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Is the Ecstasy-induced ipsilateral rotation in 6-hydroxydopamine unilaterally lesioned rats dopamine independent?

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Summary. 3,4-Methylenedioxymethamphetamine (MDMA) has recently been hypothesized to be effective against the symptoms of Parkinson's disease. Therefore we tested the effects of MDMA-derivatives in the rotational behavioural model. Male Sprague Dawley rats were lesioned unilaterally with 6-hydroxydopamine at the medial forebrain bundle. MDMA was administered at doses of 2.5, 5.0 and 10.0 mg/kg, its derivatives N-Methyl-1-(1,3-benzodioxol-5-yl)-2-butananamine (MBDB), 3,4-Methylenedioxy-N-ethylamphetamine (MDE) and 3,4-Methylenedioxyamphetamine (MDA) at 5.0 mg/kg respectively. All substances induced ipsilateral rotations, MDA being the most effective. MDMA induced rotations were attenuated by the selective serotonin reuptake inhibitor Citalopram but were only slightly reduced by pre-treatment with the selective serotonin synthesis inhibitor PCPA (para-chlorophenylalanine). The effects of MDMA can therefore not fully be explained by serotonin release or by dopaminergic activity of the drugs.

Keywords: Apomorphine, rotational behaviour, 6-OHDA.

Abbreviations

ANOVA analysis of variance, *GABA* gamma-aminobutyric acid, *MBDB* N-Methyl-1-(1,3-benzodioxol-5-yl)-2-butananamine, *MDA* 3,4-Methylenedioxyamphetamine, *MDE* 3,4-Methylenedioxy-N-ethylamphetamine, *MDMA* 3,4-Methylenedioxymethamphetamine, *MFB* medial forebrain bundle, *6-OHDA* 6-Hydroxydopamine, *PCPA* para-chlorophenylalanine, *PBS* phosphate-buffered saline, *SEM* standard error of the mean.

Introduction

Several lines of evidence point to a unique symptomatic antiparkinsonian efficacy of 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy", "X",

"e") (Schmidt et al., 2002). However, MDMA is an illegal and even toxic substance (Ricaurte, 2002) and therefore not suited for widespread use. This study is designed to analyse the mechanisms by which MDMA mediates the antiparkinsonian effect. The elucidation of MDMA's mechanism of action could represent a basis for the development of new and safe antiparkinsonian drugs.

Parkinson's disease is a progressive neurodegenerative disorder of the dopaminergic mesotelencephalic system. The currently used standard therapy with the dopamine precursor L-DOPA can not prevent the progression of the disease and induces dyskinesias. Furthermore, dopaminergic agonists may even evoke unwanted hallucinatory side effects. For these reasons there is still a need for new pharmacologically active agents in the therapy of Parkinson's disease.

A standard animal model to simulate hemiparkinsonism is the lesioning of the dopaminergic nigrostriatal system by unilateral injections of 6-hydroxy-dopamine (6-OHDA) into the medial forebrain bundle (MFB). Rotational behaviour is the major behavioural method for measuring dopaminergic activity in the rat brain. Unilateral lesioning of the dopaminergic input into the striatum results in walking in circles because the intact striatum is still functioning. This method was first described by Ungerstedt and Arbuthnott (1970). Since then, it has often been used for effective preclinical screening of substances that can elevate dopamine levels or activate dopamine receptors: drugs that release dopamine from presynaptic terminals and other stimulants induce ipsilateral rotations; drugs which activate postsynaptic dopamine receptors induce contralateral rotations. Consequently, substances which show such effects could in most cases be used as therapeutics for Parkinson's disease.

MDMA has strong motor stimulant effects in animals (Spanos and Yamamoto, 1989) and has recently been shown to counteract haloperidol induced parkinsonian symptoms in rats (Schmidt et al., 2002). However, the neurochemical basis for this stimulant effect is still not completely understood (see Discussion).

The illicit recreational use of 3,4-Methylenedioxymethamphetamine is very popular (Strote et al., 2002). Ecstasy accounted for 10% of consumed illegal drugs 2001 in Germany [Bundeskriminalamt, Rauschgiftjahresbericht 2001 (2002)]. MDMA and its derivatives MDE, MBDB and MDA share a basic amphetamine structure and are suggested to represent a novel class of drugs, named entactogens, because of their effects on human psyche (Nichols, 1986; Nichols et al., 1986).

