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Protective Effect of Coenzyme Q10 on Methamphetamine-Induced Neurotoxicity in the Mouse Brain

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ABSTRACT

We investigate the effects of Coenzyme Q10 (CoQ10) supplementation on methamphetamine (METH)-induced neurotoxicity in the mouse brain. We used 30 mice divided into three groups containing 10 animals each: a control group, a brain injury group treated with METH and a group treated with METH+CoQ10. Various assays, such as protein thiol group, glutathione total, lipid peroxidation, catalase, superoxide dismutase and glutathione peroxidase, were used to assess the damage caused by METH and the protective effects of CoQ10 on brain tissues. The METH-induced brain injury significantly increased lipid peroxidation and decreased the level of the thiol group, the glutathione total and the activity of brain antioxidant enzymes (catalase, superoxide dismutase and glutathione peroxidase). The CoQ10 supplementation prevents all of these typically observed changes in METH-treated mice. Our results reveal that CoQ10 is potentially protective against METH-induced neurotoxicity in mice.

Key words: Coenzyme Q10, methamphetamine, antioxidant enzyme, neurotoxicity, lipid peroxidation

INTRODUCTION

Coenzyme Q (2,3-dimethoxy-5-methyl-6-multiprenyl-1,4-benzoquinone) (CoQ) is composed of a tyrosine-derived quinone ring, linked to a polyisoprenoid side chain, consisting of 9 or 10 subunits in higher invertebrates and mammals. Mice can synthesize both CoQ9 and CoQ10, which differs one from each other by the length of their isoprenoid side chain. The CoQ9 is the major form in mouse. The CoQ is distributed in cellular membranes, is an essential component of the mitochondrial respiratory chain (Lucchetti *et al*., 2013). It is only lipid-soluble antioxidant that animal cells synthesize de novo. It is a redox molecule and then, can exist in reduced CoQ and oxidized CoQ forms in the biological tissues. The major form of CoQ found in the living organism is the reduced form, ubiquinol ($CoQH_2$), which is primarily responsible for the antioxidant properties of CoQ. This molecule also plays a crucial role in cellular metabolism, acting as the electron carrier between complexes I and II and the complex III of the mitochondrial respiratory chain; regulating uncoupling proteins, the transition pore, β-oxidation of fatty acids and nucleotide synthesis pathway. The CoQ is also considered as a central molecule in the maintenance of an antioxidant system for protecting membranes from peroxidation. It occupies a privileged position because it links basic aspects of cell physiology such as energy metabolism, antioxidant protection

and the regulation of cell growth and death (Bentinger *et al*., 2010). The CoQ has a potent antioxidant activity, protecting phospholipids from peroxidation (Bentinger *et al*., 2010). The CoQ endogenous can protect membrane proteins and DNA against oxidative damage mediated by lipid peroxidation (Onur *et al*., 2014). The CoQ can inhibit lipid peroxidation by preventing the production of lipid peroxyl radicals ($LOO^{\cdot}$) and moreover, $CoQH_2$ reduces the initial perferryl radical, with concomitant formation of ubisemiquinone and H_2O_2. This quenching of the initiating perferryl radicals, which prevent propagation of lipid peroxidation, protects not only lipids but also proteins from oxidation.

Methamphetamine (METH) is an abused psychostimulant drugs which have stimulant, euphoric, empathogenic and hallucinogenic effects. High or repeated methamphetamine doses produce persistent damage to dopamine (DA) and serotonin (5HT) nerve terminals, result in hyperthermia, neurotoxicity and even mortality (Cruickshank and Dyer, 2009). The METH is a substrate for both DA transporter and 5 HT transporter and is transported into the axon terminal, then it can increase in both DA and 5 HT release (Thomas *et al*., 2010). The damage associated with METH has been persisted for at least 2 years in rodents, non-human primates and humans (Halpin *et al*., 2014). Furthermore, METH exposure generated the reactive oxygen species in cytoplasmic and caused oxidative damaged axon terminals of neuron cells (Loftis and Janowsky, 2014). The METH also leads to oxidative stress via increases in reactive nitrogen species by increasing nitric oxide synthase activity (Friend *et al*., 2014). The aim of this study was to investigate the role of supplementation with CoQ10 in the prevention of neurotoxicity induced by methamphetamine in brain in mice.

