Coenzyme Q10 Mitigates Methamphetamine Induced Oxidative Stress and Neurobehavioral Deficits in Adult Male Wistar Rats

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ABSTRACT

Methamphetamine abuse has become a growing public health concern, particularly among Nigerian youths, where it is often consumed for its stimulant and euphoric effects but is associated with severe neurotoxic consequences. This study investigated whether Coenzyme Q10 can protect or restore hippocampal integrity and function in adult male Wistar rats subjected to methamphetamine-induced neurotoxicity. A total of Forty (40) male adult Wistar rat was used for the study. The animals were grouped into four, Group A -D. GROUP A: served as control and received water and feed, GROUP B: received 20mg/kg/day of methamphetamine in a binge-like pattern, with 5 mg/kg administered four times a day at least two hours apart., GROUP C: received 50mg/kg of coenzyme Q10, GROUP D: received 20mg/kg of methamphetamine and 50mg/kg of Coenzyme Q10. Neurobehavioral evaluations (Morris water maze test) were conducted during days 12–14 to capture and evaluate chronic functional outcomes. Twenty-four hours after the end of the last administration which lasted for 14days the animals were euthanised using 80 mg/kg of ketamine through intraperitoneal injection. The brain containing the hippocampus was harvested and either homogenized for biochemical studies or fixed in 10% formalin for histological analysis. Findings from this research present significant ($p < 0.05$) decrease in the weight of group B (exposed to Methamphetamine only), prolonged escape latencies, impaired motor strength, increased lipid peroxidation, and reduced antioxidant markers (MDA, GSH, GPX), with histology revealing severe neuronal degeneration with moderate perivascular edema (PE) and Vacoulation (V). These changes were mitigated using Coenzyme Q10. The study suggests that Coenzyme Q10 has mitigating effects of methamphetamine-induced hippocampus toxicity.

INTRODUCTION

Methamphetamine, commonly referred to as “METH,” is a highly potent and addictive central nervous system (CNS) stimulant belonging to the amphetamine class of drugs[1]. It is a synthetic compound produced from various chemical precursors and was initially developed for legitimate medical purposes, including the treatment of narcolepsy and as a nasal decongestant. Due to its strong euphoric and energizing effects, methamphetamine has become widely misused for recreational purposes. Although its medical applications have largely declined, it is occasionally prescribed as a second-line treatment for attention deficit hyperactivity disorder (ADHD) under strict clinical supervision [1].

In low to moderate doses, methamphetamine can elevate mood, increase alertness, concentration and energy in fatigued individuals, reduce appetite, and promote weight loss[2]. At very high doses, it can induce psychosis, breakdown of skeletal muscle, seizures, and bleeding in the brain. Chronic high-dose use can precipitate unpredictable and rapid mood swings, stimulant psychosis (e.g., paranoia, hallucinations, delirium, and delusions), and violent behavior[1]. Recreationally, methamphetamine's ability to increase energy has been reported to lift mood and increase sexual desire to such an extent that users are able to engage in sexual activity continuously for several days while binging the drug. Methamphetamine neurotoxicity causes adverse changes in brain structure and function, such as reductions in grey matter volume in several brain regions, as well as adverse changes in markers of metabolic integrity[1,2].

The hippocampus is a crucial brain structure primarily involved in learning and memory, particularly the formation of new memories and spatial navigation, this makes the hippocampus particularly susceptible to toxic

insults[3,4,5]. As a result, chronic exposure to methamphetamine is often correlated[,5] with significant hippocampal dysfunction, which manifests as memory deficits and cognitive impairments, symptoms that are well documented in both preclinical and clinical studies[40].

Coenzyme Q_{10}, also known as Ubiquinone, is a lipid-soluble molecule made in mitochondria and it can be found in most cell membranes[9].

In recent years, the neuroprotective effects of Coenzyme Q10 have garnered increasing attention, particularly in the context of neurodegenerative and neurotoxic conditions. Numerous studies have shown that Coenzyme Q10 supplementation can mitigate oxidative damage and improve neuronal survival in experimental models of diseases such as Parkinson's, Huntington's, and models of toxin-induced neurodegeneration[10]. Its antioxidant properties are especially beneficial in the central nervous system, where high metabolic activity and dense mitochondrial populations make neurons particularly vulnerable to oxidative stress[12]. By reducing lipid peroxidation and stabilizing cell membranes, CoQ10 helps preserve the integrity of neuronal structures, including synapses crucial for cognitive function[11].

