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Short communication

Effect of MK-801 on the decrease in tryptophan hydroxylase induced by methamphetamine and its methylenedioxy analog

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The role of N-methyl-D-aspartate (NMDA) receptors in the decrease in neostriatal tryptophan hydroxylase (TPH) activity induced by repeated high doses of methamphetamine or 3,4-methylenedioxymethamphetamine (MDMA) was evaluated. Rats received 4 injections of methamphetamine (15 mg/kg) or MDMA (10 mg/kg) at 6 h intervals, and were killed 18-20 h after the last administration. These treatments with methamphetamine or MDMA reduced neostriatal TPH activity to 26 and 34% of control, respectively. Coadministration of MK-801 (2.5 mg/kg) significantly attenuated the methamphetamine-induced decrease in TPH activity (66% of control), but did not alter the effect of MDMA. This study suggests that excitatory amino acids may participate in the methamphetamine-induced decline in central TPH activity, and that the mechanism by which MDMA and methamphetamine decreases TPH activity may differ.

MK-801; Methamphetamine; MDMA neurotoxicity; Tryptophan hydroxylase

1. Introduction

Repeated administration of high doses of methamphetamine or 3,4-methylenedioxymethamphetamine (MDMA) induces a decrease of central tryptophan hydroxylase (TPH) activity reflecting the destruction of serotonergic nerve terminals (Hotchkiss and Gibb, 1980; Stone et al., 1987). Central dopamine (DA) appears to mediate this response since the depletion of this transmitter attenuates the decrease in TPH activity after treatment with either drug (Hotchkiss and Gibb, 1980; Stone et al., 1988). Interestingly, the depletion of DA also protects neostriatal neurons from the damage induced by ischemia (Clemens and Phebus, 1988). Since ischemia-induced damage is apparently linked with the N-methyl-D-aspartate (NMDA) receptor (Rothman and Olney, 1987), in the present study we examined the potential role of this receptor in mediating the methamphetamine- or MDMA-induced decrease in neostriatal TPH activity. The possible role of NMDA receptors in mediating of the toxic action of methamphetamine on the central serotonergic system is further supported by the recent report of Sonsalla et al. (1989) who observed that NMDA antagonists block the neurotoxic action of methamphetamine on the dopaminergic system in mice.

2. Materials and methods

Male Sprague-Dawley rats (180-250 g) were housed 4-6 per cage in a temperature-controlled room (24°C) with a 12 h alternating light-dark cycle, and access to food and water ad libitum.

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The rats received 4 doses of methamphetamine (15 mg/kg s.c.), MDMA (10 mg/kg s.c.) or vehicle (0.9% NaCl) at 6 h intervals. The MK-801-treated animals received a 2.5 mg/kg dose i.p. 15 min prior to the injection of methamphetamine, MDMA or vehicle (drug concentrations are expressed as free base). This dose of MK-801 blocked the methamphetamine-induced decrease in mouse neostriatal DA (Sonsalla et al., 1989). The animals were killed by decapitation 18-20 h after the last treatment, and the neostriata were rapidly removed on a cold plate; all tissues were stored at −80 °C until assayed. Neostriatal TPH activity was assayed by a modified $^{14}CO_2$ trapping procedure (Stone et al., 1987) using dl-6-methyl-5,6,7,8-tetrahydrobiopterin (Sigma Chemical Co., St-Louis, MO) as cofactor.

3. Results

Figure 1 shows the effect of blocking the NMDA receptors with MK-801 on the methamphetamine- and MDMA-induced decreases in neostriatal TPH activity. Treatment with methamphetamine or MDMA decreased TPH activity to 26 and 34% of control, respectively. Coadministration of MK-801 significantly attenuated the methamphetamine-induced change in TPH activity (66% of control). In contrast, however, the MDMA effect was unaltered (30% of control) by MK-801. Administration of MK-801 alone did not affect neostriatal TPH activity.

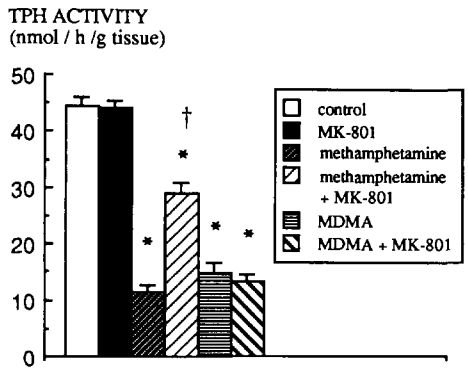

Fig. 1. Effects of MK-801 on the decrease in neostriatal TPH activity induced by methamphetamine or MDMA. The rats received 4 doses of methamphetamine (15 mg/kg s.c.), MDMA (10 mg/kg s.c.) or vehicle (0.9% NaCl) at 6 h intervals. The MK-801-treated animals received a dose of 2.5 mg/kg i.p. 15 min prior to the injection of methamphetamine, MDMA or vehicle. The animals were killed by decapitation 18-20 h after the last administration. Means of TPH activity (nmol of hydroxylated tryptophan/h per g of tissue) ± S.E. shown in this figure are the result from two separate experiments. Ten to eighteen animals were used in each group. Statistical analysis of enzymatic activities was performed with a one-way analysis of variance followed by a Scheffé multiple comparison test. Statistical significance between groups was defined at $P < 0.05$. * Significantly different from control group; † significantly different from methamphetamine-treated group.

