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Short communication

Blockade of the 3,4-methylenedioxymethamphetamine-induced changes in neurotensin and dynorphin A systems

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The levels of neurotensin-like immunoreactivity (NTLI) and dynorphin-like immunoreactivity (DLI) in the neostriatum, nucleus cumbens and substantia nigra were increased 18 h after a single administration of MDMA (3,4-methylenedioxymethampheta- ne, 10 mg/kg). Coadministration of SCH 23390, a dopamine D_1 receptor antagonist, or MK-801, a non-competitive antagonist the NMDA (N-methyl-D-aspartate) receptor complex, prevented the MDMA-induced increase of NTLI and DLI in all three ain structures while the administration of sulpiride, a dopamine D_2 receptor antagonist, failed to alter the MDMA effects. These ıdings suggest that MDMA-induced changes in neurotensin and dynorphin involve both the dopaminergic and the glutamatergic stems.

Dopamine; Dynorphin A; MDMA (3,4-methylenedioxymethamphetamine); NMDA (N-methyl-D-aspartate); Neurotensin

Introduction

Dopaminergic activity alters central neurotensin and ynorphin systems. Administration of the dopamine D_1 ceptor agonist, SKF 38393, increases neurotensin-like ımunoreactivity (NTLI) concentrations in the neostri- um and in the nucleus accumbens while the dopamine $_2$ receptor agonist LY 171555 reduces NTLI con- ntrations (Merchant et al., 1989a,b). Neostriatal dy- orphin levels are similarly altered by D_2 agonists while imulation of the D_1 receptors result in an increase in gral dynorphin levels (Nylander and Terenius, 1987).

The administration of methamphetamine, an indirect opamine agonist, produces a D_1-mediated elevation in igral and neostriatal NTLI and dynorphin-like im- ıunoreactivity (DLI) levels (Hanson et al., 1987; Letter . al., 1987). The methamphetamine analog, MDMA 3,4-methylenedioxymethamphetamine), can also in- ease neostriatal and nigral levels of NTLI and DLI in manner similar to methamphetamine (Hanson et al., 988; Merchant et al., 1987). The mechanism for the 1DMA-induced neuropeptide changes remains to be etermined. Interestingly, recent observations indicate ıat D_1-mediated responses in brain neuropeptides can be prevented by the blockade of a glutamine receptor subtype. Thus, MK-801 ([+]-5-methyl-10,11-dihydro-5H-dibenzo[a,b]cyclohepten-5,10-imine maleate), a non-competitive NMDA (N-methyl-D-aspartate) glutamine receptor antagonist, prevents the D_1-mediated meth- amphetamine-induced increase in neostriatal neuro- tensin (Singh et al., 1989), suggesting a possible interac- tion between the D_1 receptor system and the NMDA system. Thus, the purpose of this study was to identify the mechanism(s) mediating MDMA-induced changes in extrapyramidal and limbic neurotensin and dy- norphin A systems by determining the potential role of dopamine and the glutamine receptors in these effects.

2. Materials and methods

2.1. Animals and treatment

Male Sprague-Dawley rats (180-220 g, Simonsen Laboratories, Gilroy, CA) were housed six per cage in a temperature-controlled room with a 12-h light/dark cycle and given access to food and water ad libitum. Animals received a single s.c. injection of MDMA (10 mg/kg; National Institute on Drug Abuse, Rockville, MD) or 0.9% NaCl 15 min after an i.p. administration of 0.9% NaCl, sulpiride (80 mg/kg; Sigma Chemical Company, St. Louis, MO), SCH 23390 (0.5 mg/kg; Schering, Bloomfield, NJ) or MK-801 (1.7 mg/kg;

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Merck, Sharp and Dohme, Rahway, NJ). The drug doses are expressed as the free base. The animals were killed by decapitation 18 h after the last dose: the brains were rapidly removed and the neostriatum dissected out on a cold plate. After freezing the brain on dry ice, the substantia nigra and nucleus accumbens were excised with a microdissecting knife. The tissues were stored at −80 °C until assayed.

