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Assessment of Ameliorative Potential of Co-enzyme Q10 (Co_Q10) Supplementation in Brain Derived Neurotrophic Factor (BDNF) and Serum Acetylcholinesterase (AChE) Altered Rat Models

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Abstract **Original Research Article**

Neurodegenerative diseases affect millions of people worldwide. And the levels of some biomolecules like brain-derived neurotrophic factor (BDNF) and acetylcholinesterase (AChE) are known to play significant roles in different neurodegenerative diseases. The present study therefore assessed the ameliorative potential of Co-enzyme Q10 (CoQ10 or Co_Q10) supplementation in altered levels of BDNF and AChE in thioacetamide (TAA) induced hepatic encephalopathy (HE) in male Wistar rat models. Male Wistar rats weighing 250±30 g were used for the study and were randomly separated into six different groups of twenty rats each. The groups included Group 1-control and received 1ml of normal saline (intraperitoneally—ip), Group 2 received only 200 mg/kg TAA (ip) twice weekly, Group 3 received 5mg/kg Co_Q10, daily per oral (po), Group 4 received 10mg/kg Co_Q10 daily (po), Group 5 received 200 mg/kg TAA (ip) twice weekly and 5mg/kg Co_Q10 (po) daily and Group 6 received 200 mg/kg TAA (ip) twice weekly and 10mg/kg Co_Q10 (po) daily. At the end of weeks 3, 6, 9 and 12 of treatment, blood samples were immediately transferred into appropriately labeled blood sample bottles containing anticoagulant. Numerical data obtained from the study were subjected to statistical analyses using analyses of variance and Post Hoc tools of the statistical package for social sciences 21.0V software. The result indicated significantly ($P<0.05$) depressed level of BDNF and significantly ($P<0.05$) raised level of AChE in the TAA only treated Group 2 when compared to Group 1 and the rest groups. It was observed that, both of Co_Q10 only treated and Co_Q10 + TAA treated groups had marked ($P<0.05$) elevated and depressed levels of BDNF and AChE respectively in the study models. Supplementations with different doses of Co_Q10 (5 and 10mg/kg) indicated significant improvement in TAA altered levels of BDNF and AChE in a mammalian model.

Keywords: Co-enzyme Q10 (Co_Q10) supplementation; thioacetamide (TAA) induced hepatic encephalopathy; brain-derived neurotrophic factor (BDNF); acetylcholinesterase (AChE); Neurodegenerative diseases.

INTRODUCTION

Globally, neurodegenerative diseases are one of the leading causes of morbidity and disability [1, 2]. Categorically, some reliable markers of neurodegenerative disorder have been identified to be reduction in the levels of brain-derived neurotrophic factor (BD_NF) and elevation in the level of acetylcholinesterase (ACh E) [3, 4].

Brain-derived neurotrophic factor (BD_NF) is involved in neuronal modulation, which is critical for learning and memory, as well as neuronal survival and growth. It also functions as a neurotransmitter modifier [5]. On the other hand, higher acetylcholine concentrations brought about by cholinesterase inhibitors enhance neuronal communication and momentarily alleviate or stabilise dementia symptoms [6]. These important markers are known to play significant roles in different neurodegenerative diseases such as Alzheimer's and Parkinson's diseases [7].

Meanwhile, the deficiency of Coenzyme Q-10 has also been linked to some neurological abnormalities such as Alzheimer/Parkinson's diseases, seizures, dystonia (involuntary muscle contractions), spasticity (progressive muscle stiffness) [8].

Coenzyme Q-10 (CoQ10 or Co_Q10) is a natural compound found in most aerobic organisms' mitochondria (including bacteria, mammals, etc [9].

Co_Q10 primarily functions as a cofactor in the electron-transport chain, which is involved in a sequence of redox reactions that lead to the synthesis of adenosine triphosphate [9, 10]. Coenzyme Q10 supplementation has also been said to possess a number of beneficial effects on some of these neurological disorders [11, 12].

Considering the foregoing, the present study, thus, aimed at assessing the ameliorative potential of Co-enzyme Q10 (Co_Q10) supplementation in altered levels of BD_NF and ACh E in thioacetamide (TAA) induced hepatic encephalopathy in male Wistar rat models.

MATERIALS AND METHOD

Animal Handling

Male Wistar rats weighing 250±30g used for the study were procured from the Animal Farm of the Department of Pharmacology, University of Port Harcourt, Nigeria. The set up for the study was at the same location and the animals were housed in standard wire-gauze covered plastic cages with proper beddings under 12hours light/dark cycles at about 25ºC. The animals were then randomly separated into six different groups of twenty rats each.