MATERIALS AND METHODS

Materials: Methamphetamine hydrochloride, CoQ10, 5,5-dithiobis (2-nitrobenzoic acid), 1-methyl-2-phenylindole butylated hydroxytoluene, glutathione reductase enzyme, Nicotinamide adenine dinucleotide phosphate (NADPH), hydrogen peroxide, pyrogallol, Triton X-100, EDTA, all buffers and other reagents were purchased from Sigma-Aldrich.

Animals and feeding regimens: A total of 30 eight-week-old male C57BL/6J mice were used in our study. Animals were housed into enriched environmental conditions in groups of 10 animals per polycarbonate cage in a colony room under a 12 h light/dark cycle (12:00 AM-12:00 PM) under controlled temperature (25±3°C) and humidity. All animals were maintained accordingly to a protocol approved by the Ethical Committee of the Vietnam National University, Hanoi and following the international rules for animal research. Animals were received water *ad libitum* as vehicle and standard diet administration (AIN-93M). Animals were randomly divided in three groups of ten animals each: Control, METH and (CoQ10+METH). Group control received saline, group METH received 20 mg of METH/kg i.p., group (CoQ10+METH) received (20 mg of METH+10 mg of CoQ10)/kg i.p., for 7 successive days. The animals were sacrificed after 24 h following last injection by decapitation. Brain tissues were dissected and frozen in liquid nitrogen and stored in -80°C until analysis.

Tissue homogenization: Frozen tissue of brain was homogenized in 9 volumes of ice-cold tissue lysis buffer containing 150 mM sodium chloride, 1.0% NP-40, 50 mM Tris, pH 8.0 and 1 mM PMSF (phenylmethane sulfonylfluoride) with protease inhibitors (Sigma, Singapore). Homogenates were centrifuged at 1,000×g for 10 min at 4°C. The supernatant was used for the estimation of

malondialdehyde (MDA), protein thiol (SH) groups, glutathione total (GT), catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities. Protein concentration was determined by Bradford's method (Bradford, 1976).

Determination of protein thiol (SH) groups: Protein SH groups were estimated by Ellman's method (Al-Rejaie *et al*., 2013). The assay was performed in a plate 96 wells Sterilin (Fisher Scientific, UK) where 10 μL of homogenate was transferred to each well containing 180 μL of 0.1 M buffer sodium phosphate pH 8.0, 1 mM EDTA, 10 μL of 10 mM 5,5-dithiobis (2-nitrobenzoic acid) (DTNB). Absorbance was measured at 412 nm in Omega Microplate Reader (BMG Labtech, Germany) after 15 min incubation at room temperature. The SH group content was determined from a standard curve in which the L-cystein (Sigma-Aldrich, Singapore) standard equivalents present (0, 25, 50, 100 and 200 nmol) was plotted against the absorbance. The amount of sulfhydryl group was reported as nmol per mg total protein.

Lipid peroxidation assay: Measurement of malondialdehyde (MDA) has frequently been used to measure lipid peroxidation. Lipid peroxidation assay was performed by determining the reaction of malonaldehyde with two molecules of 1-methyl-2-phenylindole at 45°C (Gasparovic *et al*., 2013). The reaction mixture consisted of 0.64 mL of 10.3 mM 1-methyl-2-phenylindole, 0.2 mL of sample and 10 μL of 2 μg mL^{-1} butylated hydroxytoluene. After mixing by vortex, 0.15 mL of 37% v/v HCl was added. Mixture was incubated at 45°C for 45 min and centrifuged at 6500 rpm for 10 min. Cleared supernatant absorbance was determined at 586 nm. A calibration curve prepared from 1,1,3,3-tetramethoxypropane (Sigma-Aldrich, Singapore) was used for calculation. Peroxidized lipids are shown as nmol MDA equivalents/mg protein.

Determination of glutathione total: Whole amount of glutathione, i.e., reduced (GSH) plus oxidized (GSSG) forms, was determined by method suggested by Anderson (1985). One milliliter assay mixture contained 880 μL of 143 mM sodium phosphate buffer (pH 7.5) and 6.3 mM EDTA, 100 μL of 6 mM DTNB, 10 μL homogenates and 10 μL of 12 mM NADPH that was incubated for 10 min at 30°C. Reaction was started by addition of 5 μL Glutathione reductase enzyme (GR) 5 UI mL^{-1} and absorbance recorded for 5 min at 412 nm. Enzyme activity was calculated using the extinction coefficient of 14.15 mM^{-1} cm^{-1} for TNB and the amount of GSH was determined by using a standard curve in which the GSH standard equivalents present (5, 10, 15 and 20 nmol) is plotted against the rate of change of absorbance at 412 nm. Activity is reported as nmol per mg total protein.

