Nomifensine Attenuates d-Amphetamine-Induced Dopamine Terminal Neurotoxicity in the Striatum of Rats

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Abstract

Long-term or high dose administration of d-amphetamine (AMPH) in the rat has been shown to result in dopamine terminal neurotoxicity in the striatum of rats. This phenomenon includes depletion of dopamine content, decreased activity of tyrosine hydroxylase and diminish in the number of dopamine reuptake transporter. Recent studies implicate a role of oxidative stress induced by dopamine in the AMPH-induced neurotoxicity. However, the primary source of dopamine responsible for radical formation during AMPH challenge has remained elusive. To elucidate this issue, the study was designed to examine the effects of nomifensine, a dopamine transporter blocker, and deprenyl, a monoamine oxidase B (MAO-B) inhibitor, on the prevention of striatal dopamine neurotoxicity in AMPH-treated rats. The results showed that nomifensine but not deprenyl protected against AMPH-induced long-term dopamine depletion. Correspondingly, the hydroxyl radical formation caused by AMPH in the striatum was attenuated by nomifensine, whereas its formation was not abolished by deprenyl. In conclusion, this study suggests that intracelluar oxidative stress is more likely involved in the AMPH-induced dopamine terminal toxicity in the rat striatum, while this phenomenon is not mediated by MAO-B pathway.

Key Words: d-amphetamine, oxidative stress, dopamine transporter, monoamine oxidase, striatum

Introduction

D-amphetamine (AMPH) and its analog methamphetamine (METH) are highly abused drugs worldwide that produce both addiction and dependence. The repeated or high dose administration of AMPH or METH has been shown to cause neurotoxicity in animals including nonhuman primates. The neurotoxicity includes long-lasting depletion of dopamine, decreases in the number of dopamine transport pumps and in the activity of tyrosine hydroxylase in the striatum, indicating dopamine terminal degeneration (12, 20, 26). After its acute administration, AMPH increases the release of dopamine and simultaneously inhibits its catabolism in the presynaptic terminals, which might lead to oxidative stress and eventually cell death. This proposal is supported from several evidences. First, the formation of intra-striatal 6-hydroxydopamine was noted, shortly after the administration of a single, large dose of METH (28). Second, a correlation between oxygen-based radicals and the severity of dopamine depletion was noted (9). Third, pretreatment with antioxidants or free radical scavengers attenuated the depletion of dopamine induced by AMPH (21).

Studies further suggest that dopamine-dependent oxidative stress is the initial event in AMPH neurotoxicity (8, 27). Thus, the magnitudes of AMPH-

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induced release and subsequent striatal dopamine loss were significantly correlated (25), and the over-expression of superoxide dismutase in transgenic mice attenuated METH-induced depletion of dopamine (5). Moreover, dopamine quinone formation and protein modification has been demonstrated to associate with the striatal neurotoxicity of METH (22). These reports therefore have established the likelihood that oxidative stress produced by dopamine plays a pivotal role in the toxicity of AMPH.

Although several mechanisms have been proposed to explain the dopamine-mediated neurotoxicity during AMPH intoxication, two hypotheses are considered primarily. The first states that the drug is able to mobilize dopamine from intraneuronal stores to the extracellular space via dopamine transporter (DAT)-mediated outward transport, which results in elevated extracellular dopamine concentrations. An alternative model proposes that AMPH displaces dopamine from synaptic vesicles to the cytoplasm, allowing intraneuronal oxidative stress.

In this study, we intended to investigate the possible primary source of oxidative damage produced by dopamine either intracellularly or extracellularly after AMPH administration. Nomifensine has relatively high selective affinity to DAT in striatal preparation, which precludes dopamine uptake and increase extracellular dopamine concentration. This drug shows suppression of the neurotoxin MPTP-induced dopaminergic neurotoxicity in mice (24). On the other hand, dopamine can be catalyzed by MAO-B in the pre-synaptic terminal to form superoxide and hydrogen peroxide, which then produce hydroxyl radical in the presence of transition metals (14, 29). Inhibition of MAO-B by pretreatment with deprenyl has been shown to abolish MPTP-induced neurotoxicity in rat striatum (31). We therefore examined in vivo the effects of blockade of dopamine transporter and inhibition of MAO-B on AMPH-induced long-term depletion of dopamine in the striatum of rats.

