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Original Article

Protective Effects of Propofol Against Methamphetamine-induced Neurotoxicity

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ABSTRACT

Context: Methamphetamine (METH) is widely abused in worldwide. METH use could damage the dopaminergic system and induce neurotoxicity via oxidative stress and mitochondrial dysfunction. Propofol, a sedative-hypnotic agent, is known for its antioxidant properties. In this study, we used propofol for attenuating of METH-induced neurotoxicity in rats. **Subjects and Methods:** We used Wistar rats that the groups (six rats each group) were as follows: Control, METH (5 mg/kg IP), and propofol (5, 10 and 20 mg/kg, IP) was administered 30 min before METH. After 24 h, animals were killed, brain tissue was separated and the mitochondrial fraction was isolated, and oxidative stress markers were measured. **Results:** Our results showed that METH significantly increased oxidative stress markers such as lipid peroxidation, reactive oxygen species formation and glutathione oxidation in the brain, and isolated mitochondria. Propofol significantly inhibited METH-induced oxidative stress in the brain and isolated mitochondria. Mitochondrial function decreased dramatically after METH administration that propofol pretreatment significantly improved mitochondrial function. Mitochondrial swelling and catalase activity also increased after METH exposure but was significantly decreased with propofol pretreatment. **Conclusions:** These results suggest that propofol prevented METH-induced oxidative stress and mitochondrial dysfunction and subsequently METH-induced neurotoxicity. Therefore, the effectiveness of this antioxidant should be evaluated for the treatment of METH toxicity and neurodegenerative disease.

Key words: Methamphetamine, mitochondria, neurotoxicity, oxidative stress, propofol

INTRODUCTION

Methamphetamine (METH) is an amphetamine analog that its abuse has widely increased and become a serious public concern with more than 35 million users in worldwide.[1,2]

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It has been demonstrated that METH use could affect the central nervous system and causes neurotoxicity.[3,4] Previous studies have revealed that the increase in dopamine and glutamate in the brain plays an important role in mediating METH-induced neurotoxicity.[5-7]

Several mechanisms have been suggested for METH-induced neurotoxicity but recently the focus has been on the role

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of oxidative stress in METH-induced toxicity. Reactive oxygen species (ROS) and quinones can be generated by auto-oxidation and enzymatic oxidative metabolism of dopamine that overwhelm the antioxidant defense systems and lead to oxidative stress. METH-induced oxidative stress has been shown after administration of METH.[8,9] In addition, Açikgöz *et al*. described an increase in extracellular concentrations of oxidized glutathione (GSH) after METH administration.[10]

Indeed, it was observed that administration of some antioxidants such as Vitamin C and E partially attenuate METH-induced neurotoxicity.[11] In another study, N-acetyl cysteine pretreatment reversed the toxic effects of METH on brain cells by inhibition of GSH oxidation and reduction of METH-induced ROS formation.[2] Eskandari *et al*. showed mitochondrial membrane potential (MMP) collapse and cytochrome C release from mitochondria after METH exposure in rat hepatocytes that was inhibited by antioxidants and ROS scavenger which demonstrating the role of oxidative stress and mitochondrial dysfunction in METH-induced cytotoxicity.[12] Hence, mitochondrial dysfunction can be linked to METH toxicity and even METH-induced-ROS formation cause exacerbation of mitochondrial damage, which leads to failure of energy hemostasis and an increase in oxidative stress.

Furthermore, Pre- and post-treatment of mice with L-carnitine, a mitochondriotropic compound, revealed neuroprotective effects against METH-induced toxicity to maintain the mitochondrial permeability transition (MPT) that confirm the role of mitochondria in the initiation of cell death signaling after METH exposure.[9]

The brain is very sensitive to oxidative stress, which in part is due to high oxygen consumption, low levels of some antioxidant enzymes, and high concentrations of polyunsaturated fatty acids (PUFA).[13] On the other hand, mitochondria are an important site of ROS formation in cells and are the main source of energy production in the brain tissue.[14]

There are numerous antioxidants that are used in clinical studies for attenuating situation that oxidative stress damage is involved. In this study, we have focused on the protective role of propofol against METH-induced-oxidative stress in brain tissue and mitochondria.

