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Research Report

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

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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

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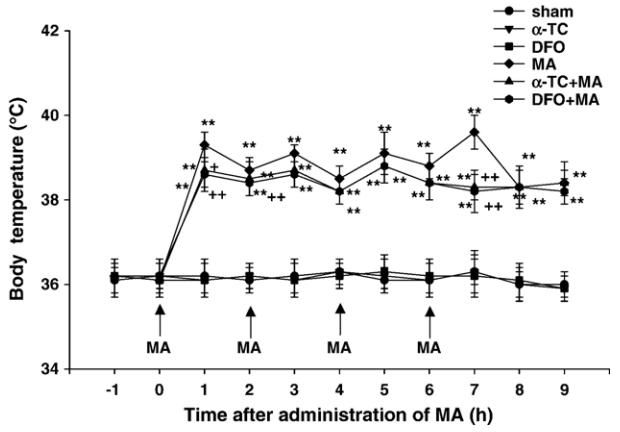

Fig. 1 – Effects of α-TC and DFO on MA-induced hyperthermia in rats. The values represent the mean ± SEM of 7–8 rats per group. ** Denotes significant differences from the sham group, $P<0.01$; +, ++ denotes significant differences from the MA group, $P<0.05$ and $P<0.01$, respectively.

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.

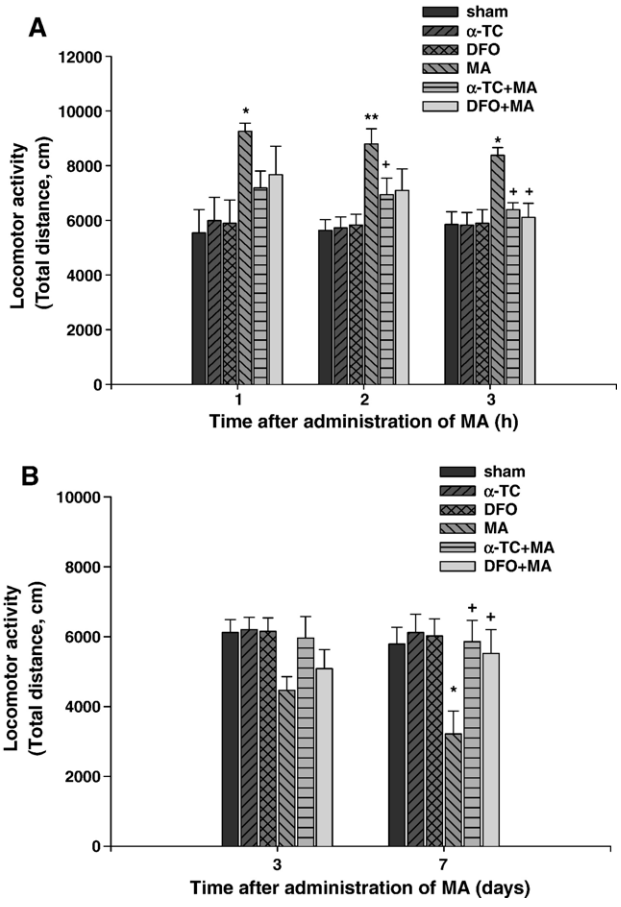

Fig. 2 – Effects of α-TC and DFO on the MA-induced behavioral changes in rats. Locomotor activity was measured 1, 2, 3h (A) and 3 and 7days (B) after the 4th injection of MA. The values represent the mean ± SEM of 9–10 animals per group. *, ** Denotes significant differences from the sham group, $P<0.05$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