MATERIALS AND METHODS

Material Used for the Research

Forty (40) male adult Wistar rats, Methamphetamine, Coenzyme Q10, Growers mash (vital feeds), Standard rat cages, Animal weighing balance (Camry, model LB11), Syringes (2ml), Cannula, Conical flask, Beaker, Measuring cylinder, Dissecting kit, Rotatory microtome, Embedding mold, paraffin mold, Hematoxylin and eosin, Photomicroscope (Olympus), spatula, Filter paper (No 1 Whatman filter paper), Cassette, cover lip and slide, plain sterile tubes and bottles, 10% formalin, Rubber gloves, sawdust, Dissecting kits, Refrigerator (Nexus), Electrical weighing scale SF-400C CHINA, Hand gloves.

Procurement and Housing of Experimental Animals

This research was carried out at the Department of Anatomy, Faculty of Basic Medical Sciences, College of Health Sciences, Nnamdi Azikiwe University, Nnewi Campus. Forty (40) male Wistar rats, of nine weeks old (63 postnatal day old), weighing 130 ± 10 g were sourced from a research enterprise, University of Ibadan, Oyo state. The animals were acclimatized for two weeks under standard laboratory conditions, housed in well-ventilated cages at room temperature with a 12-hour light/dark cycle, and maintained on standard rat chow (Agro Feed Mill, Nigeria Ltd.) and distilled water *ad libitum*. All experimental procedures complied with the National Institute of Health Guide for the Care and Use of Laboratory Animals

Drug Procurement and Preparation

Methamphetamine was obtained through the National Drug Law Enforcement Agency (NDLEA), while Coenzyme Q10 was purchased from a licensed pharmaceutical supplier Adoration Pharmacy Nnewi, Anambra state. Methamphetamine was reconstituted in distilled water following Madden et al. (2005) method[12], and Coenzyme Q10 was prepared according to the manufacturer's instructions; stock solutions were freshly prepared daily, and dosages calculated relative to body weight (mg/kg).

Experimental Design

Forty (40) acclimatized adult male Wistar rats (77 postnatal day old), weighing 140 ± 10 g were randomly assigned into four groups.

The rats in various groups were treated accordingly for 14 days; A (Control- Distilled water), B (20 mg/kg/day per oral of Methamphetamine), C (50 mg/kg/day per oral of Coenzyme Q10), D (20 mg/kg/day per oral of Methamphetamine + 50 mg/kg/day per oral of Coenzyme Q10), Methamphetamine was given in a binge-like pattern, with 5 mg/kg administered four times a day at least two hours apart. Oral administration using 24 gauge oral straight gavage needles for both Methamphetamine and Coenzyme Q10 were done daily at room temperature with a pH level of 9.2 for 14 days.

Neurobehavioral Assessments

Neurobehavioral assessments were scheduled near the end of the treatment period to evaluate chronic effects. Morris water maze training was conducted on days 12-14 with a probe trial on day 14. Morris Water Maze test involved pre-training with a visible platform followed by hidden platform trials in opaque water to assess spatial learning and memory[13,38,39].

Termination of Experiment and Sample Collection

Twenty-four hours after the final treatment (day 15), the animals were fasted overnight and anesthetized with ketamine hydrochloride (80 mg/kg, intraperitoneally). The animals were dissected by making a longitudinal incision along the midline trunk to locate the heart and the animals were cardiac perfused using 20 ml of heparinized saline followed by 20 ml of 10% neutral buffer formalin through the right ventricle of the heart. After cardiac perfusion, the brain of the animals was quickly harvested by making an occipitofrontal incision which opens the cranial vault. Three animals from each group had their entire brains prepared for biochemical examination, while the remainder had their entire brains fixed in 10% neutral buffer formalin and used for histological examination. All tissues underwent standard paraffin wax embedding with coronal sections at the same bregma level 3.20 mm which ensures a conspicuous presentation of CA1 region of the hippocampus.