Propofol (2, 6-diisopropylphenol) is an intravenous sedative-hypnotic agent that is widely used for both induction/maintenance of anesthesia and sedation.[15] Propofol's structure contains a phenolic hydroxyl group and thus is similar to some antioxidant compounds like α-tocopherol (Vitamin E). Hence, several *in vitro* and *in vivo* studies showed that this phenolic chemical structure may result in the antioxidant activity of propofol.[16]

However, there is no study about the protective effect of propofol against METH-induced neurotoxicity and mitochondrial oxidative damage. Therefore, in our study we investigated the protective role of propofol in METH-induced neurotoxicity in rats that received METH.

SUBJECTS AND METHODS

Animals treatment

Male Wistar rats (200–250 g) were housed in an air-conditioned room with controlled temperature of 22 ± 2°C and maintained on a 12:12 h light cycle with free access to food and water. All experimental procedures were conducted according to the ethical standards and protocols approved by the Committee of Animal Experimentation of Mazandaran University of Medical Sciences, Sari, Iran. All efforts were made to minimize the number of animals and their suffering.

Animals were randomly divided into six groups of six animals and the groups were as follows: Control group, METH group, METH plus different concentration of propofol group, and Vitamin E group (as positive control). All chemicals were dissolved in normal saline.

One group of animals received only normal saline and was assigned as a control. METH was administered (5 mg/kg IP) and propofol (5, 10 and 20 mg/kg, IP) was administered 30 min before METH. After 24 h, animals were killed, brain tissue was separated and then was minced and homogenized with a glass handheld homogenizer and some parts were used for mitochondrial preparation using differential centrifugation technique.[13] The isolation of mitochondria was confirmed by the measurement of succinate dehydrogenase.[17] The biochemical parameters determined included - brain tissue: Total protein, ROS, lipid peroxidation (LPO), GSH and catalase (CAT), brain mitochondria: 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay, GSH, ROS, LPO, GSH, and mitochondrial swelling.

Total protein assay

Protein concentrations were determined by the Coomassie blue protein-binding method as explained by Bradford, 1976.[18]

Quantification of reactive oxygen species level

The ROS level measurement was performed using DCFH-DA as an indicator. Briefly, DCFH-DA was added (final concentration, 10 μM) to samples (1 mg protein/ml) and then incubated for 10 min. The amount of ROS generation was determined through a Shimadzu RF5000U fluorescence spectrophotometer at 485 nm excitation and

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520 nm emission wavelength; the results were expressed as the fluorescent intensity per 1 mg protein.[19]

Measurement of glutathione content

GSH content was determined using DTNB as the indicator and the developed yellow color was read at 412 nm on a spectrophotometer (UV-1601 PC, Shimadzu, Japan). GSH content was expressed as μM.[20]

Measurement of lipid peroxidation

The content of malondialdehyde (MDA) was determined by the thiobarbituric acid (TBA) reactive substances expressed as the extent MDA of productions during an acid-heating reaction. Briefly, 0.25 ml sulfuric acid (0.05 M) was added to 0.2 ml samples (1 mg protein/ml) afterward, with the addition of 0.3 ml 0.2% TBA. All the microtubes were placed in a boiling water bath for 30 min. At the end, the tubes were shifted to an ice-bath, and 0.4 ml n-butanol was added to each tube. Then, they were centrifuged at ×3500 *g* for 10 min. The amount of MDA formed in each of the samples was assessed by measuring the absorbance of the supernatant at 532 nm with an ELISA reader (Tecan, Rainbow Thermo, Austria). Tetramethoxypropane was used as a standard and MDA content was expressed as nmol/mg protein.[21]

Catalase assay

CAT activity was assayed in the samples by measuring the absorbance decrease at 240 nm in a reaction medium containing H_2O_2 (10 mM), sodium phosphate buffer (50 mM, pH: 7.0). One unit of the enzyme is defined as 1 mol H_2O_2 as substrate consumed/min and the specific activity is reported as units/mg protein.[22]