Catalase (CAT) activity determination: The CAT activity was measured in triplicate according to the method of Aebi by monitoring the disappearance of H_2O_2 at 240 nm. Thirty μL homogenate was suspended in 2.5 mL of 50 mM phosphate buffer (pH 7.0) (Aebi, 1984). Assay started by adding 0.5 mL of 0.1 M hydrogen peroxide solution and absorbance at 240 nm was recorded every 10 sec during 2 min and used to calculate CAT activity. Hydrogen peroxide solution was substituted by phosphate buffer in the negative control. The CAT activity was determined by using the molar extinction coefficient 39.4 M^{-1} cm^{-1} for H_2O_2 and was expressed IU min^{-1} mg^{-1} protein where 1 IU activity = 1 μmol H_2O_2 converted to H_2O per min.

Superoxide dismutase (SOD) activity determination: Total SOD activity in tissue homogenates was determined following the procedure of Marklund and Marklund with some modifications (Marklund and Marklund, 1974). The method is based on the ability of SOD to inhibit

the autoxidation of pyrogallol. In 970 µL of buffer (100 mM Tris-HCl, 1 mM EDTA, pH 8.2), 10 µL of homogenates and 20 µL pyrogallol 13 mM were mixed. Assay was performed in thermostated cuvettes at 25°C and changes of absorption were recorded by a spectrophotometer (EVO 210, Thermo-Fisher, UK) in triplicate at 420 nm. The SOD activity was expressed as IU min^{-1} mg^{-1} protein where one IU of SOD activity was defined as the amount of enzyme can inhibit the auto-oxidation of 50% the total pyrogallol in the reaction.

Glutathione peroxidase (GPx) activity determination: The GPx activity was measured with a coupled enzyme assay (Flohe and Gunzler, 1984). The 1 mL assay mixture contained 770 µL of 50 mM sodium phosphate (pH 7.0), 100 µL of 10 mM GSH, 100 µL of 2 mM NADPH, 10 µL of 1.125 M sodium azide, 10 µL 100 U mL^{-1} glutathione reductase and 10 µL homogenate. The mixture was allowed to equilibrate for 10 min. The reaction was started by adding 50 µL of 5 mM H_2O_2 to the mixture and NADPH oxidation was measured during 5 min at 340 nm. One unit of glutathione peroxidase was defined as the amount of enzyme able to produce 1.0 µmol $NADP^+$ from NADPH per min. The GPx activity was determined using the molar extinction coefficient 6.22 M^{-1} cm^{-1} for NADPH at 340 nm and reported as IU per mg total protein.

Statistical analysis: All results are expressed as Mean±SEM. Serial measurements were analyzed by using two-way ANOVA with Tukey's post hoc test using Sigma Stat 3.5 program and figures were performed by using SigmaPlot 10.0 program (Systat Software Inc). The critical significance level α was 0.050 and, then, statistical significance was defined as $p<0.05$.

RESULTS

Protein thiol (SH) groups play important role in many cellular function and metabolism. The oxidation of thiol groups protects the cell in the manifestations of oxygen toxicity (Hansen *et al.*, 2009). As shown in Fig. 1, SH levels were significantly lower in METH group as compared with Control group. Interestingly, it was found that SH levels were significantly increased in mice group (METH+CoQ10) as compared with METH group.

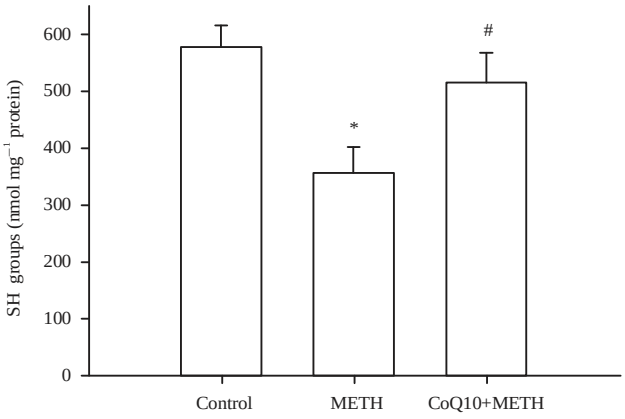

Fig. 1: Effects of CoQ10 on protein thiol (SH) group level in METH-induced neurotoxicity on mice. Values are the Mean±SEM (n = 10). *Significantly different from control mice ($p<0.05$), #Significantly different from METH-treated mice ($p<0.05$). Protein thiol group levels are indicated as nmol mg^{-1} protein