Biochemical Assays

The following biochemical markers were determined:

Lipid Peroxidation (MDA) was measured using the thiobarbituric acid reactive substances (TBARS) method[14] with absorbance set at 530 nm. Results were expressed as nmol MDA/h/g tissue.

Reduced Glutathione (GSH) was determined using Ellman's method with DTNB; absorbance at 412 nm and expressed as μmol/g tissue[15].

Gluthathione Peroxide (GPX) was measured by monitoring NBT reduction; absorbance at 560 nm and expressed as μmol/min/mg protein [16,17].

Histological Processing and Staining

Routine Histopathological Examination Using H&E Staining

The process utilized in processing of histological tissues courses through the following steps according to AlSabaawy *et al*. (2021) [18] The entire brain tissues were immersed in 10% neutral buffer formalin for 48 hours. The fixation was done immediately to prevent autolysis and putrefaction of the tissue. The tissues were subsequently immersed in alcohol for a gradual displacement of water from the tissue in an ascending concentration (70%, 80%, 90% and 100%). The tissues were further prepared for paraffin infiltration by clearing the extremely immiscible alcohol with xylene. After clearing the tissue was infiltrated with paraffin wax, which prepares the tissues for sectioning with microtome. The wax was regulated at 60o and subsequently allowed to cool at 20o which solidify the tissues for sectioning. The infiltrated tissues were placed in a tissue block where they were filled with wax which held the tissue to a fixed position for microtome sectioning. This process is referred to as embedding. The tissues were subsequently sectioned using a microtome into a 5 μm thin section.

Statistical Analysis

Data obtained from the study were analyzed using the Statistical Package for the Social Sciences (SPSS), version 27.0.1 (IBM Corp., Armonk, NY, USA). Results were expressed as mean ± standard deviation (SD). Group comparisons were performed using one-way analysis of variance (ANOVA), and statistical significance was set at $p \leq 0.05$.

RESULTS

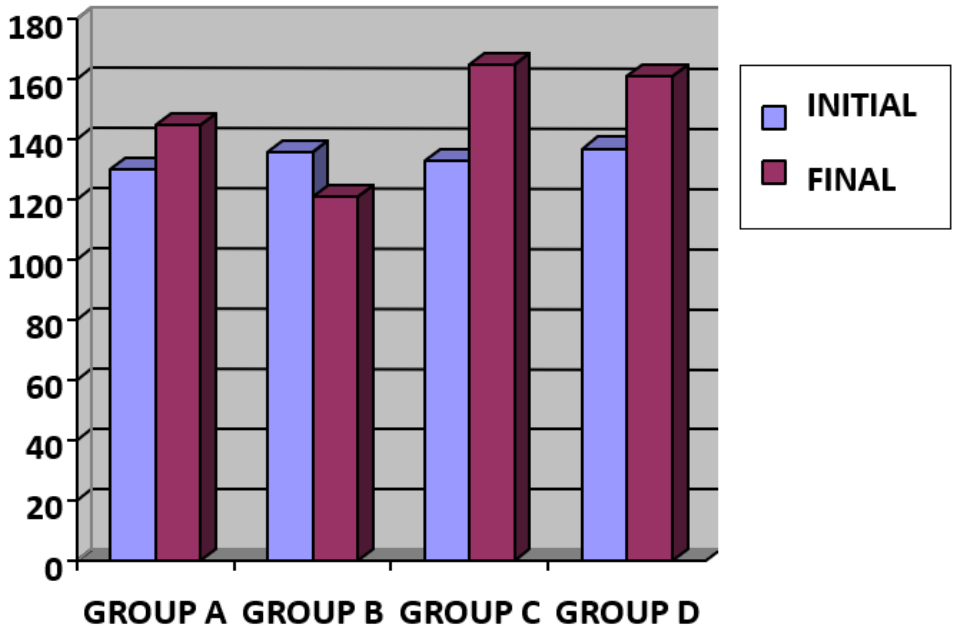
Effect of Methamphetamine and Coenzyme Q10 on Body Weight

As shown in Table 1, the control group (A) recorded an increase in body weight between the initial and final measurements. Group B, treated with methamphetamine, showed significant reduction in body weight. Groups C and D, treated with Coenzyme Q10, exhibited significant weight increases.