In this study the unilateral 6-OHDA lesion model was chosen to analyse the mechanisms of action of MDMA: At first, the question was addressed whether MDMA and its derivatives MDE, MBDB and MDA are able to induce circling; the next question concerned the direction of the circling response. Since MDMA induced ipsilateral rotations, a presynaptic mechanism of action was assumed. Thereafter it was tested how the serotonin reuptake inhibitor citalopram and serotonin depletion by PCPA affect MDMA actions.

Material and methods

Animals

Male Sprague-Dawley rats weighing between 220 and 320 g were housed in groups of five or six in a temperature- and humidity controlled environment under a 12/12 hours light-dark cycle. Water was available ad libitum and standard rat food was delivered once daily at 12 g per animal. All experiments were carried out during the light phase and were performed in accordance with international ethical standards and the German Animal-Protection Law and have been approved by the local animal care committee (Tierschutzkommission, Regierungspräsidium Tübingen, ZP5/01).

Drugs

The racemic Ecstasy-derivatives MDA, MDMA, MDE and MBDB were synthesized from Piperonal obtaining the hydrochloride salts, according to the methods of Braun and colleagues (Braun et al., 1980) and dissolved in phosphate-buffered saline (PBS, Sigma Taufkirchen, Germany). All drugs were administered subcutaneously in an injection volume of 1 ml/kg. MDMA HCl was administered at 2.5, 5.0 and 10.0 mg/kg, MBDB, MDA and MDE were administered at 5.0 mg/kg respectively. Apomorphine HCl-solution (Teclapharm, Lüneburg, Germany) was diluted in physiological saline and administered at 0.25 mg/kg subcutaneously. Citalopram-HCl-solution (Lundbeck Hamburg, Germany) was diluted in PBS (Sigma Taufkirchen, Germany) and administered at 10 mg/kg subcutaneously. Para-chlorophenylalanine methyl ester HCl (PCPA) (Sigma Taufkirchen, Germany) was dissolved in PBS (Sigma Taufkirchen, Germany) and administered subcutaneously on three consecutive days at a dose of 150 mg/kg.

Medial forebrain bundle unilateral lesion

Rats were anesthetised with Pentobarbital-Natrium (Narcoren®, Merial Hallbergmoos, Germany) 60 mg/kg, i.p. and 6-OHDA HBr (8 μg in 1 μl ascorbic acid 0.01%, both Sigma Taufkirchen, Germany), was injected into the left medial forebrain bundle at 0.1 μl per min. The stereotaxic coordinates were: A = −4.0 mm from the interaural line, L = 1.6 mm from bregma and H = 8.8 mm from the surface of the skull according to a stereotaxic atlas (Paxinos and Watson, 1998). The injection cannula was left in place for additional 4 minutes to allow diffusion of the neurotoxin. 30 min prior to the lesion, desipramine HCl (Sigma Taufkirchen, Germany) was administered i.p. at a dose of 20 mg/kg to protect noradrenergic neurons against damage by 6-OHDA. Atropinesulfate (0.2 mg per animal in 0.2 ml saline, Sigma Taufkirchen, Germany) was administered subcutaneously to ease breathing during the anaesthesia. To allow recovery from surgery, animals were single housed for one day after the surgery.

Behavioural testing

All compounds were tested in the same group of animals, in experiments lasting 120 to 220 min with a wash-out period of at least 5 days between each treatment. A slight increase in the basal rotational activity (saline treatment) was observed after this repeated testing but this by no means questiones the conclusion of the current study. Animals were placed into plastic cylinders (23 cm in diameter) and rotational behaviour (360 degree turns) was scored in 10 min intervals. Rotations in the ipsilateral and contralateral directions were counted separately and the analyses were based on the net scores (ipsilateral minus contralateral rotations); a positive score indicated that the animals exhibited a net ipsilateral bias, whereas a negative score indicated a net contralateral bias. Animals were placed into the cylinders 15 min prior to injection of substances and baseline spontaneous rotations were measured over 10 min prior to injection. Depletion of brain serotonin was induced by repeated administration of the serotonin synthesis inhibitor para-

chlorophenylalanine methyl ester HCl (PCPA) once daily on three consecutive days at 150 mg/kg. This regimen reportedly leads to a large and selective depletion of 5-HT (Koe and Weissman, 1966). Behavioural testing with MDMA was redone three days afterwards.

Statistical analysis

Data are given as means ± SEM and a p-value of 0.05 was accepted as significant.