Materials and Methods

Male Sprague-Dawley rats (270-380 g) purchased from the National Laboratory Animal Breeding and Research Center were used in this study. Rats were group-housed in wire mesh cages and allowed free access to food and water in a room with temperature control (22-26°C) and a 12:12 hr light/dark cycle. All animal use procedures were in strict accordance with the Guidance for Animal Care and Management of our country. Drugs used in this study including dopamine, (-)-deprenyl and nomifensine maleate were obtained from Research Biochemical International (MA, USA). Drugs and vehicle were administered in a volume of 1 ml/kg. To main comparable degree of AMPH neurotoxicity, ambient temperature was maintained around 26°C during the experiment. Core body temperatures of experimental animals were monitored rectally every half an hour beginning 1 h before AMPH infusion, using a digital thermometer (Harvard Apparatus, USA) coupled to a probe lubricated with mineral oil.

In this study, rats were sacrificed 10 days after the drug administration to reveal the long-term toxic effects of AMPH on striatal dopamine terminals. The AMPH-treated rats were injected twice with AMPH (10 mg/kg, i.p.) on day 1 and day 3, respectively. To examine the effects of (-)-deprenyl (5 mg/kg, i.p.) or nomifensine (10 mg/kg, i.p.) pretreatment on AMPH-induced dopamine loss and oxidative stress in the striatum, rats were divided into four groups, with pretreatment or vehicle given 20 min before receiving AMPH and saline. In this study, hydroxyl radical was trapped by salicylate (150 mg/kg, i.p.) administered 1 hr before killing the rat. It is known that salicylate can react with the hydroxyl radical to generate stable dihydroxybenzoic acid (DHBA) derivatives, particularly 2,3- and 2,5-DHBA. While both are used as the in vivo index of the hydroxyl radical, for this purpose 2,3-DHBA might be a more reliable index than 2,5-DHBA, which might in part be formed by liver cytochrome P450 (15). The striata were homogenized in 10 volumes (w/v) of 0.2 N perchloric acid and then centrifuged at 4°C for 30 min at 15,000 g. To avoid potential contamination due to storage, 5μl of supernatant was immediately injected into the HPLC electrochemical detector for the analysis of 2,3-DHBA, dopamine and its metabolite DOPAC. A Shimadzu LC-10AD pump was used in conjunction with a reverse-phase C18 column (100 × 1 mm; particle size 5 μm, Hypersil, UK). The compounds were then detected by a glassy carbon working electrode set at 700 mV with respect to an Ag/AgCl reference electrode and magnified by a detector (LC-4C, BAS, USA) using DHBA as an internal standard. The mobile phase consisted of a mixture of 30.6 mM sodium citrate, 16 mM $Na_2PO_4 \cdot H_2O$, 1.91 mM diethylamine-HCl, 0.258 mM EDTA, 0.689 mM sodium octyl sulfate, 4% CH_3CN with final pH 3.2. The retention peaks of 2,3-DHBA and dopamine were around 12.1 and 22.9 min, respectively.

All data in this study were presented as mean ± S.E.M. and analyzed by a Macintosh statistical software package (SuperANOVA, Ver. 2.0). The significant effect was determined by a two-way analysis of variance (ANOVA). If significant interactions occurred, *post-hoc* comparisons between means were analyzed by pair or unpaired *t* test, depending on the suitability. The level of significance

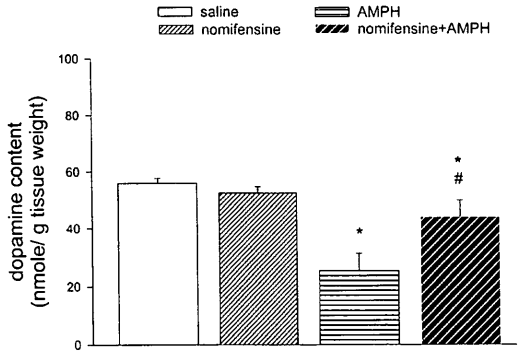

Fig. 1. The long-term toxic effect of AMPH given systemically on the level of striatal dopamine with or without nomifensine pretreatment (10 mg/kg, i.p.). Values are mean±SEM. *p<0.05, compared to saline-treated group; #p<0.05 for AMPH vs. nomifensine + AMPH group.