Experimental Protocol for the Study

The groupings of the animals and their respective treatment protocols were as stated below:
Group 1-control and received 1ml of normal saline (intraperitoneally—ip),
Group 2 received only 200 mg/kg TAA (ip) twice weekly,
Group 3 received 5mg/kg Co_Q10, daily per oral (po),
Group 4 received 10mg/kg Co_Q10 daily (po),
Group 5 received 200 mg/kg TAA (ip) twice weekly and 5mg/kg Co_Q10 (po) daily and
Group 6 received 200 mg/kg TAA (ip) twice weekly and 10mg/kg Co_Q10 (po) daily.

Harvesting of Samples from the Experiment Animals

At the end of weeks 3, 6, 9 and 12 of treatment, blood samples were obtained from the study animals via cardiac puncture after proper sedation using ketamine (70 mg/kg) and xylazine (8 mg/kg) anaesthesia. The obtained blood sample was then immediately transferred into well labeled lithium heparin bottles and presented for the appropriate laboratory investigation.

Determination of Brain-Derived Neurotrophic Factor (BD_NF) and ACh E levels

The enzyme-linked immunosorbent assay (ELISA) technique was used to determine the circulating serum levels of Brain-Derived Neurotrophic Factor (BD_NF) with commercially available ELIZA kit. It was characterized by a sensitivity limit of <2 pg/ml and an internal assay difference below 5% (Procured from Pars Biochem Co., Ltd Rat BD_NF ELISA Kit, China). The determination of ACh E was based on an improved Ellman method [13].

Method of Data Analysis

The quantitative outcomes of the present study were subjected to statistical analyses using analyses of variance and Post Hoc tools of the IBM Statistical Product and Service Solutions (SPSS) 21.0V software. The data were presented as Mean ± Standard error of mean. Differences between means were determined using Analysis of variance (ANOVA) and post-test using LSD multiple comparison test and Dunnett at 95% probability.

Ethical approval

Ethical approval for the present study was granted by the Research Ethics Committee of the University of Port Harcourt with reference number: UPH/CEREMAD/REC/MM86/045.

RESULTS

The data in Table 1 shows the effects of coenzyme Q_{10} on brain derived neurotrophic factor (BD_NF) (ng/ml) in hepatic encephalopathic rat models

Expectedly, the results indicated significant decrease (p=0.001) in the BD_NF level of the thioacetamide induced hepatic encephalopathy (TAA-HE) only animals when compared to those of all other treated groups including the control group (animals that were not on any substance). On the other hand, the administration of coenzyme Q10 alone to the study animals did not cause any significant (P>0.05) change in the serum levels of BD_NF when compared to the control group of rats across treatment weeks 3, 6, 9 and 12. It is, however, important to note that increasing doses of the coenzyme Q10 had correspondingly raised levels of the BD_NF.

Table 1: Effects of Coenzyme Q10 on Brain Derived Neurotrophic Factor (BD_NF) (ng/ml) in Hepatic Encephalopathic Rat Models

Group	Week 3	Week 6	Week 9	Week 12
TAA-HE only	9.45±0.14	8.75±0.24	7.89±0.28	7.14±0.05
Control	29.00±1.00*	31.00±0.57*	30.00±0.46*	33.00±1.00*
Co_Q10 (5mg)	29.00±0.57*	29.50±0.17*	31.60±0.20*	33.00±0.35*
Co_Q10 (10mg)	29.60±0.21*	30.20±0.07*	31.90±0.29*	33.10±0.13*
Co_Q10 (5mg+TAA)	16.00±0.49*	19.10±0.10*	22.40±0.14*	24.00±0.19*
Co_Q10 (10mg+TAA)	20.00±0.35*	24.20±0.07*	26.50±0.18*	29.00±0.40*

Values represent mean ± SEM; n=5. *=significant when compared to that of TAA-only.

Table 2: Effects of Coenzyme Q10 on acetylcholinesterase (IU/L) in thioacetamide induced hepatic encephalopathy (TAA-HE) rat models

Group	Week 3	Week 6	Week 9	Week 12
TAA—HE only	509.00±3.32	572.00±1.41	681.80±2.08	780.00±2.72
Control	489.00±3.11*	540.00±1.14*	574.00±1.14*	600.00±3.54*
Co_Q10 (5mg)	512.00±2.00	489.00±1.58*	470.00±1.70*	460.00±2.30*
Co_Q10 (10mg)	454.00±1.30*	440.00±1.70*	420.00±3.53*	400.00±1.70*
Co_Q10 (5mg+TAA)	640.00±1.41*	592.00±1.14*	579.00±1.70*	540.00±3.69*
Co_Q10 (10mg+TAA)	579.40±2.11*	565.00±1.84*	524.00±1.41*	510.00±1.84*

Values represent mean ± SEM; n=5. *=significant when compared to that of TAA group.