Data for Apomorphine and Saline were analysed by one-way analysis of variance (ANOVA) followed by Dunnett's test for comparison with baseline. For comparison of several treatments the results were analysed by two-way ANOVA with repeated measures followed by Tukey/Kramer test for multiple pairwise comparisons.

Results

Apomorphine induced contralateral rotations [$F(12,120) = 34{,}50$, $p < 0.0001$] beginning immediately after the injection and lasting approximately 80 minutes with a peak reaction 20 minutes after the injection (Fig. 1).

Injection of MDMA (5 mg/kg and 10 mg/kg) induced dose dependent rotations [$F(44,660) = 10.03$, $p < 0.0001$] in ipsilateral direction to the lesion of the MFB (Fig. 1). The administration of 2.5 mg/kg MDMA did not produce a significant effect from baseline; higher dosages of MDMA produced rotations with a peak reaction at 70 respectively 90 minutes after the injection. The rotations did not reach baseline levels by the end of registration of rotations after 220 minutes in the higher dosage. Time course of rotations

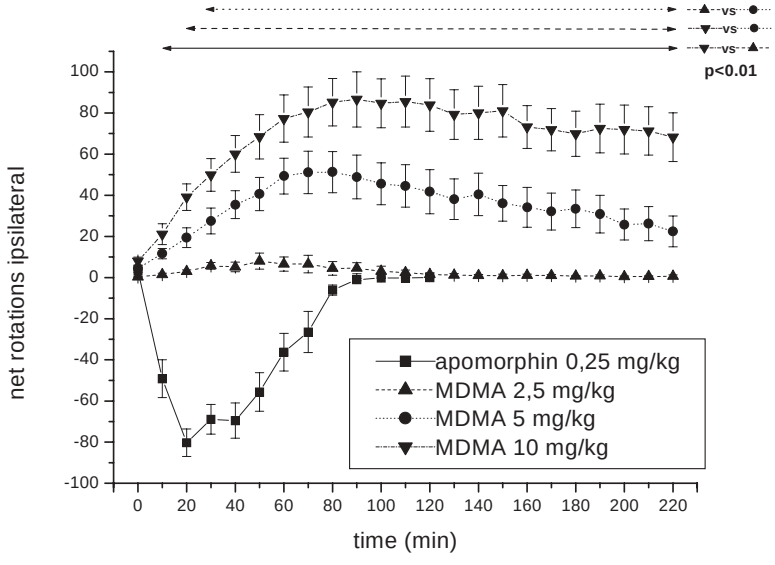

Fig. 1. Time course of rotations after administration of apomorphine and of MDMA in 6-OHDA MFB lesioned rats (means ± S.E.M., n = 11). Apomorphine induced rotations to the side contralateral to the lesion [$F(12,120) = 34{,}50$, $p < 0.0001$]. MDMA caused dose-dependent rotations to the side ipsilateral to the lesion [$F(44,660) = 10.03$, $p < 0.0001$]. Lines with arrows indicate $p < 0.01$ versus respective group

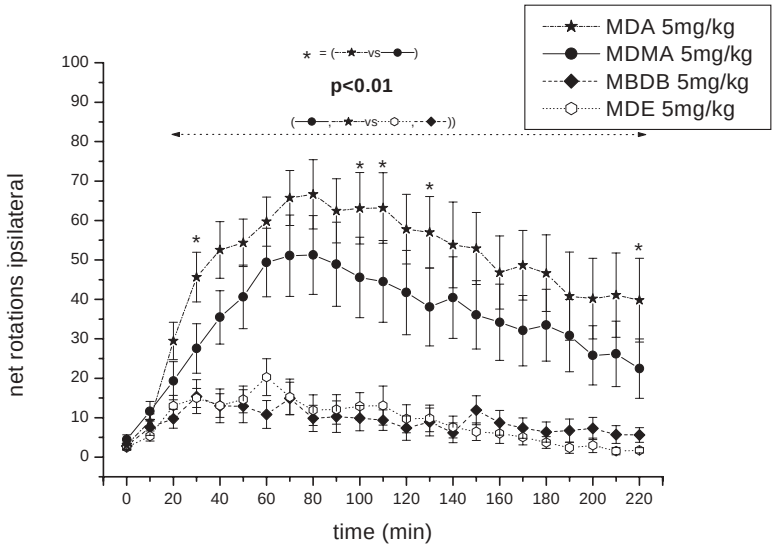

Fig. 2. Time course of rotations after administration of MDMA and its derivatives (5 mg/kg respectively) in 6-OHDA MFB lesioned rats (means ± S.E.M., n = 11) [F(66,880) = 6,59, $p < 0.0001$]. MDA is most potent at inducing ipsilateral rotations, tightly followed by MDMA, while MDE and MBDB having no detectable effect except for MDE at 60 minutes. Lines with arrows indicate $p < 0.01$ versus respective group

after administration of MDMA and its derivatives revealed significant differences [F(66,880) = 6,59, $p < 0.0001$].