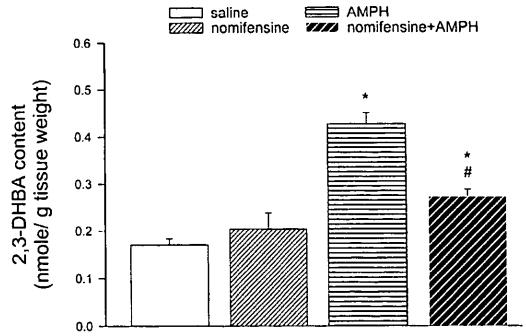

Fig. 2. The long-term toxic effect of AMPH given systemically on the level of striatal 2,3-DHBA with or without nomifensine pretreatment (10 mg/kg, i.p.). Values are mean±SEM. *p<0.05, compared to saline-treated group; #p<0.05 for AMPH vs. nomifensine + AMPH group.

was set at p<0.05.

Results

In this study, we firstly examined the effect of pretreatment with nomifensine on AMPH-induced long-term 2,3-DHBA formation and dopamine depletion. The effect of nomifensine pretreatment on AMPH-induced long-lasting dopamine depletion in the striatum is shown in Fig. 1 (total n=28). A two-way ANOVA using pretreatment and treatment as between-subject factors revealed a significant effect of AMPH [F(1,24)=10.17, p<0.01], no significant effect of nomifensine, and a significant nomifensine x AMPH interaction [F(1,24)=3.63, p<0.05]. *Post-hoc* comparisons revealed a significant effect of AMPH that decreased striatal dopamine contents in rats pretreated with saline or nomifensine (p<0.05). On the other hand, there was a significant difference between nomifensine/AMPH vs. vehicle/AMPH groups (p<0.05). Additionally, we determined whether pretreatment with nomifensine would attenuate the prolonged 2,3-DHBA production induced by AMPH (Fig. 2). A two-way ANOVA revealed a significant effect of AMPH [F(1,24)=23.45, p<0.001], no significant effect of nomifensine, and a significant nomifensine x AMPH interaction [F(1,24)=7.18, p<0.01]. *Post-hoc* comparisons showed a significant effect of AMPH that increased 2,3-DHBA levels in rats pretreated with saline or nomifensine (p<0.05), and there was a significant difference between nomifensine/AMPH vs. vehicle/AMPH groups (p< 0.05).

Secondly, we examined the effect of pretreatment with deprenyl on AMPH-induced long-term 2,3-DHBA formation and dopamine depletion. The effect of deprenyl pretreatment on AMPH-induced long-lasting dopamine depletion in the striatum is

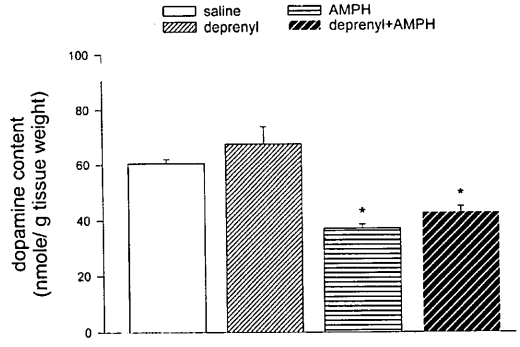

Fig. 3. The long-term toxic effect of AMPH given systemically on the level of striatal dopamine with or without (-)-deprenyl pretreatment (5 mg/kg, i.p.). Values are mean±SEM. *p<0.05, compared to saline-treated group.

depicted in Fig. 3 (total n=30). A two-way ANOVA using pretreatment and treatment as between-subject factors revealed a significant effect of AMPH [F(1,26)=9.35, p<0.01], no significant effect of deprenyl, and no significant deprenyl x AMPH interaction [F(1,26)=0.53, NS]. Additionally, we determined whether pretreatment with deprenyl would attenuate the prolonged 2,3-DHBA production induced by AMPH (Fig. 4). A two-way ANOVA revealed a significant effect of AMPH [F(1,26)=17.30, p<0.001], no significant effect of deprenyl, and no significant deprenyl x AMPH interaction [F(1,26)=1.04, NS].

