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Effect of α-tocopherol and deferoxamine on methamphetamine-induced neurotoxicity

Mee-Jung Park[a], *Sang-Ki Lee*[a], *Mi-Ae Lim*[a], *Hee-Sun Chung*[a], *Sung-Ig Cho*[b], *Choon-Gon Jang*[c], *Sun-Mee Lee*[c,*]

[a]*Dept. of Forensic science, National Institute of Scientific Investigation, Yangchon-ku, Seoul, 158-707, Korea*
[b]*Brain Disease Research Center, School of Medicine, Ajou University, Suwon 443-721, Korea*
[c]*College of Pharmacy, Sungkyunkwan University, Suwon 440-746, Korea*

ARTICLE INFO

Article history:
Accepted 13 June 2006
Available online 17 July 2006

Keywords:
Methamphetamine
Free radical
Neuronal damage
Dopamine

Abbreviations:
DA, dopamine
DFO, deferoxamine
DOPAC, dihydroxyphenylacetic acid
GSH, reduced glutathione
GSSG, oxidized glutathione
5-HIAA, 5-hydroxyindole acetic acid
HVA, homovanillic acid
MA, methamphetamine
ROS, reactive oxygen species
TBARS, thiobarbituric acid reactive substances
α-TC, α-tocopherol

ABSTRACT

Methamphetamine (MA)-induced dopaminergic neurotoxicity is believed to be associated with the increased formation of free radicals. This study examined the effect of α-tocopherol (α-TC), a scavenger of reactive oxygen species, and deferoxamine (DFO), an iron chelator, on the MA-induced neurotoxicity. Male rats were treated with MA (10 mg/kg, every 2 h for four injections). The rat received either α-TC (20 mg/kg) intraperitoneally for 3 days and 30 min prior to MA administration or DFO (50 mg/kg) subcutaneously 30 min before MA administration. The concentrations of dopamine (DA), serotonin and their metabolites decreased significantly after MA administration, which was inhibited by the α-TC and DFO pretreatment. α-TC and DFO attenuated the MA-induced hyperthermia as well as the alterations in the locomotor activity. The level of lipid peroxidation was higher and the reduced glutathione concentration was lower in the MA-treated rats. These changes were significantly attenuated by α-TC and DFO. This suggests that α-TC and DFO ameliorate the MA-induced neuronal damage by decreasing the level of oxidative stress.

1. Introduction

Methamphetamine (MA) is a commonly abused drug worldwide. MA is a cationic lipophilic molecule that can cause degeneration in various regions of the brain. The administration of MA releases high levels of the neurotransmitter dopamine (DA), which stimulates brain cells, enhancing the mood and body movement. In experimental animals, high MA

* *Corresponding author*. Fax: +82 31 292 8800.
E-mail address: sunmee@skku.edu (S.-M. Lee).

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doi:10.1016/j.brainres.2006.06.030

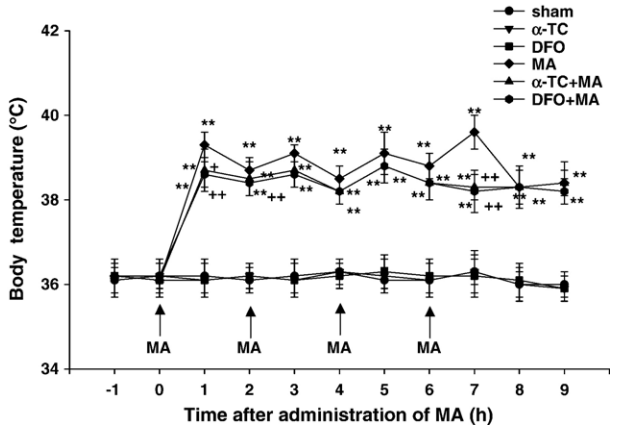

Fig. 1 – Effects of α-TC and DFO on MA-induced hyperthermia in rats. The values represent the mean ± SEM of 7–8 rats per group. ** Denotes significant differences from the sham group, $P<0.01$; +, ++ denotes significant differences from the MA group, $P<0.05$ and $P<0.01$, respectively.

