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Exposure of mice to tobacco smoke attenuates the toxic effect of methamphetamine on dopamine systems

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Abstract

Methamphetamine treatment of mice rapidly and severely depleted levels of dopamine and its metabolites, homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC) in the caudate nucleus. Exposure of mice to cigarette smoke by means of nose-only breathing apparatus for 20 min twice daily over 3 days prior to drug treatment significantly attenuated the neurotoxicity of methamphetamine as judged by a lesser depletion of dopamine, DOPAC and HVA. The lesser effect of methamphetamine upon content of serotonin level was unaltered by prior inhalation of smoke. Results suggest a specific protective effect of inhaled tobacco smoke upon the effects of methamphetamine upon dopaminergic circuitry.

Keywords: Tobacco smoke; Nicotine; Methamphetamine; Dopamine; Cigarettes; Parkinson's disease

1. Introduction

There are several reports concerning the protective properties of nicotine upon the dopaminergic system following its exposure to specific toxins. Thus, neuroprotective properties of nicotine against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and methamphetamine in rats, mice and monkeys have been described in both biochemical and behavioral terms (Maggio et al., 1997, 1998; Kuribara, 1999; Schneider et al., 1999). Environmental factors may contribute toward the incidence of Parkinson's disease (PD) (Langston, 1998), and MPTP and methamphetamine provide useful animal models for some aspects of this neurodegenerative disorder.

Chronic administration of nicotine in man or experimental animals increases the number of nicotine receptors in brain, which are diminished in both PD and Alzheimer's disease (James and Nordberg, 1995). Several mechanisms by which such protection by nicotine may occur have been proposed. These include the induction of neurotrophic factors (Maggio et al., 1998), the inhibition of monoamine oxidase B (Fowler et al., 1998) and anti-oxidant effect (Linert et al., 1999). In

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addition, cigarette smoke may contain antioxidant species that are not nicotine (Kamisaki et al., 1997).

Since there are epidemiological data suggesting that cigarette smoking may have a delaying effect on the onset of PD (Gorell et al., 1999), it was of interest to determine whether inhalation of tobacco smoke can be neuroprotective against a drug with powerful dopamine-depleting properties.

The current study focused upon the effect of exposure of experimental animals to inhaled cigarette smoke upon the capacity of methamphetamine treatment to deplete both dopamine and its metabolites in the striatum.

2. Materials and methods

2.1. Smoke inhalation

Adult male C57 mice were exposed to tobacco smoke derived from University of Kentucky reference cigarette 1R3, using a nose-only exposure system (Kleinman et al., 2000). Smoke was delivered to an annular chamber with baffles to promote uniform distribution of particles to each nose only port. Mice were randomized into different ports each exposure to minimize any exposure biases. Samples collected from the breathing zone of the mice were used to document the exposure to smoke in terms of $\mu g/m^3$ of air. There was some cigarette to cigarette variability. The average concentration was 7.4 ± 2.5 mg/m^3 (mean $\pm$ 5.0).

Mice were exposed to smoke or purified air in two groups of six mice each. The smoke-exposed mice received the equivalent of the smoke from two cigarettes administered by inhalation over a 30-min. period, twice a day (morning and afternoon) for 3 consecutive days. The control group received purified air, following the same protocol. Immediately after the last inhalation exposure, the mice were injected intraperitoneally with 10 mg/kg methamphetamine. This course of treatment was carried out four times at four-hourly intervals. Other experimental groups received either no smoke, or injections of isotonic saline in place of methamphetamine or neither smoke nor drug, and four to seven animals were used in each group.

The mice were killed 4 h after the last injection by cervical dislocation. Brains were removed and the caudate nucleus dissected out and frozen at $-70°$.

2.2. Assay of monoamines and metabolites

In order to determine concentration of dopamine, serotonin and their metabolites, tissues were homogenized in 10% (v/v) 0.2 N perchloric acid containing 100 ng/ml of dihydroxybenzylamine as an internal standard, and then sonicated. After centrifugation ($15\,000 \times g$, 7 min) 150 μl of supernatant was filtered through a 0.2 μm Nylon-66 microfilter (Bioanalytic Systems, W. Lafayette, IN). Aliquots of 25 μl, representing 25-mg tissue were injected into a high performance liquid chromatography (HPLC) combined with electrochemical detection (EC) (HPLC/EC) system for separation of monoamines (Ali et al., 1994).