2.2. Neurotensin and dynorphin assays

The response of the neurotensin and dynorphin A systems was assessed by measuring the concentrations of NTLI and DLI according to previously reported techniques (Hanson et al., 1987; Letter et al., 1987) employing selective neurotensin and dynorphin antisera in a radioimmunoassay which reliably detected 5 pg and 8 pg of NTLI and DLI, respectively. The neuropeptide concentrations were calculated as pg/mg protein. Differences between the means were analyzed by an ANOVA test followed by a Fisher test with the level of significance set at $P < 0.05$.

3. Results

3.1. Effects of blocking dopamine and NMDA receptors on the MDMA-induced increase in NTLI

Figure 1 demonstrates the effects of sulpiride, SCH 23390 and MK-801 on the MDMA-induced increase in NTLI concentrations measured in the neostriatum (fig. 1A), substantia nigra (fig. 1B) and nucleus accumbens (fig. 1C). A single dose of MDMA (MDMA/saline) increased NTLI concentrations to 274, 269 and 145% of control in the neostriatum (fig. 1A), substantia nigra (fig. 1B) and nucleus accumbens (fig. 1C), respectively. Blockade of the D_2 receptor with sulpiride did not alter significantly the MDMA-induced increase in NTLI measured in all three brain areas surveyed. However, blockade of the D_1 receptor with SCH 23390 resulted in the blockade of the MDMA-induced increase in neostriatal and nigral neuropeptide concentration. The blockade of NMDA receptors with MK-801 also completely blocked the MDMA-induced change in neostriatal and nigral NTLI. In the nucleus accumbens (fig. 1C), however, NTLI levels measured in the MDMA-treated animals receiving SCH 23390 or MK-801 failed to differ significantly from the concentration measured in the animals treated with saline or MDMA alone. This may result from the relatively small increase induced by MDMA as well as from the small non-significant increase in NTLI induced by the three receptor antagonists alone. None of the receptor antagonists altered significantly NTLI levels in the three brain areas when administered alone.

3.2. Effects of blocking dopamine and NMDA receptors on the MDMA-induced increase in DLI

Figure 2 demonstrates the effects of sulpiride, SCH 23390 and MK-801 on the MDMA-induced increase in DLI concentrations measured in the neostriatum (fig