doses can lead to a persistent, irreversible decrease in DA as well as other biochemical markers of the neuronal integrity in the striatal nerve terminal (O'Callaghan and Miller, 1994; Richarte et al., 1983). Although the cellular and molecular mechanisms involved in MA-induced toxicity are unclear, the role of oxygen-based radicals is well supported (Cadet and Brannock, 1997). MA releases DA in the striatum, and the presence of DA itself is one source of MA-induced oxidative stress, which is unique to dopaminergic neurons, because DA reacts with molecular oxygen to form quinones and semiquinones as well as reactive oxygen species (ROS), namely the superoxide anion as well as hydroxyl radicals and hydrogen peroxides (Graham, 1978). In contrast, antioxidants and free radical spin trapping agents acting as free radical scavengers attenuated the decrease in striatal DA content (Cappon et al., 1996; DeVito and Wagner, 1989).

α-Tocopherol (α-TC) is an endogenous major lipid-soluble chain-breaking antioxidant that protect cells from the diverse actions of ROS by donating its hydrogen atom (Burton et al., 1988). Many physiological effects have been attributed to α-TC, including actions as a membrane stabilizer, an enzyme repressor, and an enhancer of the effects of vitamin A (Burton and Ingold, 1989). There are also various reports demonstrating that animals given α-TC-deficient diets have greater neurological deficits compared with animals on a α-TC-rich diet (Goss-Sampson et al., 1988). Van der Worp et al. (1998) demonstrated that vitamin E supplementation in deficient rats reduced the effects of a permanent middle cerebral artery occlusion. More recently, a co-treatment of α-TC with MA for 48h partially reversed the neurotoxic action and apoptotic features in cerebellar granule neurons (Jimenez et al., 2004). Iron catalyzes the generation of hydroxyl radicals from hydrogen peroxide via the Fenton reaction. Deferoxamine (DFO) is an iron chelator that is used to treat iron overload diseases such as thalassemia (Modell et al., 1982) by decreasing the concentration of oxidative radicals by inhibiting the iron-catalyzed production of radicals. Furthermore, the local perfusion of DFO in the striatum attenuated the long-term depletion of the striatal DA content produced by MA (Yamamoto and Zhu, 1998).

Therefore, this study examined the effects of α-TC and DFO on MA-induced neurotoxicity in a rat brain.

2. Results

2.1. Body temperature and locomotor activity

Fig. 1 shows the changes in body temperature of the rats given MA. Repeated administration of MA to rats increased the body temperature significantly compared with the sham-operated rats. The increase in body temperature was attenuated by α-TC and DFO 1, 7 and 1, 2, 7h after MA administration. The locomotor activity increased significantly 1, 2 and 3h after the 4th administration of MA. The increase in locomotor activity observed 3h after the 4th administration of MA was attenuated by α-TC and DFO (Fig. 2A). The locomotor activity was unchanged in any of the experimental groups 3days after MA administration.

