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European Journal of Pharmacology 516 (2005) 34 – 39

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# 3,4-Methylenedioxymethamphetamine and naloxone in rat rotational behaviour and open field

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Received 14 February 2005; received in revised form 13 April 2005; accepted 14 April 2005
Available online 17 May 2005

**Abstract**

It has recently been shown that 3,4-Methylenedioxymethamphetamine (MDMA) has an anti-parkinsonian effect in rodent models of Parkinson's disease. The mechanism of this anti-parkinsonian action is unknown.

Opioids have been suggested to play a role in MDMA-induced behaviour.

We therefore investigated MDMA and naloxone in the rat rotational behavioural model. Male Sprague–Dawley rats were lesioned unilaterally with 6-hydroxydopamine at the medial forebrain bundle. Administration of R/S-MDMA (5 mg/kg, s.c.) produced ipsilateral rotations. Naloxone (2, 5, 10 mg/kg, s.c.) did not produce rotations on its own but reduced the number of MDMA-induced ipsilateral rotations. This effect was not dose-dependent. In contrast to reports on mice, in unlesioned animals, naloxone (10 mg/kg, s.c.) did not block MDMA (5 mg/kg, s.c.)-induced hyperactivity in an open field in our experiment.

It is concluded that endogenous opioids play a role in MDMA's action in the rat rotational behavioural model.


*Keywords:* MDMA (3,4-Methylenedioxymethamphetamine); 6-OHDA (6-hydroxydopamine); Serotonin; Dopamine; Endogenous opioid; Parkinson's disease

## 1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") is a recreational drug which has gained wide popularity over the past 20 years because of its ability to produce strong feelings of euphoria, empathy, and connection to others (Vollenweider et al., 1998; Cami et al., 2000). It is most frequently used orally and rarely snorted. MDMA was declared illegal in the Schedule I of the International Convention on Psychotropic Substances.

MDMA is chemically related to amphetamine-like stimulants and hallucinogens (Shulgin and Nichols, 1978).

Its most prominent acute pharmacological effect is to block the reuptake of serotonin (5-HT) and reverse the flow at the serotonin transporter resulting in enhanced release of serotonin from nerve terminals (Schmidt et al., 1986; Nichols et al., 1982). Additionally, MDMA causes transporter-mediated release of central dopamine and norepinephrine.

In rodents, it elicits dramatic increases in locomotion. As MDMA is a releaser of both serotonin and dopamine (Nichols et al., 1982; Schmidt et al., 1987; Nash and Yamamoto, 1992), it is not clear if the locomotor-stimulating effects are due primarily to direct effects on dopamine release or indirectly by the influence of serotonin release upon dopamine transmission (Callaway et al., 1990; Callaway et al., 1991; Geyer and Callaway, 1994). Interactions between serotonergic and dopaminergic systems of the brain have been described on numerous investigations. There is evidence that MDMA increases dopamine release through carrier-mediated processes (Hansen et al., 2002; Crespi et al., 1997; Metzger et al., 1998; Bogen et al., 2003), but also that released serotonin increases dopamine release via

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doi:10.1016/j.ejphar.2005.04.020

stimulation of 5-HT2 receptors (Schmidt et al., 1992; Lucas and Spampinato, 2000).

However, not all effects of MDMA are explained by these mechanisms of action. The anti-parkinsonian action of MDMA and its derivates is not fully understood. We have recently shown that MDMA induces ipsilateral rotation in 6-hydroxydopamine unilaterally lesioned rats (Lebsanft et al., 2003) and that MDMA counteracts catalepsy (Schmidt et al., 2002). These effects could not be fully explained by serotonergic or dopaminergic activity of the drug.

Recently, it has been shown that enkephalin contributes to the locomotor stimulating effects of MDMA in mice (Compan et al., 2003). μ-Opioid-receptor activation by morphine is known to induce burst-like increases of locomotion (Babbini and Davis, 1972). On the other hand, morphine is known to induce catalepsy at higher doses (Turski et al., 1982; De Ryck et al., 1980).

Here, the question is addressed to which extent μ-receptor activation is involved in the locomotor stimulating effects of MDMA in rats in an open field and in the MDMA-induced ipsilateral rotation in unilaterally 6-OHDA (6-hydroxydopamine) lesioned rats.

## 2. Materials and methods

### 2.1. Animals

All rats (male, Sprague–Dawley, 7–8 weeks old, and 226–250 g body weight at the beginning of the experiments, Charles River, Germany) were acclimatized and handled by the experimenter for about one week before start of the experiments. The rats were housed in groups of six in a 22.5 °C room temperature- and 55% humidity-controlled environment under a 12/12 h 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, ZP 05/01).