Table 1. Effect of methamphetamine and Coenzyme Q10 on body weight of experimental Wistar rats

GROUPS	WEIGHT (g)	MEAN± SEM	p-value
GROUP A	Initial Final	130.40±2.03 145.96±0.02	0.007
GROUP B	Initial Final	136.20±4.83 121.04±6.01	0.001
GROUP C	Initial Final	133.60±1.02 165.00±2.20	0.003
GROUP D	Initial Final	137.60±3.21 161.30±0.03	0.000

Fig 1. Effect of methamphetamine and Coenzyme Q10 on body weight of experimental Wistar rats



Data was analyzed using Student dependent T-test and values were considered significant at P<0.05

Effect of Methamphetamine and Coenzyme Q10 on Spatial Learning and Memory (Morris Water Maze Test)

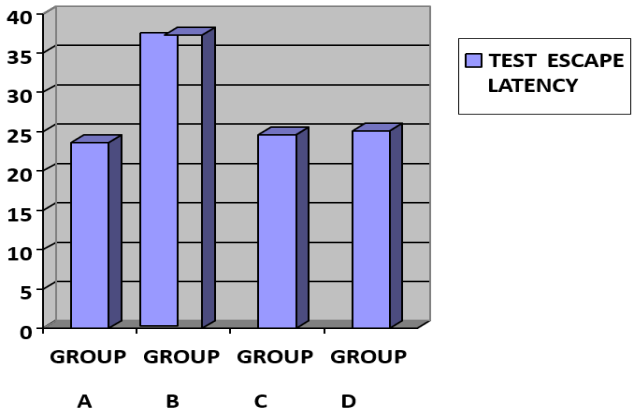
The mean escape latency times of the rats in the Morris water maze are presented in Table 2. Control animals

(Group A) recorded an average latency of 23.60 ± 3.46 seconds. Rats administered methamphetamine alone (Groups B) exhibited significantly prolonged escape latencies (37.31 ± 0.05 seconds; $p < 0.05$) compared to the control. In contrast, animals treated with Coenzyme Q10 alone (Groups C) or in combination with methamphetamine (Groups D) demonstrated latency times (24.60 ± 0.10, and 25.60 ± 0.83 seconds, respectively) that were comparable to the control group. One-way ANOVA yielded a significant overall effect across groups ($F = 5.218$, $p < 0.05$).

Table 2: Result of Morris Water Maze Test

	Groups	**Mean ± SEM**	**p-value**	**F-value**
Morris Water Maze Test- Escape latency (Seconds)	Group A	23.60 ± 3.46		5.218
	Group B	37.31± 0.05	0.004	
	Group C	24.60 ±0.10	0.000	
	Group D	25.10± 0.83	0.002	

Fig .2: Result of Morris Water Maze Test



Values are expressed as Mean ± SEM (n = 5). Statistical significance was determined using one-way ANOVA; $p \leq 0.05$ considered significant.

Biochemical Analysis

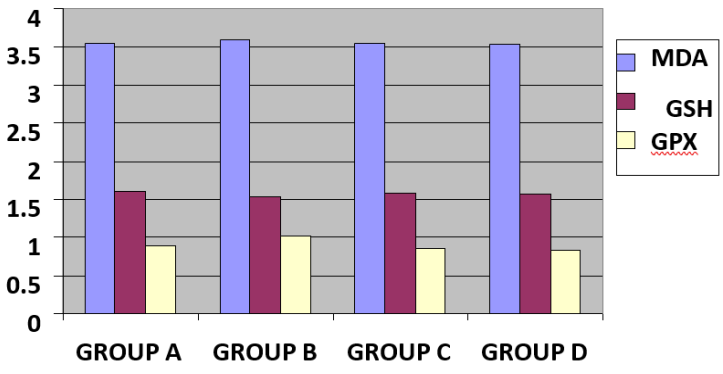
Effects of Methamphetamine and Coenzymes on Oxidative Stress Parameters

Table 3 shows the effects of methamphetamine and CoenzymeQ10 on oxidative stress biomarkers in the hippocampus of Wistar rats. Methamphetamine significantly increased malondialdehyde (MDA) levels compared with the control, while co-treatment with Coenzyme Q10 attenuated this effect Glutathione Peroxide (GPX) activity was significantly altered across groups, whereas reduced glutathione (GSH) concentrations did not differ significantly among the treatment groups.