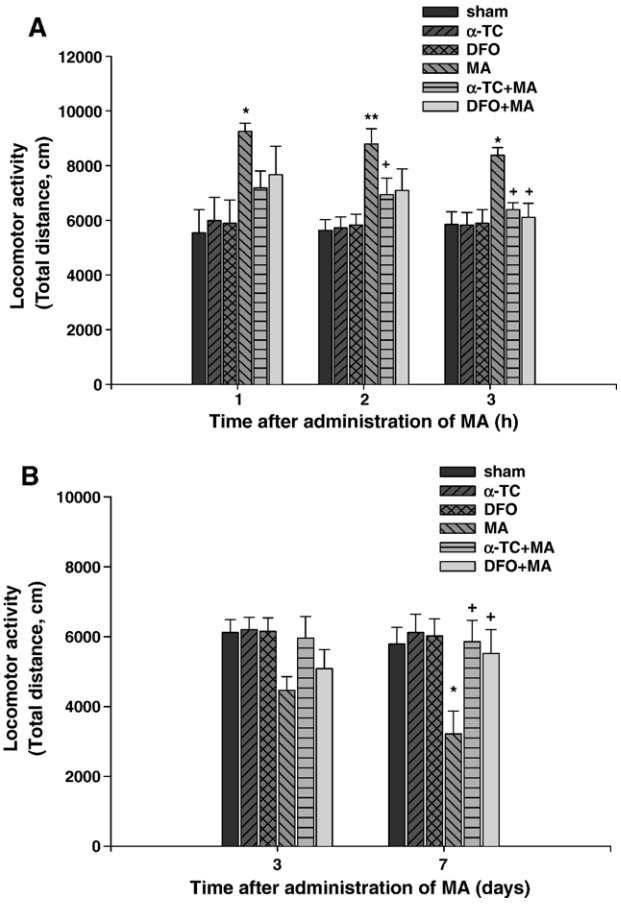

Fig. 2 – Effects of α-TC and DFO on the MA-induced behavioral changes in rats. Locomotor activity was measured 1, 2, 3h (A) and 3 and 7days (B) after the 4th injection of MA. The values represent the mean ± SEM of 9–10 animals per group. *, ** Denotes significant differences from the sham group, $P<0.05$ and $P<0.01$, respectively; + denotes significant differences from the MA group, $P<0.05$.

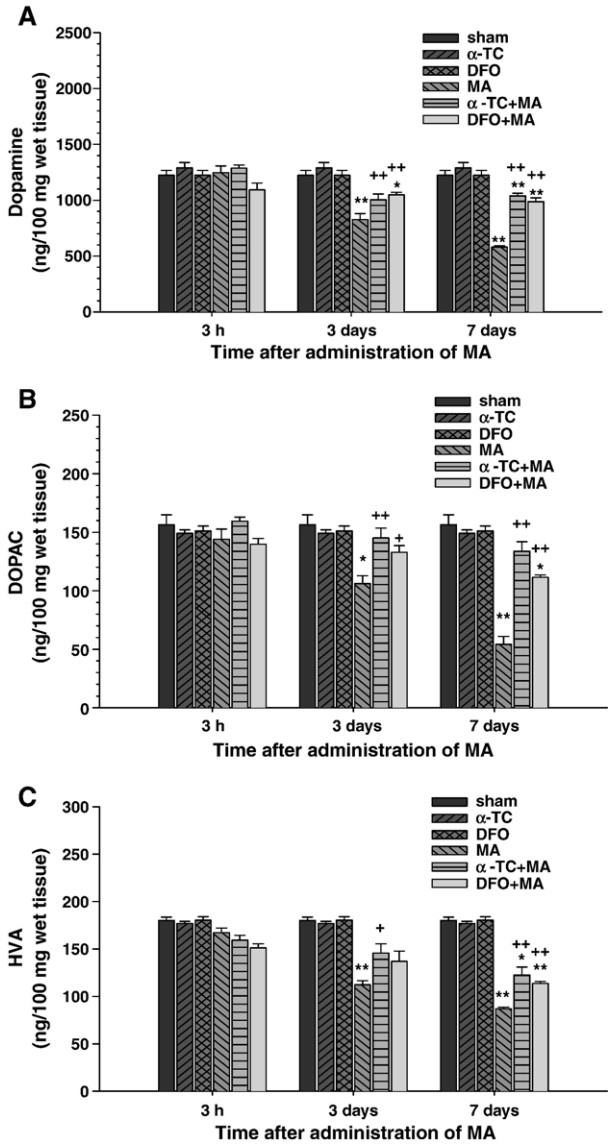

Fig. 3 – Effects of α-TC and DFO on the MA-induced deficits of the striatal DA (A), DOPAC (B) and HVA (C) contents. The values represent the mean ± SEM of 8–9 animals per group. *, ** Denotes significant differences from the sham group, $P<0.05$ and $P<0.01$, respectively; +, ++ denotes significant differences from the MA group, $P<0.05$ and $P<0.01$, respectively.

However, the locomotor activity decreased significantly 7 days after MA administration but was significantly attenuated by α-TC and DFO (Fig. 2B).