4. Discussion

This study demonstrates that MK-801 attenuates the decrease in neostriatal TPH activity by methamphetamine but does not influence the response of this enzyme to MDMA administration. This differential effect of MK-801 on the methamphetamine and MDMA responses suggests that the decrease in enzyme activity induced by these drugs may occur by different mechanisms. The mechanisms by which methamphetamine and MDMA destroy serotonergic terminals, as reflected by the decline in TPH activity, have not yet been elucidated. We have previously described evidence that methamphetamine-released DA, or one of its metabolites, is required for the methamphetamine-induced decline in TPH activity (Hotchkiss and Gibb, 1980). DA could produce its toxic effect either by generating a metabolite resulting from auto-oxidation, via oxidative stress, or by some unknown condition detrimental to the serotonergic system. The present data suggest that the NMDA receptor may play a role in mediating the DA-dependent neurotoxicity caused by methamphetamine administration. The recent observation made by Sonsalla et al. (1989) that MK-801 and other NMDA antagonists protect the dopaminergic system from the methamphetamine-induced toxicity in mice suggests that NMDA receptors are involved in the action of methamphetamine on both the dopaminergic and serotonergic systems.

NMDA receptors have been linked to the development of neuronal damage is other conditions. For instance, NMDA receptors stimulated by excitatory amino acids appear to mediate neu-

ronal damage induced by ischemia (Rothman and Olney, 1987); the neuronal degeneration can be prevented by administration of NMDA antagonists (Rothman and Olney, 1987). Like the methamphetamine neurotoxicity (Hotchkiss and Gibb, 1980), the ischemia-induced changes in the neostriatal dopaminergic and serotonergic systems are attenuated by inhibiting DA synthesis (Weinberger et al., 1985). Since DA and NMDA receptors appear to play a role in toxicity related to methamphetamine treatment and ischemia, it is possible that the neuronal damage in these conditions results from a common mechanism. If this is true, the respective role of DA and NMDA receptors in mediating the neurotoxic response must be elucidated. Although glutamate releases DA in certain conditions (Chéramy et al., 1986), it is unlikely that blockade of NMDA receptors altered the release of DA by methamphetamine, and consequently the alterations in the serotonergic system, since methamphetamine causes release of cytosolic DA by a calcium-independent mechanism. On the other hand, DA released by methamphetamine could influence the synaptic concentration of glutamate, and the activation of NMDA receptors; Kerkerian et al. (1987) recently demonstrated that DA inhibits neostriatal glutamate reuptake. Interestingly, administration of the DA receptor antagonist, haloperidol, increases glutamate uptake (Kerkerian et al., 1987), a treatment that protects the serotonergic system from methamphetamine effects (Hotchkiss and Gibb, 1980). Further studies are required to determine the relevance of DA/glutamate interactions on the present findings.

The inability of MK-801 to protect neostriatal TPH activity from the effects of MDMA treatment suggests that NMDA receptors may not be involved in mediating the neurotoxicity induced by this drug. In earlier studies we demonstrated additional differences in the neurotoxic mechanisms of methamphetamine and MDMA. For instance, haloperidol treatment blocks the methamphetamine-induced response, but fails to substantially protect the serotonergic system from MDMA (Stone et al., 1986). Moreover, although DA is required for the MDMA effects on the serotonergic system (Stone et al., 1988), inhibition of DA synthesis with α-methyl-p-tyrosine is less effective in protecting against the effects of MDMA than against methamphetamine treatment (Hotchkiss and Gibb, 1980; Stone et al., 1988). These observations indicate that although DA represents a common denominator in the mechanisms by which methamphetamine and MDMA alter the central serotonergic system, other factors may also be involved in mediating their effects.

This study demonstrated that MK-801 alters the methamphetamine-induced decrease in neostriatal TPH activity, indicating that excitatory amino acids may be involved in this drug-induced change. In contrast, the toxicity associated with the methylenedioxy congener of methamphetamine, MDMA, is not altered by coadministration of the NMDA antagonist, MK-801. The interrelationship between the DA and glutamate systems in mediating this response remains to be determined.

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