2.3. Statistical analyses

The data obtained were statistically evaluated using analysis of variance (ANOVA) followed by Tukey's multiple comparison test. Accepted level of significance was $P \leq 0.05$ using two-tailed analysis.

3. Results and discussion

None of the inhalation treatments caused any perceptible changes in body weight. Final body weights of mice (g) were 22.1 ± 0.2 for the control air breathing group, 22.3 ± 0.4 for the smoke-treated group, 21.1 ± 1.7 for the methamphetamine-injected group, and 22.7 ± 0.8 for the group receiving both smoke and drug following the fourth methamphetamine injection, mortality occurred in some of the mice that were not smoke-exposed. The experiment was, therefore, terminated at that time.

As expected from prior studies (Ali et al., 1994, 1996), methamphetamine treatment led to a pro-

found depression of levels of dopamine to 18% of control levels, and to lesser reductions of dopamine metabolites homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC), significant in the case of DOPAC (Fig. 1). The extent of depression of dopamine content by methamphetamine was significantly attenuated by prior exposure to tobacco smoke, to 57% of the level in untreated mice. This protective effect was also reflected by a non-significant parallel trend in levels of HVA and DOPAC in smoke-inhaling, methamphetamine-treated mice. It is possible that the expression of enzymes metabolizing metamphetamine could have been altered by the tobacco smoke exposure. Smoke exposure alone led to a minor, non-significant depression of levels of dopamine and its metabolites. This is consistent with reports describing an increase in dopamine release in nicotine-treated rats (Di Chiara and Imperato, 1988; Blaha and Winn, 1993). Methamphetamine injection depressed levels of serotonin significantly, but to a much lesser degree, to 71% of the corresponding controls. This reduction was not attenuated in the group of mice receiving tobacco smoke, and in fact smoke, alone, depressed serotonin levels. Effects of smoke and methamphetamine were not additive (Fig. 2). Concentrations of the serotonin metabolite, 5-HIAA were not markedly modified by any treatment.

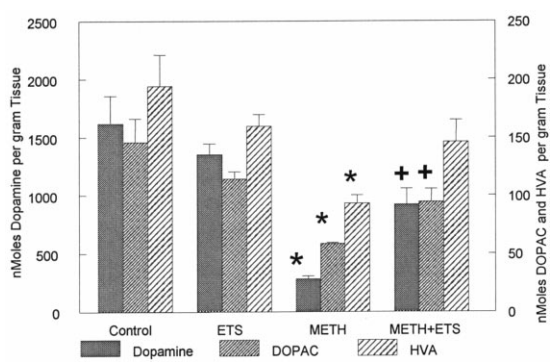

Fig. 1. Effect of environmental tobacco smoke on concentration of dopamine and metabolites in caudate nucleus of mice treated with methamphetamine. *, Value differs from corresponding value from all other groups; +, value differs significantly from both control level and value for mice treated solely with methamphetamine; ETS, environmental tobacco smoke; MET, methamphetamine.

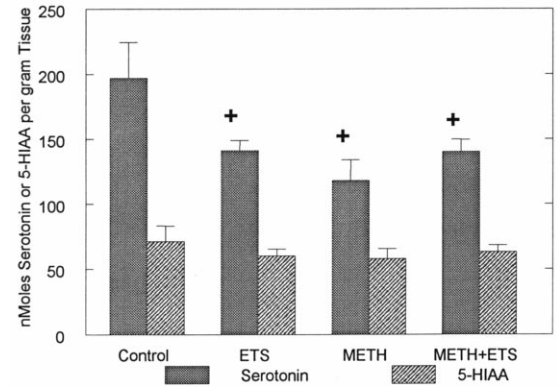

Fig. 2. Effect of environmental tobacco smoke on concentration of serotonin and 5-HIAA in caudate nucleus of mice treated with methamphetamine. +, Value differs significantly from corresponding control; ETS, environmental tobacco smoke; MET, methamphetamine.

4. Conclusion

These results demonstrate for the first time that tobacco smoke is able to reduce the transmitter-depleting properties of a well-recognized dopaminergic neurotoxin. The data thus provide a link between epidemiological reports concerning the incidence of PD among smokers, and the effects of nicotine administration upon dopamine metabolism is experimental systems. A moderate and intermittent level of inhalation of tobacco smoke may provide a level of nicotine sufficient to protect dopamine systems from responding to a toxic insult. It remains to be determined whether nicotine is the sole protective constituent of tobacco smoke or whether other neuromodulatory agents are present in this complex mixture.

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