2.2. *Monoamine tissue content*

The striatal DA concentrations of the sham-operated rats were 1223.7 ± 43.4, 1231.1 ± 52.1 and 1219.0 ± 42.8 ng/100 mg wet tissue at 3 h, 3 days and 7 days after MA administration, respectively. Although there were no changes observed until 3 h after MA administration, the concentrations of DA in the MA-treated rats after 3 and 7 days were approximately 76% and 48% lower than those in the sham rats, respectively. The corresponding DA concentrations in the rats treated with α-TC 3 and 7 days after MA administration were 82% and 85% of those in the sham rats, respectively. The DA concentrations were higher in the DFO + MA group than in the MA-treated rats. Similar to DA, the striatal DOPAC and HVA concentrations, which are the major metabolites of DA, were significantly lower after 3 days and decreased further 7 days after MA administration. This decrease was prevented by α-TC and DFO (Fig. 3). In the sham-operated rats, the serotonin and 5-HIAA concentrations in the striatum remained constant at approximately 123 and 101 ng/100 mg wet tissue throughout the experiment, respectively. Three hours after MA administration, there were no changes in the serotonin and 5-HIAA concentrations observed in the MA-treated rats compared with the sham-operated rats. The serotonin and 5-HIAA concentrations decreased markedly 3 and 7 days after MA administration, which was prevented by the α-TC and DFO pretreatment (Fig. 4).

2.3. *Lipid peroxidation*

Fig. 5 shows the data on the formation of thiobarbituric acid reactive substances (TBARS), which is an indicator of

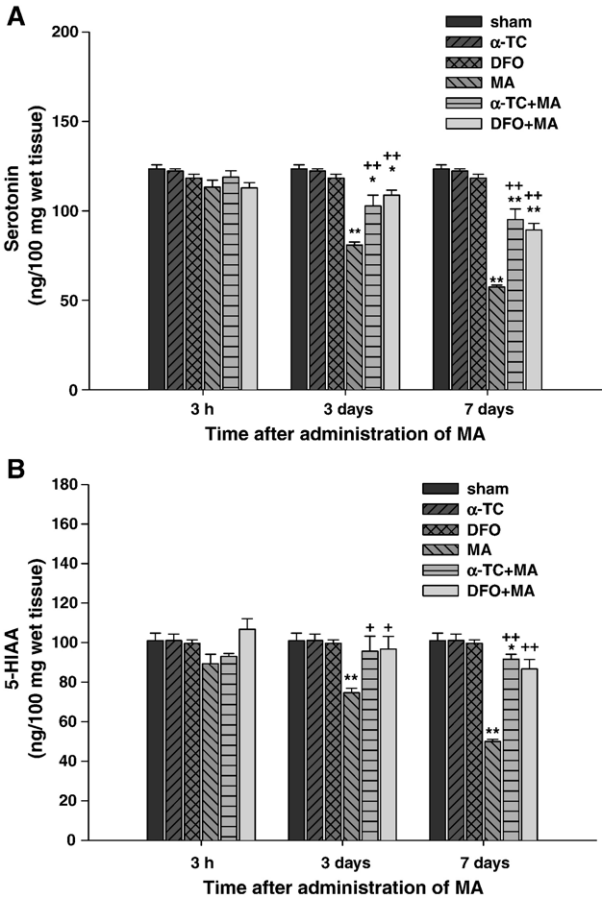

Fig. 4 – Effects of α-TC and DFO on the MA-induced deficits of the striatal serotonin (A) and 5-HIAA (B) contents. The values represent the mean ± SEM of 8–9 animals per group. *, ** Denotes significant differences from the sham group, $P<0.05$, $P<0.01$, respectively; +, ++ denotes significant differences from the MA group, $P<0.05$, $P<0.01$, respectively.