Glutathione (GT) is an important antioxidant in cells, preventing damage to important cellular components caused by reactive oxygen species such as free radicals, peroxides, lipid peroxides and heavy metals (Chen *et al*., 2013). We estimated the levels of critical endogenous antioxidant GT in brain of three animals groups in order to determine the effects of METH and CoQ10 in the synthesis of GT. As shown in Fig. 2, GT levels were significantly lower in METH group as compared with control group. Interestingly, it was found that GT levels were significantly increased in mice group (METH+CoQ10).

Lipid peroxidation of biomembranes is one of the principal degenerative effects of free radicals. Figure 3 shows the amount of lipid peroxidation in the three groups of animals. There was a significant increase in the levels of MDA in METH group. Treatment with CoQ10 significantly decreased the elevated levels of MDA in METH-treated mice.

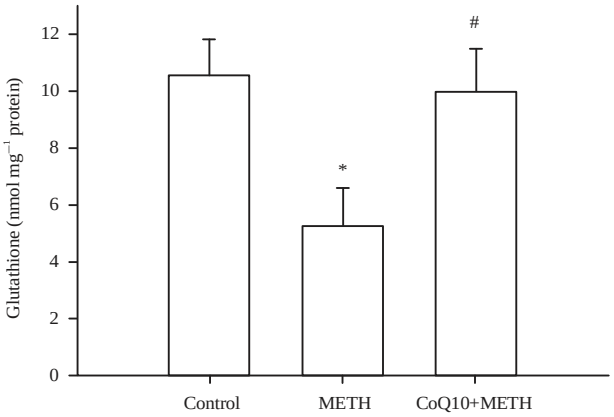

Fig. 2: Effects of CoQ10 on glutathione level in METH-induced neurotoxicity on mice. Values are the Mean±SEM (n = 10). *Significantly different from control mice ($p<0.05$), #Significantly different from METH-treated mice ($p<0.05$). Glutathione levels are indicated as nmol mg^{-1} protein

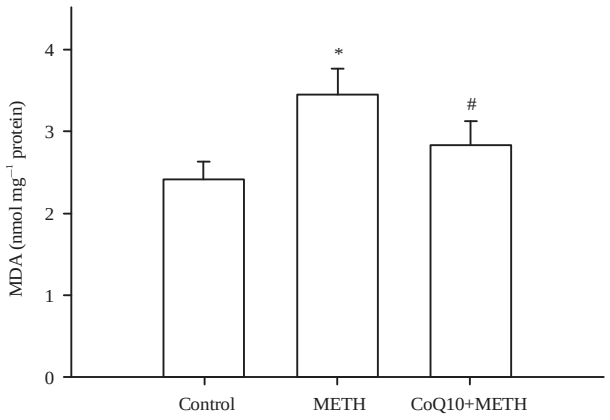

Fig. 3: Effects of CoQ10 on MDA level in METH-induced neurotoxicity on mice. Values are the Mean±SEM (n = 10). *Significantly different from control mice ($p<0.05$), #Significantly different from METH-treated mice ($p<0.05$). MDA levels are indicated as nmol mg^{-1} protein

Antioxidant enzymes play important role to protect cellular components from oxidative damage. SOD, CAT and GPx are important enzymes in the elimination of reactive oxygen species. In this study, we determined the SOD, CAT and GPx activities as an index of antioxidant status of brain tissues.

The CAT activity was showed in Fig. 4. It was significantly decreased in METH-treated mice compared to that in normal controls. However, activity of this enzyme was a near normal in mice treated with METH combined with CoQ10.

Total SOD activity was also decreased by METH as shown in Fig. 5. Significantly lower activities of liver SOD were observed in METH group as compared to the normal control group. There were significant increases in SOD activity in the (METH-CoQ10) groups compared to the METH group ($p<0.05$).