Table 3: Effects of Methamphetamine and Coenzymes on Oxidative Stress Parameters

	Groups	Mean ± SEM	p-value	F-value
MDA (mm^{-1})	Group A	3.55± 0.02		33.625
	Group B	3.60 ± 0.18	0.000	
	Group C	3.55 ± 0.03	0.004	
	Group D	3.53 ± 1.74	0.001	
GSH (mm^{-1})	Group A	1.60 ± 0.02		11.065
	Group B	1.54 ± 0.01	0.002	
	Group C	1.58 ± 1.54	0.000	
	Group D	1.57± 2.54	0.006	
GPX (u/l)	Group A	0.89 ± 0.06		45.876
	Group B	1.02 ± 0.03	0.000	
	Group C	0.86 ± 0.03	0.000	
	Group D	0.84 ± 0.10	0.000	

Fig 3. Effects of Methamphetamine and Coenzymes on Oxidative Stress Parameters



Data were analyzed using One-way ANOVA, followed by Post HOC Fisher's LSD multiple comparison, and data was considered significant at $P<0.05$

MDA= Malondialdehyde, GSH= gluthathione, GPX= gluthathione peroxide

Histological Findings

Histlogy of the Hippocampus stained with H and E staining techniques

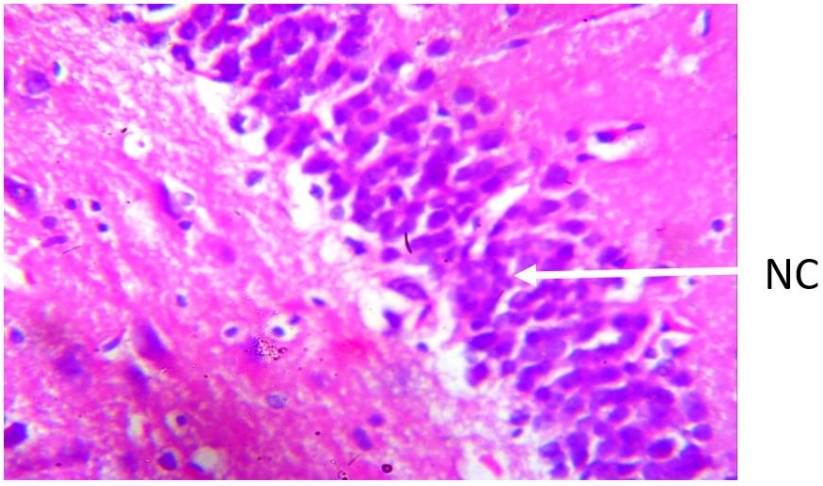


Plate 1(group A): Photomicrograph of section of hippocampus (x400) (H/E) shows active neuronal cells.

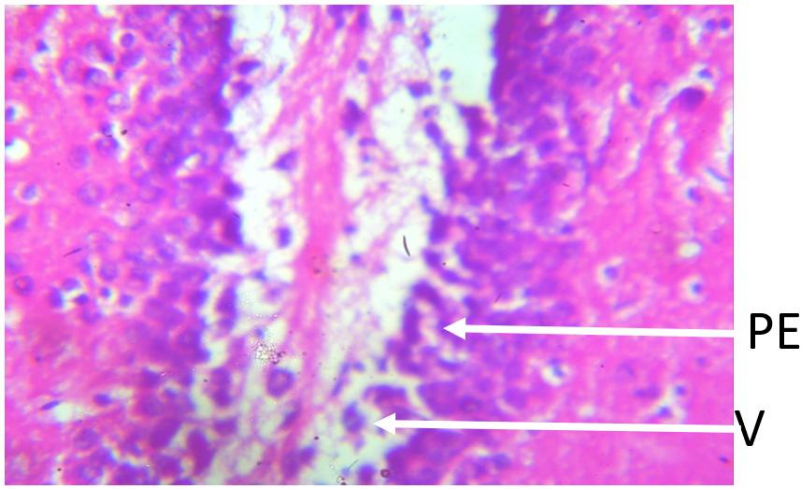


Plate 2.Group B Photomicrograph of gp B section of hippocampus lobe induced with meth only (x400) (H/E) shows severe neuronal degeneration with moderate perivascular edema (PE) and Vacoulation (V).