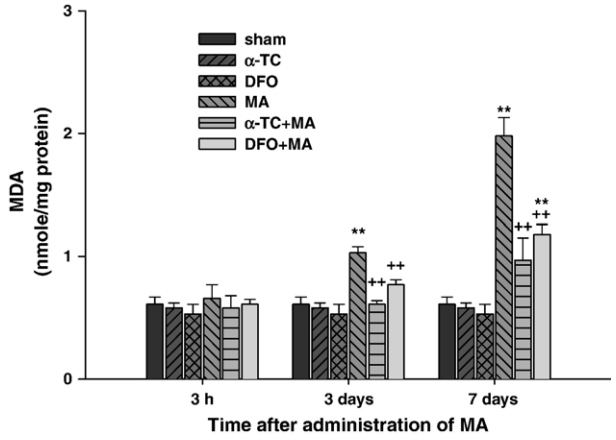

Fig. 5 – Effects of α-TC and DFO on the MA-induced striatal lipid peroxidation. The values represent the mean ± SEM of 8–9 animals per group. ** Denotes significant differences from the sham group, $P<0.01$; ++ denotes significant differences from the MA group, $P<0.01$.

lipid peroxidation. In the sham-operated rats, the level of the TBARS remained constant throughout the whole experimental period. Although the TBARS level was similar in all experimental groups at 3 h, it had increased markedly by 3 days and increased further 7 days after MA administration. This increase was prevented by the α-TC and DFO pretreatment.

2.4. *Glutathione content*

The concentration of striatal reduced glutathione (GSH) in the sham-operated rats was 3.33 ± 0.09, 3.34 ± 0.08 and 3.33 ± 0.07 μmol/g tissue at 3 h, 3 days and 7 days, respectively. The GSH concentration decreased significantly 3 h after MA administration, and this decrease was attenuated by a α-TC and DFO pretreatment. At 3 and 7 days, the GSH concentration was similar in all experimental groups. The striatal oxidized glutathione (GSSG) concentration was unchanged in all experimental groups. The GSH to GSSG ratio (an indicator of the cellular redox state) decreased markedly 3 h after MA administration. The decrease in the GSH/GSSG ratio was attenuated by a α-TC and DFO pretreatment (Table 1).

3. Discussion

This study examined the effect of MA on the markers of oxidative stress in the striatum. MA increased the level of lipid peroxidation and decreased the GSH concentration in vivo. In addition, a separate series of experiments was performed to test the possibility of a pharmacological reversal or attenuation by antioxidants on the multiple high-dose MA-induced depletion of the striatal DA, serotonin, hyperthermia and locomotor activity. The results suggest that the systemic administration of α-TC and DFO attenuated the neurotoxicity produced by MA.

The repeated administration of MA has been shown to cause permanent damage to the dopaminergic and serotonergic neurons in the striatum. These results showed that the striatal concentrations of DA and its metabolites DOPAC and HVA decreased significantly 3 days after MA administration with further decreases being observed 4 days later. A number of animal studies have shown that the repeated administration of MA can damage the nerve terminals of the DA neurons. Furthermore, a recent postmortem study reported that chronic MA users have significantly lower levels of DA and DA transporters in the striatum (Wilson et al., 1996). This study also showed a decrease in the level of serotonin and its primary metabolite, 5-HIAA in the striatum. These results are similar to those reported by Cass (2000) in that an acute toxic dose of MA reduced the evoked efflux of serotonin in the striatum after 1 week and 1 month but was normalized 6 months after treatment, suggesting some similarities in the MA-induced neurotoxicity in the serotonin system to that in the DA system.

Although the mechanism for neurotoxicity is unclear, there is evidence suggesting that free radicals are responsible for the MA-induced neurotoxicity. DA itself can produce neurotoxicity and generate hydroxyl radicals (Graham, 1978). The enzymatic degradation or auto-oxidation of DA results in the formation of hydrogen peroxide and superoxide radicals. Oxidative stress occurs when the level of ROS production exceeds their depletion or ROS are sequestered away from the several endogenous antioxidants that are present in the host. An ideal agent for potential therapeutic consideration is α-TC. α-TC is a potent natural antioxidant and the most common form found in the cellular membranes (Traber and Packer, 1995). α-TC has been described as the major chain-breaking

Table 1 – Effects of α-TC and DFO on the concentrations of striatal GSH, GSSG and GSH/GSSG ratio after MA administration