Assessment of mitochondrial toxicity

Mitochondrial toxicity was assessed by measuring the reduction of MTT with minor modification of Ghazi-Khansari *et al*., 2007. This assay is a quantitative colorimetric method to determine the mitochondrial functionality that the yellow tetrazolium salt (MTT) is metabolized from mitochondrial succinate dehydrogenase to purple formazan. Briefly, 100 μL of mitochondrial suspensions (1 mg protein/ml) was incubated according to the individual experiment at 37°C for 60 min; then, 0.4% of MTT was added to the medium and incubated at 37°C for 30 min. The product of formazan crystals were dissolved in 100 μL dimethyl sulfoxide, and the absorbance at 570 nm was measured with an ELISA reader (Tecan, Rainbow Thermo, Austria).[23]

Determination of mitochondrial swelling

Analysis of mitochondrial swelling was performed through changes in light scattering as monitored spectrophotometrically at 540 nm.[24] Briefly, isolated mitochondria were suspended in swelling buffer (70 mM sucrose, 230 mM mannitol, 3 mM hepes, 2 mM trisphosphate, 5 mM succinate, and 1 μM of rotenone) and the absorbance was measured at 540 nm with an ELISA reader (Tecan, Rainbow Thermo, Austria). A decrease in absorbance indicates an increase in mitochondrial swelling.

Statistical analysis

Results are presented as mean ± standard error. All statistical analyses were performed using the SPSS Statistics for Windows, Version 21.0 (IBM Corp. Armonk, NY). Assays were performed in triplicate, and the mean was used for statistical analysis. Statistical significance was determined using the one-way ANOVA test, followed by the *post-hoc* Tukey test. Statistical significance was set at $P < 0.05$.

RESULTS

Reactive oxygen species formation

In brain tissue: As shown in Figure 1a, METH exposure increased ROS formation as compared to control group ($P < 0.05$), whereas propofol pretreatment at doses (5 and 10 mg/kg) did not cause significant change in ROS formation as compared to METH group. However, pretreatment with 20 mg/kg of propofol resulted in significant reduction of METH-induced ROS formation as compared to METH group ($P < 0.05$). Furthermore, Vitamin E administration significantly ($P < 0.05$) decreased METH-induced-ROS formation.

In brain mitochondria: Administration of METH increased ROS formation as compared to control group ($P < 0.05$). Propofol (20 mg/kg) significantly prevented METH-induced-ROS formation in brain mitochondria but did not change ROS level when administrated at doses of 5 and 10 mg/kg. Vitamin E pretreatment did not have any effect on METH-induced-ROS formation [Figure 1b].

Lipid peroxidation

In brain tissue: As shown in Figure 2a, following METH exposure, MDA level was significantly increased in brain tissue as compared to control, while MDA level was significantly ($P < 0.05$) inhibited by pretreatment propofol (20 mg/kg) and Vitamin E ($P < 0.05$).

In brain mitochondria: Administration of METH significantly increased MDA level as compared to control group ($P < 0.05$). Pretreatment with propofol decreased METH-induced-LPO as dose dependent manner that was significant ($P < 0.05$) at doses of 10 and 20 mg/kg. Propofol at doses of 5 mg/kg did not have any effect on

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METH-induced-LPO. The same effect was observed by administration of Vitamin E [Figure 2b].

Glutathione concentration

In brain tissue: The brain GSH concentration was found to be decreased as a consequence of ROS formation in METH-treated rats compared with control group ($P < 0.05$). Also, pretreatment of propofol (20 mg/kg) significantly ($P < 0.05$) inhibited the METH-induced GSH oxidation in brain tissue [Figure 3a].

In brain mitochondria: Administration of METH significantly decreased GSH content as compared to control group ($P < 0.05$). Pretreatment with propofol decreased METH-induced-GSH oxidation as dose dependent manner that was significant ($P < 0.05$) at a dose of 20 mg/kg. Administration of Vitamin E did not significantly change GSH content when compared to METH group [Figure 3b].

Catalase activity

Administration of METH significantly ($P < 0.05$) increased CAT activity as compared to control group in brain tissue. Propofol at doses of 5 mg/kg did not significantly change CAT activity compared to METH group but at doses of 10 and 20 mg/kg of propofol significantly decreased brain CAT activity compared to METH group [Figure 4].