In this experiment, the effects of pretreatment with nomifensine or deprenyl on the core temperature change after systemic AMPH administration were studied (total n=18). As shown in Fig. 5, a two-way ANOVA using different treatment as the between-subject factor and time course as the within-subject factor revealed a significant effect on treatment [F(2,60)=3.82, p<0.01], and a significant treatment x time interaction [F(10,60)=2.37, p<0.05]. *Post-hoc*

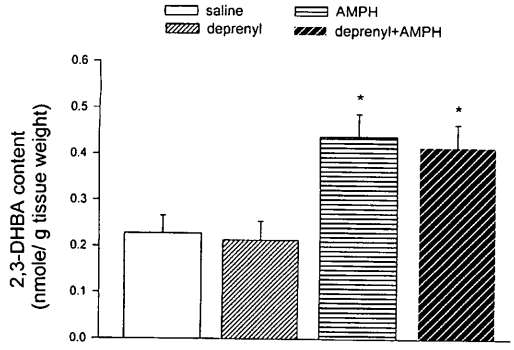

Fig. 4. The long-term toxic effect of AMPH given systemically on the level of striatal 2,3-DHBA with or without (-)-deprenyl pretreatment (5 mg/kg, i.p.). Values are mean±SEM. *p< 0.05, compared to saline-treated group.

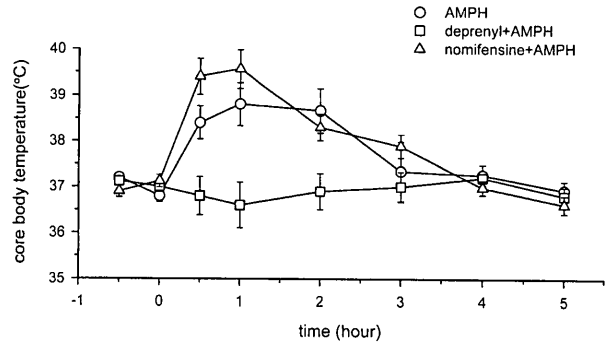

Fig. 5. Effects of pretreatment with nomifensine or (-)-deprenyl on core temperature changes induced by systemic AMPH administration. Systemic AMPH injection (10 mg/kg, at 0 hr) caused significant increases in core body temperature from 0.5 to 2 hr; this effect was abolished by (-)-deprenyl pretreatment (5 mg/kg). Pretreatment with nomifensine (10 mg/kg) did not affect the core temperature in rats treated with AMPH. Results are expressed as mean±SEM.

comparisons revealed that systemic administration of AMPH significantly elevated core temperatures of rats in 2 hr ($p<0.05$, compared to 0 hr); this effect of AMPH was abolished by pretreatment with deprenyl ($p<0.05$, at 0.5, 1 and 2 hr). The core temperature, however, was not significantly changed in rats pretreated with nomifensine.

Discussion

We have previously shown in rats that pretreatment with α-methyl-para-tyrosine, a dopamine synthesis inhibitor, significantly inhibited the hydroxyl radical formation produced by AMPH in the striatum of rats (18). In this study, we extended our previous findings and showed that the dopamine reuptake blocker nomifensine could attenuate hydroxyl radical formation and protect against long-term dopamine depletion induced by systemic administration of a large dose of AMPH. This finding firstly implicates an involvement of hydroxyl radical in AMPH-induced dopamine neurotoxicity in the striatum of rats. Consistent with this concept, we have demonstrated that intra-striatal infusion of AMPH induced acute hydroxyl radical formation (35), and systemic administration of AMPH elicited a sustained lipid peroxidation in the rat striatum measured 7 days after AMPH administration (33).

Secondly, the result indicates an intraneuronal oxidative stress that leads to striatal dopamine depletion during AMPH intoxication. Catecholamines including dopamine have been shown to be toxic via mechanisms of oxidative damage (16). The mechanism underlying dopamine-induced toxicity is thought to involve the inherent instability of the catechol moeity of the molecule. Dopamine readily oxidizes to form reactive oxygen species and quinones, a process that can occur either spontaneously in the presence of transition metal ions or via an enzymatically catalyzed reaction (14, 29). In fact, dopamine appears to be involved in the striatal neurotoxicity associated with several conditions, including ischemia, exposure to high level of excitatory amino acids and AMPH administration (3, 8, 11). Several characteristics of dopaminergic terminals enhance their susceptibility to the toxic effects of dopamine. For example, the presence of a high affinity DAT could result in accumulation of large amounts of dopamine from the extracellular space into the terminal. In this study, nomifensine successfully prevented AMPH-induced hydroxyl radical formation and dopamine depletion, presumably via inhibiting reuptake of dopamine and AMPH into presynaptic terminals and thus attenuating intracellular oxidative damage. Additionally, inhibition of the high affinity DAT system is supposed to increase extracellular dopamine level, and, hence, the extraneuronal dopamine metabolism. However, in the study we observed a protective effect of nomifensine, which did not support a role of extracellualar dopamine on the AMPH-induced toxicity in the striatum. In line with this finding, a recent study done by LaVoie et al. have shown that the toxicity of METH and the associated increase in dopamine oxidation were not the result of increases in extracellular dopamine (22). In addition, Caron and his associates have shown that DAT is required for, and dopamine is an essential mediator of, METH-induced striatal dopaminergic neurotoxicity (13).