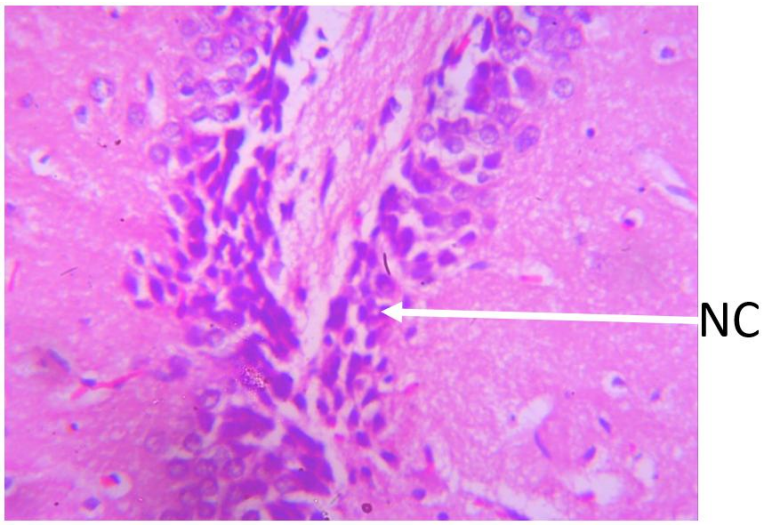


Plate 3. Group C: Photomicrograph of gp C Q10 section of hippocampus administered with Q10 low dose x400) (H/E) shows active neuronal cells

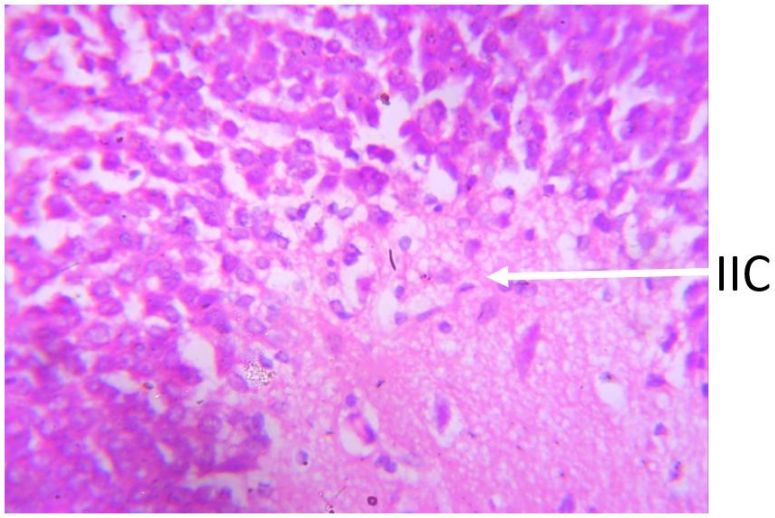


Plate 4. Group D: Photomicrograph of gp D Q10 section of hippocampus induced with methamphetamine and treated Coenzyme Q10 (x100(x400) (H/E) shows moderate healing with mild infiltration of inflammatory cells (IIC)

DISCUSSION

Methamphetamine is a powerful stimulant, which doctors use to treat sleep problems(narcolepsy), attention deficit hyperactivity disorder (ADHD), and severe overweight problems. In small doses, methamphetamine can increase wakefulness and physical activity and decrease appetite. However, in high doses, it can increase body temperature to dangerous and possibly deadly levels, as well as cause seizures[6,7].