Both MBDB and MDE at 5 mg/kg did not induce significant ipsilateral rotations from baseline except for MDE after 60 minutes. There was a slight tendency for rotations but MBDB and MDE were far less potent than MDMA at the same dosage (Fig. 2). The number of net rotations induced by MBDB did not differ at any point from MDE in the time course of this study. MDA was even more potent than MDMA with the net number of ipsilateral rotations peaking at 80 minutes (Fig. 2). The time course of rotations after MDA was similar to that of MDMA at the same dosage.

The selective serotonin reuptake inhibitor citalopram (10 mg/kg) markedly attenuated MDMA- (5 mg/kg) induced rotations in combined treatment while citalopram administration itself had no effect [F(44,660) = 9,11, $p < 0.0001$] (Fig. 3). The time course of the reaction in combined treatment was also delayed with a peak effect only seen after 160 minutes.

After a serotonin depleting regimen of PCPA, MDMA induced rotations were slightly reduced [F(44,660) = 8,53, $p < 0.0001$] (Fig. 4). The time course of MDMA induced rotations was also delayed after PCPA treatment with a peak reaction at 130 minutes in comparison to a peak reaction at 70 minutes before PCPA administration. Acute effects of PCPA administration on rotational behaviour were also registered at the first time of PCPA administration but no significant effect could be observed (Fig. 4).

After Saline-administration slight ipsilateral rotations were observed [F(17,170) = 2,01, $p < 0.013$].

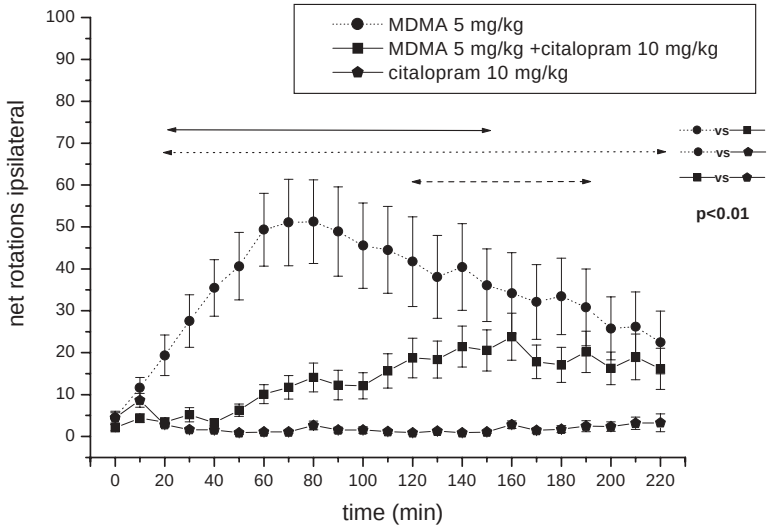

Fig. 3. Effect of citalopram (10 mg/kg) administration on MDMA (5 mg/kg)-induced rotations in 6-OHDA MFB lesioned rats (means ± S.E.M., n = 11) [$F(44,660) = 9{,}11$, $p < 0.0001$]. Citalopram attenuated and delayed rotations in combined treatment with MDMA while having no effect on its own. Lines with arrows indicate $p < 0.01$ versus respective group