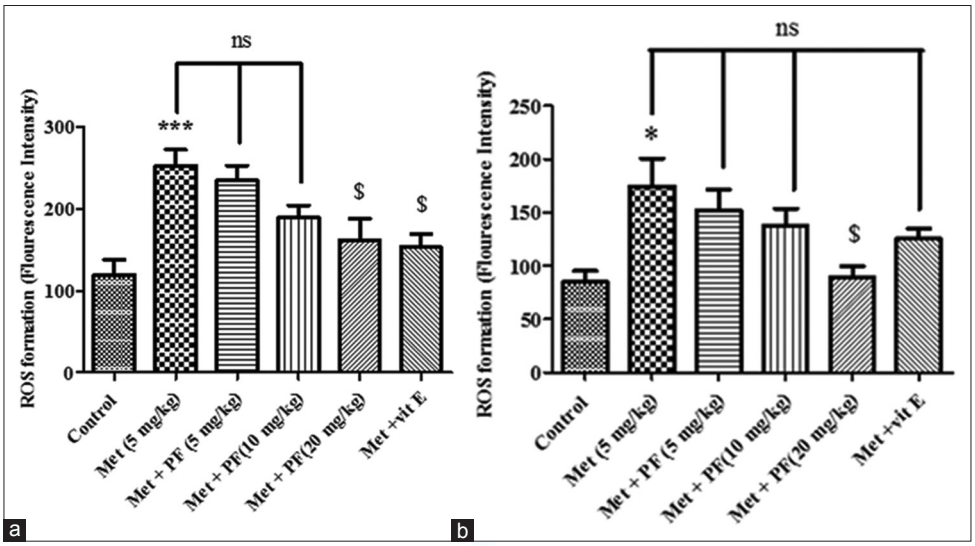


Figure 1: Effects of propofol on methamphetamine-induced reactive oxygen species production in: (a) Brain tissue, and (b) brain isolated mitochondria. Data were expressed as mean ± standard error of mean ($n = 6$). Reactive oxygen species production was evaluated by dichlorofluorescein as an indicator as described in Materials and Methods. *Significantly different from control group ($P < 0.05$), $^{\$}$significantly different from methamphetamine group ($P < 0.05$)

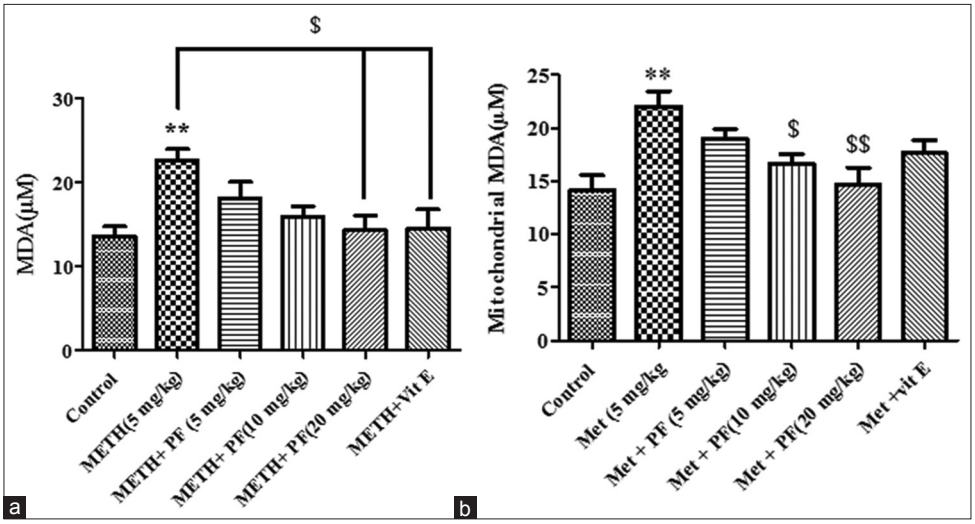


Figure 2: Effects of propofol on methamphetamine-induced lipid peroxidation in: (a) Brain tissue, and (b) brain isolated mitochondria. Data were expressed as mean ± standard error of mean ($n = 6$). Lipid peroxidation was evaluated by thiobarbituric acid as an indicator as described in Materials and Methods. *Significantly different from control group ($P < 0.05$), $^{\$}$significantly different from methamphetamine group ($P < 0.05$)