The hippocampus plays essential roles in emotions, motivation, hormonal activity, autonomic activity, and memory formation. Its most recognized function is learning and memory, which involve the interaction of individuals with the environment and large distributed networks[7].

Findings from this research present notable decrease in the weight of group exposed to 20 mg/kg/day per oral of Methamphetamine when compared to the control and a significant increase in final weight between group C exposed to 50 mg/kg/day per oral of Coenzyme Q10), and group D exposed to 20 mg/kg/day per oral of Methamphetamine + 50 mg/kg/day per oral of Coenzyme Q10. Methamphetamine increases the release of dopamine, norepinephrine, and serotonin in the brain, these neurotransmitters suppress appetite by acting on the hypothalamus, the region that controls hunger. Thus, resulting to reduced food intake that eventually leads to weight lost [19]. CoQ10 is capable of rendering anti-inflammatory effects that leads to the reduction of inflammation in the central nervous system, also the release of Cytokine release (TNF-α, IL-6), helping to improve appetite and digestion which will eventually result to weight gain [20]. Also, in animals stressed by Methamphetamine, CoQ10 protects tissues from wasting through its potent antioxidant properties that reduces Reactive oxygen species (ROS), Lipid peroxidation, Mitochondrial injury, preventing weight loss, supporting normal metabolism [20].

There was a significant increase in Spatial learning and memory (Morris water maze test) among the group exposed to 20 mg/kg/day per oral of Methamphetamine (Group B), a lesser increase in group C exposed to 50 mg/kg/day per oral of Coenzyme Q10), and group D exposed to 20 mg/kg/day per oral of Methamphetamine + 50 mg/kg/day per oral of Coenzyme Q10 compare to the control. Methamphetamine is said to lead to increased synaptic dopamine and norepinephrine when administered in Low doses, resulting to improve Attention, working memory, motivation, learning[21]. Also, Dopamine in the hippocampus and prefrontal cortex boosts spatial navigation ability, which the Morris Water Maze heavily depends on[22]. CoQ10 does not increase dopamine and does not enhance arousal, leading to subtle improvements [23,24]. However, CoQ10 enhances ATP production in neurons that leads to improved synaptic efficiency. Also, the antioxidant properties possessed by CoQ10 protects hippocampal neurons, improving learning and memory [25].

There was a slight increase in Malondialdehyde activity among the group exposed to 20 mg/kg/day per oral of Methamphetamine (Group B), no significant effect (increase or decrease) in group C exposed to 50 mg/kg/day

per oral of Coenzyme Q10), and a slight decrease in group D exposed to 20 mg/kg/day per oral of Methamphetamine + 50 mg/kg/day per oral of Coenzyme Q10 compare to the control. METH promotes dopamine oxidation, mitochondrial dysfunction and activation of oxidative enzymatic pathways, these processes increase reactive oxygen/nitrogen species that attack membrane lipids, leading to a rise in MDA level [26]. However, in healthy animals with normal redox balance, exogenous antioxidants often do not lower MDA significantly because there is little excess lipid peroxidation to correct as the antioxidant benefit of CoQ10 is most apparent in models with elevated oxidative stress [27]. CoQ10 acts as a lipophilic antioxidant (preventing lipid chain-propagation) in the mitochondrial electron transport chain. Therefore, when METH elevates ROS it is neutralized by CoQ10, lowering formation of MDA [20].

There was a slight decrease in gluthathione activity among the group exposed to 20 mg/kg/day per oral of Methamphetamine (Group B), in group C exposed to 50 mg/kg/day per oral of Coenzyme Q10), and group D exposed to 20 mg/kg/day per oral of Methamphetamine + 50 mg/kg/day per oral of Coenzyme Q10 compare to the control. The excessive dopamine release/oxidation, mitochondrial dysfunction, and activation of ROS-generating enzymes (e.g., NOX) property of Methamphetamine increases intracellular reactive oxygen species (ROS). The produced ROS react with membrane lipids and proteins and are detoxified by GSH, which is therefore oxidized to GSSG and consumed producing a net decrease in reduced GSH levels [28]. CoQ10 can enhance activity of GPx using GSH as substrate or shift redox balance transiently, resulting in increased GSH turnover (temporary reduction of reduced GSH) [29]. Also, the continues production of ROS enable continues glutathione used by GPx and glutathione S-transferases; CoQ10 may reduce ROS generation but not immediately refill intracellular reduced GSH pools [30].