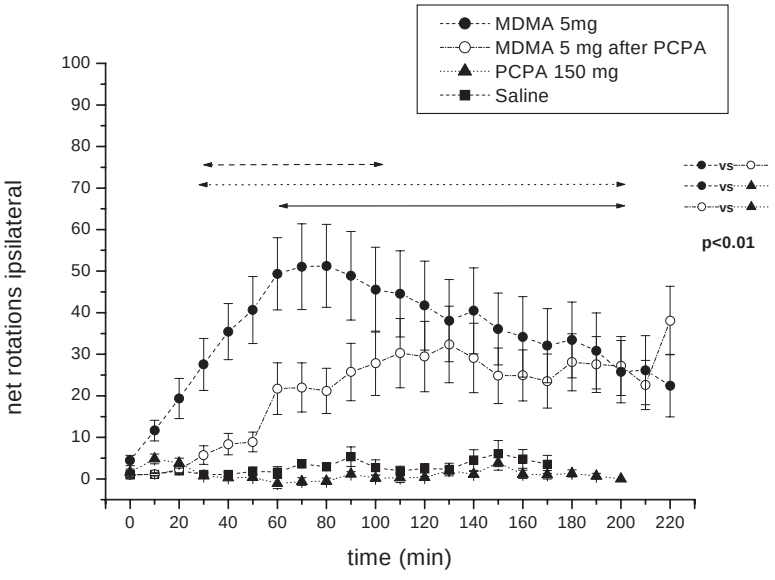

Fig. 4. Effect of PCPA pretreatment on MDMA (5 mg/kg)-induced rotations [$F(44,660) = 8{,}53$, $p < 0.0001$] and conditioned effect of Saline treatment [$F(17,170) = 2{,}01$, $p < 0.013$] after repeated testing in 6-OHDA MFB lesioned rats (means ± S.E.M., n = 11)]. Serotonin depletion by treatment with PCPA attenuated and delayed the effect of MDMA on rotational behaviour while having no acute effect on its own. After repeated testing with several drugs, the animals rotated after administration of Saline. Lines with arrows indicate $p < 0.01$ versus respective group

Discussion

MDMA caused ipsilateral rotations in a dose-dependent and reproducible manner. The strength of this ipsilateral rotational behaviour increased within the following order of the MDMA-derivatives: MBDB, MDE, MDMA, MDA.

Citalopram attenuated MDMA induced rotations but did not induce rotations if administered alone. Serotonin depletion by PCPA also slightly attenuated MDMA-induced rotations but did not completely abolish rotations. Saline-administration after all treatments revealed a slight rotation to the ipsilateral side, this is interpreted as conditioned effect that has been described before (Carey, 1986a,b, 1988).

The rotational behaviour test is one of the most powerful tools to screen potential anti-Parkinsonian agents which either stimulate dopamine release from presynaptic terminals or activate postsynaptic dopamine receptors. In order to verify the lesion, apomorphine was administered. All animals in the current study rotated contralaterally to the side of lesion and were therefore considered hemiparkinsonian (Hefti et al., 1980; Hudson et al., 1993; Barnéoud et al., 1995; Przedborski et al., 1995).

For the induction of contralateral rotations, postsynaptic receptor specifity of the respective drugs is required. In contrast, ipsilateral rotations can not be considered to be specific for a direct dopamine releasing action because there are many actions in the nervous system that indirectly induce presynaptic dopamine release from nigrostriatal neurons. Because in our experiments MDMA induced ipsilateral rotations, primarily presynaptic mechanisms are discussed.

The direction of rotations after administration of MDMA was the same as after injection of amphetamine which is thought to mediate this effect by releasing dopamine from presynaptic terminals. Predominantly amphetamine-like rotation has also been observed in unlesioned animals after administration of MDMA (Kulmala et al., 1987). Amphetamine shares some behavioural properties with MDMA but the two substances also differ in other behavioural and neurochemical effects and MDMA is therefore thought to represent a class of drug different from psychomotor stimulants (Nichols et al., 1986).

It can not be ignored that MDMA, like amphetamine, releases dopamine (Nash, 1990; Nash and Nichols, 1991; McKenna et al., 1991; Colado and Green, 1994; White et al., 1996; Kankaanpaa et al., 1998; Bankson and Cunningham, 2001). A role for the mesolimbic dopamine system in the psychostimulant actions of MDMA has been discussed since DA depletion with the DA neurotoxin 6-OHDA attenuated the behavioural effects of MDMA (Gold et al., 1989).

The potency to release striatal dopamine decreases in the following order: MDA, MDMA, MDE, MBDB (Nash and Nichols, 1991; Johnson et al., 1986). In our experiments, the same order was seen in rotational behaviour. The time course of rotations after MDMA and MDA was very similar though MDA being more effective. This suggests that both substances are inducing

rotations by similar mechanisms. But it seems rather unlikely that direct dopamine release mediates ipsilateral rotations, since combined treatment with Citalopram markedly reduced the number of MDMA-induced rotations. It has been shown that MDMA-induced serotonin release is inhibited by serotonin reuptake inhibitors but dopamine release is not altered (Mechan et al., 2002). It is assumed that blockade of the serotonintransporter with citalopram prevents MDMA from entering serotonergic neurons leaving dopamine neurons unaffected.