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Mitochondrial function

The mitochondrial function can be evaluated by MTT test. In this assay, the yellow tetrazolium salt (MTT) metabolized by mitochondrial dehydrogenase enzyme to yield a purple formazan reaction product that is an indicator of mitochondrial function. METH administration significantly ($P < 0.05$) decreased mitochondrial function as compared to control group in brain mitochondria. Propofol attenuated METH-induced-mitochondrial toxicity as dose dependent manner that was significant ($P < 0.05$) at doses of 20 mg/kg of propofol. Vitamin E pretreatment also significantly ($P < 0.05$) inhibited METH-induced-mitochondrial toxicity [Figure 5].

Mitochondrial swelling

Mitochondrial swelling is an indicator of mitochondrial membrane permeability that can be monitored by the changes of absorbance at 540 nm (A540). Administration of METH leads to mitochondrial swelling that was significant as compared to control group. Furthermore, Vitamin E and propofol (20 mg/kg) significantly ($P < 0.05$) suppressed the decline in A540 of brain mitochondria treated with METH [Figure 6].

DISCUSSION

There is evidence showing that oxidative stress and mitochondrial dysfunction contributed in neurodegenerative diseases such as Alzheimer and Parkinson and Mania disease.[25-28] Also, studies showed the relation between oxidative damage and amphetamine-induced behavior disturbance.[29] It is clear that amphetamines decreased the activities of the erythrocyte antioxidant enzymes GSH peroxidase, CAT, and superoxide dismutase, and these implicated the potential role of oxidative stress in amphetamine-induced neurotoxicity.[30] Mitochondria as the main cellular ATP supplier has an important role in maintaining neuronal homeostasis. In addition, mitochondria are the major source of ROS production and have a key role in cell death. Hence, mitochondrial dysfunction leads to excessive production of ROS that could contribute to neuronal injury.[31,32]

METH abuse is a serious public in worldwide[1,2] and could cause various organ toxicity like neurotoxicity.[3,4] The precise cellular mechanism of METH-induced neurotoxicity is still unknown.[33] Recently, studies showed the role of oxidative stress in METH-induced neurotoxicity. Also, it was suggested that oxidative damage of mitochondria might be the initial step in tissue damage caused by METH.[33,34] Another study showed that amphetamines enhance hepatotoxicity in isolated rat hepatocyte by GSH oxidation and oxidative stress.[35] In the present study, we

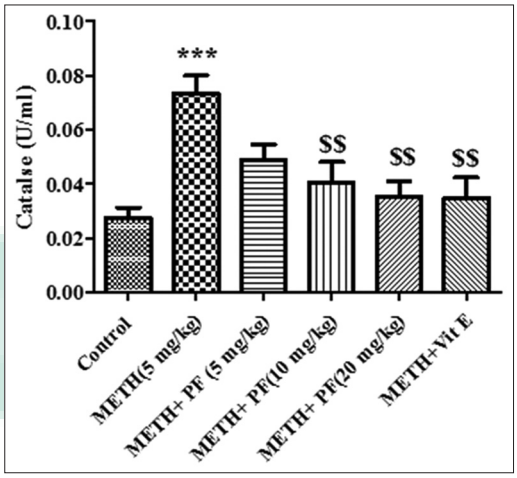


Figure 4: Effects of propofol and methamphetamine on catalase activity in brain tissue. Data were expressed as mean ± standard error of mean ($n = 6$). Catalase activity was evaluated as described in Materials and Methods. *Significantly different from control group ($P < 0.05$), $^{\$}$significantly different from methamphetamine group ($P < 0.05$)