Group	GSH (μmol/g striatal tissue)			GSSG (μmol/g striatal tissue)			GSH/GSSG ratio		
	3 h	3 days	7 days	3 h	3 days	7 days	3 h	3 days	7 days
Sham	3.33 ± 0.09	3.34 ± 0.08	3.33 ± 0.07	0.26 ± 0.01	0.28 ± 0.02	0.27 ± 0.01	12.80 ± 0.40	11.92 ± 0.30	12.33 ± 0.28
α-TC	3.34 ± 0.08	3.33 ± 0.09	3.34 ± 0.06	0.28 ± 0.01	0.27 ± 0.01	0.26 ± 0.02	11.92 ± 0.66	12.33 ± 0.39	12.84 ± 0.41
DFO	3.33 ± 0.07	3.33 ± 0.06	3.34 ± 0.08	0.27 ± 0.01	0.26 ± 0.02	0.27 ± 0.01	12.33 ± 0.80	12.80 ± 0.38	12.37 ± 0.55
MA	2.65 ± 0.04**	3.07 ± 0.09	3.21 ± 0.09	0.30 ± 0.01	0.28 ± 0.01	0.31 ± 0.02	8.83 ± 0.40**	11.15 ± 0.30	11.25 ± 0.28
α-TC + MA	3.12 ± 0.06++	3.27 ± 0.10	3.40 ± 0.05	0.31 ± 0.02	0.28 ± 0.02	0.31 ± 0.01	10.91 ± 0.30++	11.29 ± 0.39	11.16 ± 0.41
DFO + MA	3.48 ± 0.11++	3.30 ± 0.04	3.30 ± 0.05	0.31 ± 0.01	0.29 ± 0.01	0.30 ± 0.02	11.24 ± 0.28++	11.83 ± 0.38	11.22 ± 0.55

Values are means ± SEM of 8–9 animals per group. **Denotes significant differences from the sham group, $P<0.01$; ++Denotes significant differences from the MA group, $P<0.01$.

antioxidant in mammalian cellular membranes on account of its efficient antioxidant capacity interrupting the chain of membrane lipid peroxidation (Packer, 1992). DeVito and Wagner (1989) demonstrated that a treatment with α-TC reduced the level of MA-induced neuronal damage. In this study, a treatment with 20 mg/kg of α-TC attenuated the release of DA and its metabolites at both 3 and 7 days after MA administration. However, this was not observed in the rats treated with 5 or 10 mg/kg α-TC.

An increase in the iron concentration might be critical because of its role in catalyzing free radical formation via the reduction of hydrogen peroxide known as the Fenton reaction. The Fenton reaction generates potentially damaging hydroxyl radicals from hydrogen peroxide and ferrous ions (Halliwell and Gutteridge, 1992). DFO is the most widely investigated iron-chelator in the setting of brain injury and it offers neuroprotection through multiple mechanisms. In a cold-induced model of brain injury, DFO significantly reduced edema and blood-brain barrier disruption (Ikeda et al., 1989). Furthermore, DFO reduced free iron level and preserved cerebral energy metabolism and electrical brain activity (Peeters-Scholte et al., 2003). In this study, high doses of DFO (100 and 150 mg/kg) had apparent toxic effects resulting in high mortality (data not shown). A low dose of DFO (50 mg/kg) attenuated the depletion of the striatal DA and serotonin content produced by repeated MA injections. This is the first in vivo evidence of free iron being involved in mediating the neurotoxicity observed after MA. The chelation of free iron with DFO might block the MA-induced formation of hydroxyl radicals and consequently attenuate the depletion of DA and serotonin content. However, it remains to be determined whether the free iron concentration, existing as Fe^{+3} or Fe^{+2}, is increased by MA. These results are consistent with the suggested role of iron in the degeneration of nigrostriatal DA neurons in Parkinson's disease (Sofic et al., 1991). Overall, these results suggest that ROS may be responsible for the neurotoxicity induced by MA.