It has been shown that MDMA releases serotonin and norepinephrine more potently than dopamine (Rothman et al., 2001). However, in general, an elevated serotonin level is not associated with reduced parkinsonism; on the contrary, serotonin release or reuptake inhibition rather enhances parkinsonian symptoms in the catalepsy model in rats (Wadenberg, 1996) and there have also been reports of de novo onset of parkinsonian symptoms in humans (Stadtland et al., 2000). These effects are thought to be caused by inhibition of dopaminergic neurons by serotonergic mechanisms (Kelland et al., 1990; Neal-Beliveau et al., 1993).

Citalopram is acting at the serotonin reuptake carrier and prevents MDMA from entering cells via this carrier and therefore, MDMA can not reverse this carrier. From the attenuation of MDMA induced rotations by Citalopram, it can be concluded that the effect of MDMA on rotational behaviour is at least in part mediated via uptake into serotonergic neurons. But it is rather unlikely, that the rotations are elicited by a simple blockade of reuptake and enhanced extracellular levels of serotonin, for Citalopram in the current study did not induce rotations by itself. In contrast to MDMA, Citalopram is reported not to influence dopamine and norepinephrine but only to increase serotonin levels (Millan et al., 2000). Findings in other studies with Citalopram also suggest that physiological effects of MDMA in humans are partially due to an interaction of MDMA with the serotonin carrier and a subsequent release of serotonin (Liechti and Vollenweider, 2000) and some of the behavioural effects of MDMA are blocked by the SSRI Citalopram (Liechti et al., 2000). MDMA-induced serotonin release can not fully account for all the positive effects of MDMA in animal models of Parkinson's disease for another reason: all derivatives of MDMA are equipotent releasers of serotonin but their effects on catalepsy differ considerably (Schmidt et al., 2002; Bankson and Cunningham, 2002). Additionally, our experiments yield another evidence that serotonin can not be the only key for understanding the antiparkinsonian effect of MDMA: serotonin depletion with PCPA failed to block rotations induced by MDMA in our experiments though it has been shown that pre-treatment with PCPA attenuated (+)-MDMA induced hyperactivity (Callaway et al., 1990) and completely blocked the acute increase in the extracellular concentrations of serotonin produced by MDMA (Brodkin et al., 1993). Therefore both, the SSRI Citalopram and the serotonin synthesis inhibitor PCPA have similar effects on MDMA induced rotations and question an exclusive role of serotonin in this regard.

However, it has also been suggested that the excitatory effects of MDMA on dopaminergic neurons of the rat substantia nigra are mediated by 5-HT_2

receptors (Nash, 1990; Yamamoto et al., 1995; Gudelsky et al., 1994). Enhancement of striatal dopamine release by serotonin has been reported (Benloucif and Galloway, 1991; Bonhomme et al., 1995; Yadid et al., 1994). There is also evidence for MDMA inhibiting the dopamine reuptake carrier (Metzger et al., 1998). In addition, there is evidence that serotonin can mediate an excitatory action on a subset of nigrostriatal neurons by inhibiting striatonigral GABAergic afferents (Johnson et al., 1992). Other findings indicate that, in the striatum, endogenous serotonin has no influence on dopamine release under basal conditions, but positively modulates dopamine outflow when nigro-striatal DA transmission is activated (Lucas et al., 2000). Tanaka et al. (1999) have suggested that serotonergic terminals in the striatum can convert administered L-DOPA into dopamine exogenously and in the absence of dopaminergic terminals. Dopamine would be released instead of serotonin and drugs acting to stabilize serotonergic neurons could help to prevent side effects of L-DOPA.

MDMA has also been found to increase extracellular levels of norepinephrine and to alter brain levels of neuropeptides (White et al., 1996). Enhancing norepinephrine activity has shown only some weak antiparkinsonian activity (Rückert, 2001), although there are several hints of neuroprotective actions of norepinephrine in Parkinson's disease (Gesi et al., 2000). Moreover, electrophysiological studies have shown that the main effect of norepinephrine is to inhibit the firing rate of nigrostriatal dopaminergic neurons (Collingridge and Davies, 1981). For these reasons it seems unlikely that the observed effects of MDMA are simply due to its action on the norepinephrine system.

It is concluded that either a combination of the effects on various neurotransmitter systems is responsible for the anti-Parkinsonian effect of MDMA or a so far unknown mechanism of MDMA results in these positive effects.

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