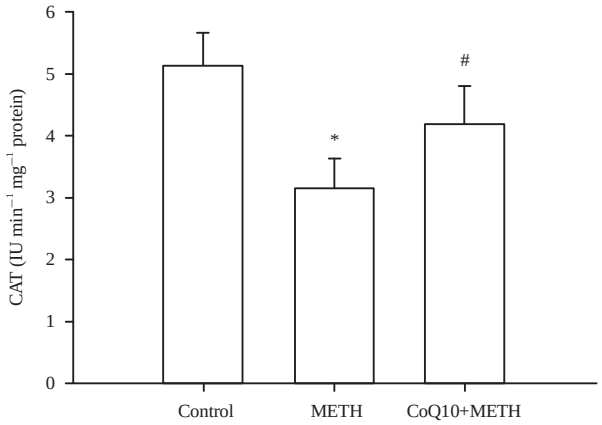

Fig. 4: Effects of CoQ10 on CAT activity in METH-induced neurotoxicity on mice. Values are the Mean±SEM (n = 10). *Significantly different from control mice ($p<0.05$), #Significantly different from METH-treated mice ($p<0.05$). Activities are indicated as IU min^{-1} mg^{-1} protein

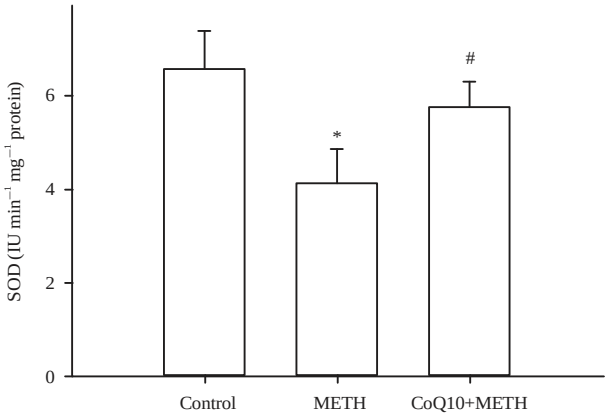

Fig. 5: Effects of CoQ10 on SOD activity in METH-induced neurotoxicity on mice. Values are the Mean±SEM (n = 10). *Significantly different from control mice ($p<0.05$), #Significantly different from METH-treated mice ($p<0.05$). Activities are indicated as IU min^{-1} mg^{-1} protein

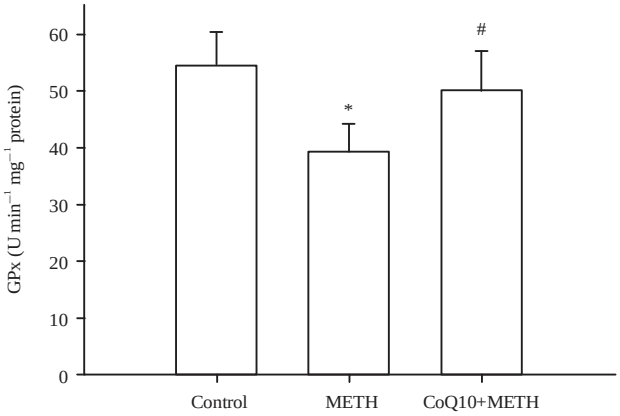

Fig. 6: Effects of CoQ10 on GPx activity in METH-induced neurotoxicity on mice. Values are the Mean±SEM (n = 10). *Significantly different from control mice ($p<0.05$), #Significantly different from METH-treated mice ($p<0.05$). Activities are indicated as IU min^{-1} mg^{-1} protein

The GPx is an antioxidant enzyme that converts hydrogen peroxide and lipid peroxides to their corresponding alcohols. Enzymatic activity of GPx showed a significant drop by METH as showed in Fig. 6. This activity was also increased significantly by treatment with CoQ10.

DISCUSSION

In this study, we examined the protective effect of CoQ10 against METH-induced neurotoxicity. Our data showed that (1) METH induced oxidative stress on brain tissues and decreased level of SH group, glutathione, enzymatic antioxidant activity and increased MDA levels, (2) brain oxidative enzymatic activity was enhanced and lipid peroxidation was alleviated by CoQ10. Our findings suggest that treatment with CoQ10 may provide an effective method for protecting the brain against damage following METH administration in mice.

Previous studies demonstrate that generation of ROS and oxidative stress after consumed of METH. Animal studies show that the activities of enzymatic antioxidant systems decrease and the products of lipid peroxidation increase after METH administration (Halpin *et al*., 2014; Loftis and Janowsky, 2014). In our study, lipid peroxidation product as MDA were increased in the METH-treated group. Our data was agree with Acikgoz *et al*. (1998) which published that the METH induced the lipid peroxidation in brain. Lipid peroxidative degradation of the biomembrane is one of the principal mechanisms for the generation of free radicals. The increase of MDA levels lead to damage brain tissue and failure of antioxidant defense mechanisms to prevent the formation of excessive free radicals (Amresh *et al*., 2007). The CoQ10 with antioxidant properties may provide endogenous defense systems and reduce both the initiation and propagation of reactive oxygen species. The CoQ10 effectively reduced levels of MDA in brain tissues.