A more definitive characterization of oxidative stress produced by MA should include evidence of oxidative damage. The glutathione system is a major antioxidant defense against the toxic effects of ROS (Griffith and Mulcahy, 1999). The reaction between tripeptide GSH with ROS leads to the conversion of GSH to its oxidized form, GSSG, the latter then being reconverted to GSH via glutathione reductase. Oxidative stress can cause either a decrease or increase in the GSH level depending on the severity of the stress, the experimental system and the time at which the GSH levels are measured. In contrast, GSSG levels often but not always increase (Benzi and Moretti, 1995). Therefore, mild oxidative stress often results in an increase in GSSG followed by an adaptation increase in the GSH levels, whereas severe oxidative stress typically causes GSH depletion (Seyfried et al., 2000). ROS attack on biological membranes can lead to oxidative destruction of the membrane polyunsaturated fatty acids via lipid peroxidation. It has been reported that the levels of the lipid peroxidation products are lowered when GSH is added to organ fluids (Bryan et al., 1994). The striatal content of GSH decreased significantly 3 h after MA administration. In contrast, the level of striatal lipid peroxidation increased significantly 3 and 7 days after MA administration. These results suggest that ROS, when produced in MA-related oxidative stress, cause direct cell damage through thiol oxidation and subsequent lipid peroxidation. Moreover, a treatment with α-TC and DFO attenuated the decrease in the striatal GSH content and lipid peroxidation, which suggests that they increase the striatal pool of GSH and reduce the level of oxidative stress.

Although the neurochemical consequences of MA-induced toxicity are well documented, less is known regarding whether or not functional effects accompany the long-term depletion of DA. MA is a psychomotor stimulant that increases the locomotor activity when administered at low doses and elicits stereotypic behavior when administered at high doses (Segal and Kuczenski, 1997). While receiving a repeated high dose of MA, the animals initially exhibited hyperexcitability and eventually appear exhausted and weakened. When the regimen was completed, the animal entered a "depression phase". The administration of large doses of MA over several days attenuated the subsequent MA-stimulated locomotor activity in rats (Lucot et al., 1980). In MA-treated rats, increases in the locomotor activity appeared 1, 2 and 3 h after MA administration, followed by decreases in locomotor activity 7 days later. However, the striatal concentration of DA decreased significantly 3 and 7 days after MA administration. Therefore, there does not appear to be a correlation between the MA-induced DA depletion and the observed behavioral effects. The effect of α-TC and DFO in blocking the behavioral changes in rats caused by MA suggests a role of oxidative stress in the behavioral changes after MA administration.

In conclusion, α-TC and DFO reduce the level of MA-induced neuronal damage, which prevents oxidant stress and lipid peroxidation.

4. Experimental procedures

4.1. *Animals*

Male Sprague–Dawley rats, 230–280 g in weight, were randomized, housed three or four per cage and kept in an animal care facility with a 12-h light/dark cycle, controlled temperature and humidity. The rats were given access to food and water ad libitum. All animals were treated humanely under the Sungkyunkwan University Animal Care Committee guidelines.

4.2. *Chemicals*

MA hydrochloride was provided by the National Institute of Scientific Investigation (Seoul, Korea). The DA, dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), serotonin, 5-hydroxyindole acetic acid (5-HIAA), 2-thiobarbituric acid and α-TC were purchased from Sigma Chemicals Co. (St. Louis, MO, USA). The DFO mesylate was purchased from Norvatis Pharmaceuticals (Seoul, Korea). All other chemicals used were of reagent grade and were locally and commercially available.

4.3. Administration of drugs and experimental groups

MA was dissolved in saline and administered via an intraperitoneal injection of 10 mg/kg over a 6-h period at 2 h intervals (four times). In the sham-operated rats, saline was injected in the same volume and manner as with MA. α-TC was dissolved in corn oil (20 mg/ml/kg) and injected intraperitoneally for 3 days and 30 min prior to MA administration. DFO was dissolved in physiological saline and administered by a subcutaneous injection of 50 mg/kg of body weight 30 min prior to MA administration. The dose of α-TC and DFO was selected on the basis of their efficacy in decreasing the brain injury during oxidative stress (Hurn et al., 1995; Niu et al., 2003). Six experimental groups were examined: (a) vehicle-treated sham, Sham; (b) α-TC-treated sham, α-TC; (c) DFO-treated sham, DFO; (d) MA-treated control, MA; (e) α-TC-pretreated MA, α-TC+MA; and (f) DFO-pretreated MA, DFO+MA. Because there were no differences observed in any of the parameters between the saline- and corn oil-treated rats in both sham group and MA-treated control group, the results of two treatments were pooled and are referred to as sham and MA, respectively.