The data displayed in Table 2 indicates the effects of Coenzyme Q10 on ACh E (IU/L) in thioacetamide induced hepatic encephalopathy (TAA-HE) rat models.

The results indicated that TAA-HE group had a significant increase (p=0.001) in ACh E level when compared to the rest of other treated groups including that of the control.

The treatment with coenzyme Q10 alone in the respective group did not result in any significant (P>0.05) changes in the serum levels of ACh E, when compared to that of the control. Notably, also, the Co_Q10 (10mg+TAA) treated was able to marginally (P>0.05) better reduce the TAA-HE when compared to that of the Co_Q10 (5mg+TAA) treated.

DISCUSSION

It is known that tissues and cells involved in immune and other related functions are highly energy-dependent and thus demand a sufficient supply of nutrients or agents that enable optimal function; Co_Q10 has been reported to play a significant role in enhancing both the immune system and physical performance [9]. Further, the treatment of ageing, stroke, neuromuscular disorders, Alzheimer's, Parkinson's, amongst others, has included the widespread use of Co_Q10 supplements [14]. Thus the present study, assessed the ameliorative potential of Co-enzyme Q10 (Co_Q10) supplementation in altered levels of BD_NF and ACh E in thioacetamide (TAA) induced hepatic encephalopathy in male Wistar rat models and the findings as so discussed in the following paragraphs.

In the present study, an acute hepatic encephalopathy (HE) model was established using the thioacetamide (TAA) induction method; as explained by Guo *et al*., [15].

Expectedly, it was observed that administration of TAA led to a marked rise in the serum ACh E level and this finding was in line with the reports of Mladenović *et al.*, [16]. Of course the mechanism has been stated to be due to the breakdown of TAA in liver cells by cytochrome P450 oxidase and lipid peroxidation, liver metabolic disease, and other damage are brought about by the produced toxic TAA sulphur oxide [15]. Similarly, this increase in ACh E activity has also been suggested to be due to an increase in oxidative stress caused by the hepatic TAA metabolism [16, 17].

It is evident that a strong connection exist between oxidative stress and alterations in neurotransmission in the development of hepatic encephalopathy (HE) and this may result in impaired synaptic transmission and cognitive impairment in the HE condition [16, 17]. Conversely, the present study found that the treatment of animals exposed to TAA with Coenzyme Co_Q10 significantly reversed the toxic impact on ACh E activity, thus indicating its possible safe modulating potential on ACh E level. Such a finding may be attributed to Co_Q10's antioxidant potentials.

This line of thought is consistent with the earlier submission of Salama *et al*., [14] that stated that virtually, all cells and tissues of the body can be shielded by the antioxidant effects of coenzyme Q10.

It is understood that, adjusting and normalizing cholinergic transmission may potentially prevent neurodegeneration and reduce neuro-inflammation [18]; it is thus suggestive to state that the ameliorative changes observed in the level of ACh E may have contributed to the oxidative injury in hepatic encephalopathy in the study models.

In another finding of the present study, it was observed that administration of thioacetamide caused a marked drop in the blood levels of brain derived neurotrophic factors (BD_NF). This result agrees with the report of Keshk and Zahran, [19] who observed that thioacetamide caused a marked decrease in cAMP, BD_NF, and CREB in a TAA-HE rat model, thus indicating that thioacetamide administration led to a reduction in BD_NF expression.

On the other hand, treatment of animals exposed to thioacetamide with Co_Q10, considerably reversed the severe neurotoxic drop in BD_NF levels back to normal range. Knowing that Co_Q10 possess

antioxidant properties, it could be inferred that this ability to reverse the levels of BD_NF may be due to the possible anti-oxidant properties [20, 21, 22]. The foregoing outcome of the present study highlights the potential of Co_Q10 in counteracting experimentally induced oxidative stress.

CONCLUSION

The outcome of the present study has shown that supplementations with different doses of Co_Q10 (5 and 10mg/kg) indicated marked improvement in TAA altered levels of BD_NF and ACh E in Wistar rats model at different intervals (including after weeks 3, 6, 9 and 12). It is an indication that the Co_Q10 possess the potential to ameliorate adversely altered levels of BD_NF and ACh E. With the understanding that the main mechanism of TAA-HE is the induction of oxidative stress, it is suggestive to state that the possible anti-oxidant attributes of Co_Q10 maybe potent to counteract initial effects of TAA-HE.

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