The rapid metabolism of intracellular dopamine to DOPAC by MAO intracellularly with the concomitant production of hydrogen peroxide could result in oxidative stress, with hydrogen peroxide acting as both a strong oxidant and a generator of

hydroxyl radical via Fenton reaction (4). However, since there is no significant effect of deprenyl on the prevention of hydroxyl radical formation and dopamine depletion produced by AMPH administration, the study does not favor the MAO pathway in mediating AMPH-induced dopamine terminal toxicity in the striatum of rats. Deprenyl has been shown to be effective in reducing the MPTP-induced neurotoxicity (31). This effect may be derived from a mechanism by direct inhibiting the transformation of MPP^+ from MPTP. It is known that MPTP can be transported into striatal dopamine terminals where converted to MPP^+ by MAO-B to exert its toxic effects. Other reports have indicated that deprenyl could exert its protective action through the induction of superoxide dismutase and catalase, enzymes involved in the scavenging of free radicals (6). This mechanism, however, is not supported by our results.

Studies have suggested that many toxic effects of AMPH given systemically are a result of AMPH-induced hyperthermia (2). First, hyperthermia can potentiate the production of 6-hydoxydopamine and related reactive oxygen radicals during AMPH exposure (28). Second, the formation of hydroxyl radical in the brain is modulated by temperature manipulation (19). Additionally, environmental cooling or pharmacologic agents that produce hypothermia were noted to decrease METH neurotoxicity in mice (1). In the present study, however, nomifensine shows a significant neuroprotective action against AMPH-induced dopamine neurotoxicity but did not affect its action on hyperthermia. In contrast, deprenyl could not prevent AMPH neurotoxicity, whereas this agent lowered core body temperature of rats. Accordingly, reserpine has been shown fails to protect against AMPH-induced neurotoxicity, despite producing hypothermina (32). Thus, it appears that hyperthermia is not the sole mediator of AMPH neurotoxicity.

In addition to the involvement of dopamine and oxidative stress in AMPH neurotoxicity, several other ways have also been proposed to mediate the neurotoxic effects of AMPH and its analogs. Recently, energy impairment has been proposed to mediate AMPH-induced neurotoxicity, based on the finding that supplement of energy with nicotinamide attenuated the rapid ATP loss and long-lasting DA depletion in the striatum produced by systemic AMPH (34). In addition, metabolic perturbations caused by AMPH and its analogs could disrupt ionic equilibrium and depolarize the neuron (9), which render DA terminal susceptible to glutamate excitotoxicity (17, 30). This would further activate NMDA glutamate receptors and result in nitric oxide (NO) formation that is modulated by Ca^{2+} channels (7). NO either serves as a neurotoxin or increases the AMPH-induced striatal dopamine metabolism, causing free radical formation and energy depletion which leads to cell death (4). We have indeed shown that systemic administration of a single large dose of AMPH resulted in a delayed but persistent NO production and related it to the development of long-term dopamine neurotoxicity (23).

In summary, the study demonstrated that the dopamine reputake blocker nomifensine significantly attenuated the increase in hydroxyl radical formation and long-lasting dopamine depletion produced by systemic administration of AMPH. To the contrary, the MAO-B inhibitor deprenyl did not protect against AMPH-induced dopamine neurotoxicity in the striatum of rats. Taken together, the results suggest a pivotal role of oxidative stress caused by intracellular dopamine in AMPH neurotoxicity; nevertheless, MAO-B pathway is less likely involved, implicating that alternative pathways including auto-oxidation of dopamine may underlie the toxic effects of AMPH on dopaminergic terminals in the rat striatum. Further studies are under way in our laboratory to elucidate the detail mechanism responsible for AMPH neurotoxicity.

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