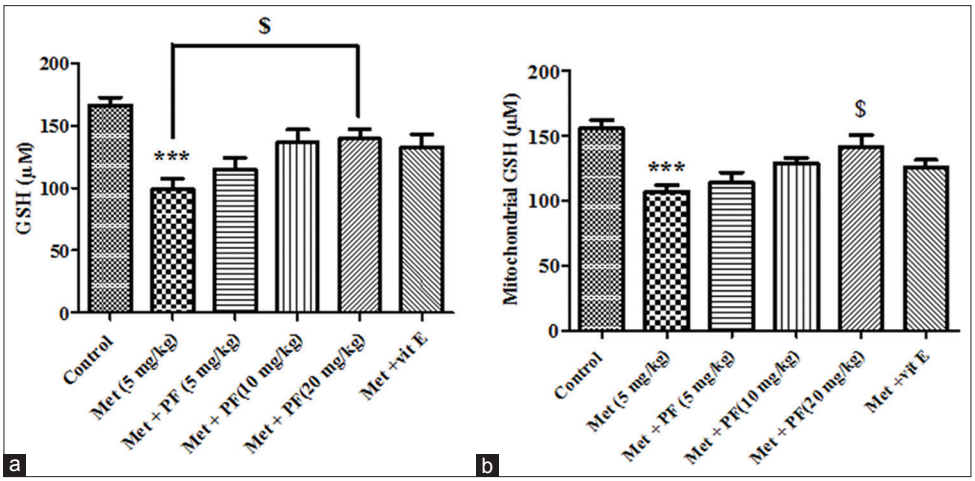


Figure 3: Effects of propofol on methamphetamine-induced glutathione content in: (a) Brain tissue and (b) brain isolated mitochondria. Data were expressed as mean ± standard error of mean ($n = 6$). Glutathione content was evaluated by DTNB as an indicator as described in Materials and Methods. *significantly different from control group ($P < 0.05$), $^{\$}$significantly different from methamphetamine group ($P < 0.05$)

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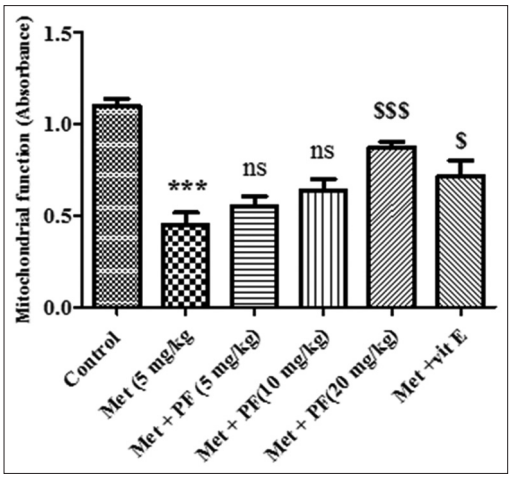


Figure 5: Effects of propofol on methamphetamine-induced mitochondrial toxicity in brain isolated mitochondria. Data were expressed as mean ± standard error of mean (n = 6). Mitochondrial toxicity was evaluated by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide test as described in Materials and Methods. *Significantly different from control group (P < 0.05), $^{\$}$significantly different from methamphetamine group (P < 0.05)

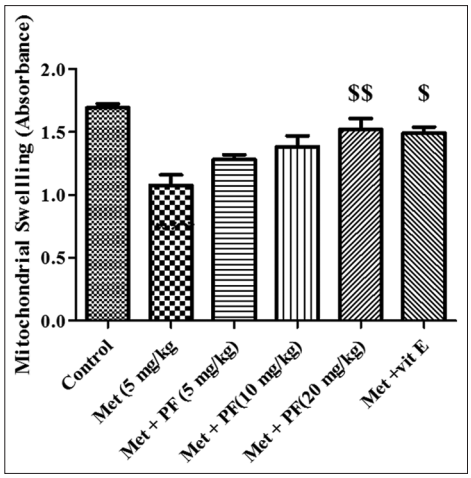


Figure 6: Effects of propofol on methamphetamine-induced mitochondrial swelling in brain isolated mitochondria. Data were expressed as mean ± standard error of mean (n = 6). Mitochondrial swelling was evaluated as described in Materials and Methods. *Significantly different from control group (P < 0.05), $^{\$}$significantly different from methamphetamine group (P < 0.05)

evaluated the role of oxidative stress and mitochondrial damage in METH-induced neurotoxicity and ability of propofol for attenuating toxic effects of METH.