There was a significant increase in glutathione peroxide activity among the group exposed to 20 mg/kg/day per oral of Methamphetamine (Group B), a slight decrease in group C exposed to 50 mg/kg/day per oral of Coenzyme Q10), and group D exposed to 20 mg/kg/day per oral of Methamphetamine + 50 mg/kg/day per oral of Coenzyme Q10 compare to the control. At moderate oxidative challenge GPx, is not immediately depleted; instead acts as an adaptive response while the system is still coping (before severe depletion sets in) [29]. This aligns with the slight increase noticed among the group exposed to 20 mg/kg/day per oral of Methamphetamine. CoQ10 improves mitochondrial efficiency and reduces oxidative stress; this action results to a fewer and low production of peroxides thus, the organism may not maintain GPx at a high activity level.

Histological photomicrographic view shows severe neuronal degeneration with moderate perivascular edema (PE) and Vacoulation (V) in group B induced with meth only, active neuronal cells in group C administered with Q10 low dose, moderate healing with mild infiltration of inflammatory cells (IIC) in group D induced with methamphetamine and treated Coenzyme Q10 compare to the control group (group A) that shows active neuronal cells. Methamphetamine (METH) increases cytosolic dopamine and its redox cycling, producing reactive oxygen/nitrogen species and damaging mitochondria; when ATP production collapses, neurons cannot maintain ion gradients or membrane integrity, leading to structural breakdown (degeneration) [31]. Also, METH exposure activates microglia and pro-inflammatory cascades, which amplify oxidative damage and promote further neuronal injury [32]. When mitochondria and endoplasmic reticulum are stressed, they swell and degenerate. histologically this appears as cytoplasmic clearing/vacuoles alongside degenerating neurons [33]. CoQ10 is a key carrier in the electron transport chain that improves mitochondrial efficiency helping neurons maintain energy-dependent processes such as ion pumps, synaptic transmission, repair, which preserves [34]. Also, CoQ10 possess antioxidant/mitochondria-stabilizing actions that helps keep ROS generation low and prevent the cascade that would otherwise push neurons toward degeneration keeping the tissue largely normal [35]. CoQ10 attenuates METH-associated neurotoxicity, reducing the initial damage burden after injury, lowering the inflammation profile compare to the intense destructive inflammation seen with unchecked toxicity [33].

A limitation of this study is that behavioral assessments were carried out only at the end of the 14-day experiment. While this timing allowed for the evaluation of chronic outcomes, it did not capture the progression of changes over time. Future studies should therefore incorporate both interim and terminal assessments to better distinguish acute from long-term effects of METH exposure and Coenzyme Q10 supplementation.

CONCLUSION

This study demonstrates that methamphetamine exerts significant neurotoxic effects on the hippocampus of adult male Wistar rats, characterized by oxidative stress, anxiety-related behaviors, neuronal degeneration, and

disruption of hippocampal architecture. These findings are consistent with previous reports showing that methamphetamine triggers neuronal damage primarily through oxidative stress, neuroinflammation, and excitotoxicity

Importantly, co-administration of Coenzyme Q10 mitigated many of the methamphetamine-induced alterations. Rats receiving combined treatment exhibited preserved hippocampal structure, reduced signs of neuronal degeneration, and improved overall neurobehavioral outcomes. This supports existing evidence that Coenzyme Q10, particularly in its reduced form, functions as a potent antioxidant and mitochondrial stabilizer capable of protecting neural tissue from toxic degeneration

Overall, the study reinforces the neurotoxic potential of methamphetamine on hippocampal integrity and highlights Coenzyme Q10 as a promising neuroprotective agent. Its antioxidant and anti-inflammatory actions may offer therapeutic value against methamphetamine-induced brain injury.

Conflict of interests: The authors have no conflict of interests to declare

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Authors' contribution: All the authors contributed to the research conception and design, data interpretation, drafting, and revising the manuscript.

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