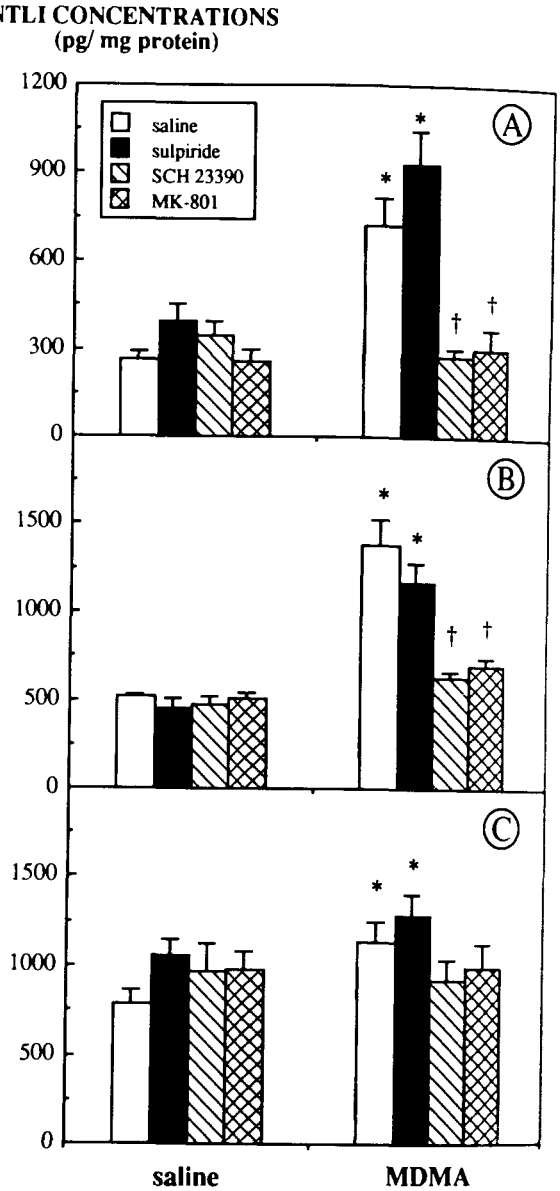

Fig. 1. Effects of dopamine receptor antagonists and MK-801 on the MDMA-induced increase in NTLI concentrations measured in the neostriatum (A), substantia nigra (B) and nucleus accumbens (C). Rats were given one dose of 0.9% NaCl or MDMA (10 mg/kg s.c.) 15 min after administration of the D_2 antagonist, sulpiride (80 mg/kg i.p.), the D_1-selective antagonist, SCH 23390 (0.5 mg/kg i.p.), the NMDA antagonist, MK-801 (1.7 mg/kg i.p.), or 0.9% NaCl and were killed 18 h after the last dose. Each bar represents the mean ± S.E. for each treatment group, expressed as pg of NTLI per mg protein (n = 6-7 per group). * $P < 0.05$ versus control. † $P < 0.05$ versus MDMA-treated group.

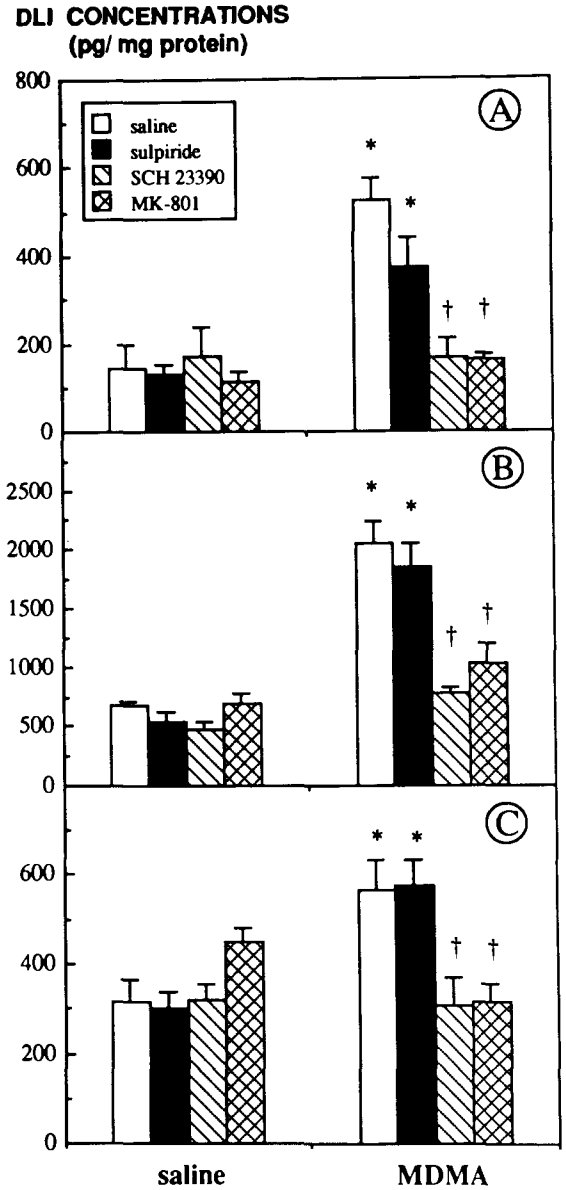

Fig. 2. Effects of dopamine receptor antagonists and MK-801 on the MDMA-induced increase in DLI concentrations measured in the neostriatum (A), substantia nigra (B) and nucleus accumbens (C). Refer to fig. 1 legend for drug treatment. Each bar represents the mean ± S.E. for each treatment group, expressed as pg of DLI per mg protein (n = 4-7). * $P < 0.05$ versus control. † $P < 0.05$ versus MDMA-treated group.

2A), substantia nigra (fig. 2B) and nucleus accumbens (fig. 2C). MDMA increased DLI levels to 366, 308 and 181% of control in the neostriatum, substantia nigra and nucleus accumbens, respectively. SCH 23390 or MK-801 totally blocked this increase while sulpiride administration failed to alter significantly the MDMA-induced change. The administration of SCH 23390, sulpiride or MK-801 alone had no significant impact on the DLI levels measured in all three brain structures.