The SH groups are potential sites of reversible oxidative modification by S-glutathiolation and S-nitrosylation but they are also susceptible to irreversible damage by oxidative conditions. The increased amount of SH groups damage may be critically important to the function of signal-transduction and transcription events that utilize proteins containing these reactive sites (Brandes *et al*., 2009). The SH groups play important role in the metabolism as antioxidant protectors and in detoxification reactions. Free SH groups are needed for the activity of many

enzymes, for example lactate dehydrogenases and other enzymes in the respiratory chain (Medina-Navarro *et al*., 2010). Our study showed that METH decreased the SH groups and CoQ10 could revert this damage. Our results are in agreement with the study of Chandramani Shivalingappa *et al*. (2012) which reported that METH induced dopaminergic neurodegeneration and reduced this SH group.

Glutathione is a tripeptide composed of glutamate, cysteine and glycine that exists in thiol-reduced (GSH) and disulfide-oxidized (GSSG) form. The peptide has an important role in detoxifying reactions such as scavenging cellular hydrogen peroxide and conjugation of electrophilic metabolites of xenobiotics (Franco and Cidlowski, 2012). Our data have shown that the METH decreased the level of GT and this level in animals treated with the CoQ10 could be increased. Our results are consistent with similar studies reported by other investigators (Klongpanichapak *et al*., 2006; Shivalingappa *et al*., 2012).

Among the antioxidant enzymes, the superoxide dismutase (SOD) is considered to be the first line of defense against oxidative stress, since they convert to O_2 and H_2O_2 (Fukai and Ushio-Fukai, 2011), which is subsequently transformed into H_2O by catalase. The SOD family is ubiquitously distributed in almost all forms of aerobic lives and classified into four classes based on associated metal cofactors, namely copper/zinc SOD (Cu/ZnSOD), manganese SOD (MnSOD), iron SOD (FeSOD) and nickel SOD (NiSOD) (Fukai and Ushio-Fukai, 2011). In this study, the total SOD enzyme was elevated in (METH+CoQ10) group. CoQ10 caused direct activation of SOD enzyme to catalyze O^{2-} produced by METH.

Catalase is a homotetramer with a subunit molecular mass of ~60 kDa and belongs to a group of monofunctional catalases with small subunit size (Zamocky *et al*., 2008), found mainly in peroxisomes, converts H_2O_2 to water and molecular oxygen (Kirkman and Gaetani, 2007). In the present study, the catalase activity was elevated by CoQ10 administration against METH-induced neurotoxicity. Therefore, CoQ10 may have a synergistic effect with catalase as it causes a direct activation of catalase by eliminating the ROS molecules from the system.

Glutathione peroxidase (GPx) is an enzyme which prevents the generation of hydrogen peroxide and alkyl hydroperoxides in association with glutathione and glutathione reductase, as well as the generation of more harmful metabolites such as the hydroxyl radical. The GPx converts hydrogen peroxide and lipid peroxides to their corresponding alcohols and glutathione is oxidized to glutathione disulfide (Parodi, 2007). In this study, the GPx activity were significantly increased in all the METH+CoQ10-treated mice compared to METH-treated mice alone. Our findings showed that CoQ10 increased GPx activity and level of GT, thiol group to exhibit its antioxidant mechanism. Our data are in agreement with previous studies which showed that CoQ10 supplements at a dose of 500 mg day^{-1} can decrease oxidative stress and increase antioxidant enzyme activity in patients with multiple sclerosis (Sanoobar *et al*., 2013). Also, Ishrat *et al*. (2006) have shown the neuroprotective effect of CoQ10 on cognitive impairments and oxidative damage in hippocampus and cerebral cortex of intracerebroventricular-streptozotocin infused rats. They have demonstrated that CoQ10 significant decreased the markers of oxidative damage and increased the level of ATP in the hippocampus and cerebral cortex of rat (Ishrat *et al*., 2006).

The present findings demonstrated that CoQ10 protects neuronal cells against METH-induced neurotoxicity. This molecular may be considered as a potent therapeutic agent for neurodegeneration associated with free radical generation in the central nervous system. Others experiments are needed to clarify the mechanisms of this CoQ10.

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