4.4. Body temperature

The body temperature was measured 1 h before the first injection of MA and every 1 h thereafter, for a total of 9 h. The temperature measurement was taken by a BAT-12 thermometer coupled to a RET-2 rat rectal probe (Physitemp Instrument, Clifton, NJ, USA).

4.5. Behavioral changes

The rats were introduced to the testing room 1 h before being tested. Each animal was placed in an activity cage (opaque plastic, 40×40×40 cm) coupled with a videotracking system (Neuro Vision, Pusan, Korea), and video recordings were made under red illumination (25 Lux). After a 30-min habituation period to the new environment, the locomotor activity was recorded after the 4th injection of MA every 1 h thereafter, for a total of 3 h. Three and 7 days later, the locomotor activity was measured during a 1-h period using the methodology shown above.

4.6. Monoamine tissue content

The rats were decapitated 3 h, 3 days and 7 days after MA administration. The brains were rapidly removed and dissected on an ice-cold glass plate. The striatum was isolated, weighed, frozen in liquid nitrogen and stored at −80 °C until the assay. The tissue samples were homogenized with 7 volumes of 0.2 M perchloric acid containing 700 ng/ml of an internal standard, 3,4-dihydroxybenzylamine. The homogenate was centrifuged at 15,000×*g* for 5 min and the supernatant was filtered through a 0.45 μm pore membrane (Millex-LH, 4 mm; Millipore, Tokyo, Japan). The striatal concentrations of DA, serotonin and their metabolites were measured using an HPLC system. The HPLC system consisted of a liquid chromatograph pump (Dionex Inc. Sunnyvale, CA, USA), a reversed phase column (Altima C_{18}, Alltech Associates, Inc., Deerfield, IL, USA), an electrochemical detector (Shimadzu, Tokyo, Japan) and a data processor (Dionex Inc. Sunnyvale, CA, USA).

The mobile phase consisted of methanol, isopropanol and 0.15 M of a monochloroacetic acid buffer (pH 3.0) containing 2.7 mM EDTA and 3.2 mM of sodium octylsulfonate with a ratio of 6:6:88, as reported previously (Ali et al., 1994). The flow rate of the mobile phase was set to 0.8 ml/min and 30 μl of the sample solution was injected.

4.7. Striatal lipid peroxidation

Lipid peroxidation was estimated by determining levels of TBARS using the method reported by Buege and Aust (1978). One volume of striatal homogenate was mixed with 4 volumes of a 0.25 N HCl solution containing 15% (w/v) trichloroacetic acid and 0.375% (w/v) thiobarbituric acid. The mixture was heated in boiling water for 30 min. After cooling at room temperature, the precipitate was removed by centrifugation at 1000×*g* for 10 min. The absorbance of the clear supernatant was determined at 535 nm, and the malondialdehyde concentration was calculated using $1.56\times10^5 M^{-1}cm^{-1}$ as the molar extinction coefficient.

4.8. Striatal glutathione content

The total glutathione concentration was determined in the striatal homogenates at a wavelength of 412 nm after precipitation with 1% picric acid using yeast-glutathione reductase, 5,5′-dithio-bis(2-nitrobenzoic acid) and NADPH. The GSSG concentration was determined using the same method in the presence of 2-vinylpyridine, and the GSH level was calculated from the difference between the total glutathione level and GSSG (Anderson, 1985).

4.9. Statistical analysis

The overall significance was tested by two-way ANOVA. The differences between the groups at specific time points were considered significant at $P<0.05$ with the appropriate Bonferroni correction being made for multiple comparisons. All the results are presented as a mean±standard error of the mean (SEM).

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