent clinical studies have shown that CoQ10 administration either in combination with basic treatments or alone increased CoQ10 levels in tissues and improves cognitive functioning[34,35,36]. In this study, the metronidazole + CoQ10 or CoQ10 alone treated rats showed an improvement in cognitive function in the various cognitive and antioxidant tests carried out when compared with the metronidazole treated rats.

CONCLUSION

This study has demonstrated that metronidazole induces cognitive dysfunction in treated rats and that induction of oxidative stress is a possible mechanism. Likewise, combining antioxidants with basic treatment has been suggested for attenuating tissue damage caused by oxidative stress as they have shown positive patient outcomes in several clinical trials. In conclusion, we suggest that CoQ10 improves cognitive function and could be explored to alleviate the occurrence of metronidazole-induced neurotoxicity.

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Conflict of interest

The author declares that there isn't any conflict of interest regarding the publication of this paper.

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