4. Discussion

The results presented in this study indicate that the MDMA-induced increases in NTLI and DLI levels measured in the neostriatum and substantia nigra are mediated through the dopamine D_1 receptors. Interestingly, this study demonstrates for the first time that these MDMA-induced increases in NTLI and DLI can also be blocked by the non-competitive NMDA antagonist, MK-801, thus suggesting that an excitatory amino acid system contributes to MDMA effects. DLI levels in the nucleus accumbens were regulated as in the two others brain structures. The lack of difference in the nucleus accumbens between the NTLI levels of the control and the MDMA-treated animals after SCH 23390 or MK-801 (fig. 1C) could suggest that the NTLI levels are regulated as for DLI levels. However, this conclusion should be withheld until further experiments demonstrate a significant blockade of the MDMA-induced increase by SCH 23390 or MK-801. These observations suggest that the mechanism whereby MDMA alters the peptide concentrations is similar to that of its analog, methamphetamine.

Our observations that a D_1 receptor antagonist blocks the MDMA-induced increases in NTLI and DLI levels in extrapyramidal or limbic structures suggests that these changes are dopamine-mediated. As with MDMA, SCH 23390 blocks the methamphetamine-induced increase in neostriatal, nigral and nucleus accumbens NTLI concentrations and neostriatal and nigral DLI concentrations (Hanson et al., 1987; Letter et al., 1987; Merchant et al., 1989b). Moreover, blocking D_2 receptors with sulpiride failed to block both the MDMA- or methamphetamine-induced changes in neostriatal and nigral NTLI concentrations (fig. 1A and B; Letter et al., 1987). These observations indicate that methamphetamine- and MDMA-induced changes in these peptides are mediated through a similar mechanism. However, the present study reveals a discrepancy between the DLI response to methamphetamine and MDMA. Sulpiride is reported to attenuate the methamphetamine-induced increase in nigral DLI (Hanson et al., 1987) but had no effect on MDMA-related nigral DLI changes (fig. 2B). This discrepancy may result from different dosing schedules, but it is also possible that the role of D_1 and D_2 receptors in mediating the neuropeptide changes is different for these amphetamine analogs.

The blockade by MK-801 of the MDMA-induced changes in neurotensin and dynorphin suggests that the glutamatergic system is involved in the mediation of the response. This is supported by a recent observation that administration of NMDA increases neostriatal and nigral NTLI concentrations (Singh et al., 1989). It is not yet clear if the dopaminergic and the glutamatergic systems act independently or in sequence to alter

peptidergic systems. However, there are three possibilities which could explain the present results: (1) MDMA induces the release of dopamine which in turn alters glutamatergic systems that control the peptidergic system, (2) MDMA alters the glutamatergic system which in turn enhances dopaminergic activity and causes changes in the peptidergic systems, or (3) both the monoaminergic and excitatory amino acid systems act directly on the peptidergic system, and both must be activated to regulate the peptidergic response. In support of the third explanation, it has recently been reported a diminution in the number of neostriatal D_1 receptors following the lesion induced by the NMDA agonist, quinolinic acid, suggesting that both D_1 and NMDA receptors can exist on the same neuron (Norman et al., 1990). This implies that this neuron could be controlled by the dopaminergic and glutamatergic systems. There is also some support for the second explanation as stimulation of NMDA receptors can directly induce dopamine release (Clow and Jhamandas, 1989). MDMA, however, causes release of dopamine from the cytoplasmic pool through a calcium-independent mechanism; thus it is unlikely that stimulation of NMDA receptors is necessary for dopamine release. Consequently, blockade of NMDA receptors with MK-801 would not likely interfere with the ability of MDMA to release dopamine, thus arguing against the second possibility. Further experiments are required in order to verify these possible explanations.

This study suggests that the changes in extrapyramidal neurotensin and in extrapyramidal and limbic dynorphin content induced by MDMA are mediated by both the dopaminergic and glutamatergic pathway. Thus, it is possible that these transmitter systems significantly contribute to the pharmacological effects of this popular drug of abuse. In addition, because MDMA is a dopamine releaser, the ability of the NMDA antagonist to block the dopamine-mediated action suggests that interaction between these two systems is necessary to induce the peptide changes.

Acknowledgements

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