Our results revealed the impairment of the antioxidant defense system in the brain tissue and also isolated brain mitochondria (decreased GSH and increased CAT activity) in the METH group. This depletion of the antioxidant system could be as results of METH-induced-oxidative stress that was well showed by increased ROS formation and LPO. Our data confirmed the results of previous studies that showed METH decreased intracellular GSH, increased MDA levels, and intracellular ROS production.[2,36]

Both *in vivo* and *in vitro* studies showed that METH increased dopamine release in neurons and increased ROS formation after METH exposure, can be as a result of auto-oxidation of cytosolic free dopamine.[33]

Brain tissue has a high content of PUFA that can be attacked by ROS and caused LPO and damage to cell or mitochondrial membrane. On the other hand, the brain has low antioxidant enzyme capacity that makes it sensitive to oxidative stress.[13]

Our results showed that METH administration significantly induced LPO in brain tissue and isolated mitochondria as a consequence of METH-ROS formation, which finally could lead to blood-brain barrier disruption. The elevation of LPO was reported in several neurodegenerative diseases such as Alzheimer disease, Parkinson disease, and amyotrophic lateral sclerosis.[37,38] In addition, both *in vivo* and *in vitro* studies showed increased oxidative stress after METH exposure in SH-SY5Y neuroblastoma cells[39] and in rat brain tissues.[40,41]

Indeed, elevation of LPO in mitochondria not only cause disruption of the mitochondrial membrane but also induces the collapse of MMP land, the release of cytochrome C.[42] Furthermore, GSH is required for the maintenance of reduced form of thiol groups in the mitochondrial membrane proteins. Oxidation of mitochondrial membrane thiol may induce conformational changes in the MPT pores structure that leads to MPT.[43] Depletion of GSH content, as well as mitochondrial swelling, was shown after METH administration. Mitochondrial swelling is critically related to loss of mitochondrial membrane integrity and finally brain cell death and tissue damage. Our findings strongly suggested a central role of oxidative stress and mitochondrial dysfunction in the mechanism underlying METH neurotoxicity.

Previous studies showed protective effects of some antioxidant such as N-acetyl cysteine, ascorbic acid, Vitamin E, and selenium against METH toxic effects.[11,44,45]

Propofol is an intravenous sedative-hypnotic agent now-a-day is used for induction and maintenance of general anesthesia as well as for sedation. Propofol has a similar structure to that of α-tocopherol and showed antioxidant effects in various experimental models.[15] Previous studies showed that propofol is able to scavenge free radicals and inhibition of LPO.[46] In this basis, we used propofol for increased antioxidant capacity, protection against oxidative stress, and subsequently decreased METH-induced neurotoxicity.

As indicated in the results section, propofol significantly attenuated ROS formation and LPO both in brain tissue and isolated brain mitochondria. These data confirmed

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earlier reports about the ability of propofol to inhibition of LPO.[47,48]

Propofol also significantly inhibited METH-induced GSH oxidation that might be linked to induction of expression of antioxidant enzymes.[49] Previous studies reported that propofol significantly inhibited mitochondrial dysfunction following CCL4 administration due to its antioxidant effects.[50] Our study showed that propofol significantly reversed METH-induced mitochondrial toxicity. It has been shown that propofol could inhibit MPT pore opening, MMP collapse, and inhibiting mitochondrial pathway of apoptosis signaling.[51,52]

Our results also showed that propofol strongly inhibited mitochondrial swelling as an indicator of MPT pore opening.

CONCLUSION

Our results showed that METH could induce oxidative stress and mitochondrial damage in the brain that probably is contributed in METH neurotoxicity. On the other hand, propofol, with its free radical scavenging and antioxidant properties reduced METH-induced oxidative stress and mitochondrial toxicity. Hence, it seems that can be a highly promising agent in protecting against METH-induced oxidative damage. As a conclusion, we believe that the use of propofol may provide an advantage in ameliorating the METH neurotoxicity.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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