### 2.2. Drugs

All drugs were freshly dissolved on the day of testing and administered subcutaneously in an injection volume of 1 ml/kg. Racemic MDMA HCl was kindly supplied by the Pharmaceutical Institute, Department of Pharmaceutical Chemistry/Analysis, University of Tuebingen, Germany and dissolved in phosphate-buffered saline (PBS, Sigma, Taufkirchen, Germany). MDMA HCl was administered at 5.0 mg/kg. Naloxone hydrochloride dihydrate (Sigma, Taufkirchen, Germany) was dissolved in PBS and administered at doses of 2, 5, and 10 mg/kg, respectively.

### 2.3. Open field experiment

Rats were treated with PBS vehicle ($n=10$), MDMA 5 mg/kg ($n=10$), naloxone 10 mg/kg ($n=10$), or combined MDMA 5 mg/kg and naloxone 10 mg/kg ($n=10$). Both drugs were injected subcutaneously and simultaneously 1 h before behavioural analysis. During that time, animals were kept in their home cages in the experimental room. Animals were placed gently into the plastic boxes of a light-beam rodent activity box monitoring system (47 cm × 47 cm × 44 cm, TSE, Technical and Scientific Equipment GmbH, 61350 Bad Homburg, Germany) and locomotor behaviour and rearings were recorded over a time span of 10 min.

The path length travelled, number and time span of rearings, and time active and inactive by each animal were recorded.

### 2.4. Rotational experiment

After acclimatization rats were lesioned by 6-OHDA application into the medial forebrain bundle.

24 rats were anaesthetized 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 min 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. Atropinesulphate (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 singly housed for 1 day after the surgery. The retrograde degeneration of the dopaminergic cells originating in the substantia nigra was allowed to fully develop during the next 29 days. During that period, the rats were kept in their home cages. All compounds were tested in the same rats, in experiments lasting 130 min with a wash-out period of at least 5 days between each treatment. For each treatment, rats were regrouped in a counter-balanced manner respective to their pre-treatment.

Animals were placed into the plastic bowls of a rotameter system (TSE, Technical and Scientific Equipment GmbH, 61350 Bad Homburg, Germany) and baseline rotational behaviour (360 degree turns) was recorded over a time span of 10 min. Immediately afterwards, rats were given MDMA and naloxone subcutaneuosly and rotational behaviour was recorded for further 120 min. Rotations in the ipsilateral (counter clockwise) and contralateral (clockwise) directions were counted separately and the analyses were based on the net scores (counter clockwise minus clockwise rotations); a positive score indicated that the animals exhibited a net ipsilateral bias.

Data were recorded by the TSE rotameter software as *.dat file and stored as *txt in ASCII format. Export files *.csv compatible to *.xls (Microsoft EXCEL) were generated.

### 2.5. Statistical analysis

Statistical analysis was performed by analysis of variance (ANOVA) followed by post hoc tests using GB STAT version 7.0.

Data are given as means±S.E.M. and a $P$-value of 0.05 was accepted as significant.

For comparison of several treatments in the rotational experiment, the results were analysed by two-way ANOVA with repeated

measures design followed by Fisher's LSD protected *t*-test for multiple pair wise comparisons.

The measurements of distance, running time, number of rearings, and rearing time in the open field experiment were analysed using two-factor ANOVA for completely randomized groups. Post hoc comparisons were done with Tukey/Kramer Procedure.

## 3. Results

The ability of naloxone to affect MDMA (5 mg/kg) evoked behaviour was assessed in two rat models.

Ipsilateral rotations in 6-OHDA hemilesioned rats were significantly higher after MDMA treatment ($F_{4,55}=6.179$, $P=0.0004$) in the time span from 1 h to 2 h after application of the respective drugs. This time span was selected for statistical analysis because the rotational peak effect was achieved after 1 h.

Naloxone did not induce rotations in 6-OHDA hemilesioned rats but significantly diminished rotations induced by MDMA. As naloxone in dosages 2 mg, 5 mg, and 10 mg per kg all had the same effect, this reduction of MDMA-induced ipsilateral rotations is not dose-dependent. The results of the rotational experiment are depicted in Fig. 1.

In the open field experiment, MDMA stimulated locomotion; it augmented the total distance travelled ($F_{1,36}=175.860$, $P<0.0001$) from 35 m in vehicle treated rats to 87 m in MDMA treated animals. Running time in MDMA treated animals was also significantly augmented ($F_{1,36}=318.129$, $P<0.0001$), the number of rearings only showed a tendency to be increased by MDMA. Naloxone treatment did not produce any differences in open field behaviour compared with vehicle treatment. Under combined MDMA and naloxone treatment, naloxone did not change the effects of MDMA: distance travelled and running time were increased compared to vehicle treatment and naloxone treatment but not significantly different from MDMA treatment.

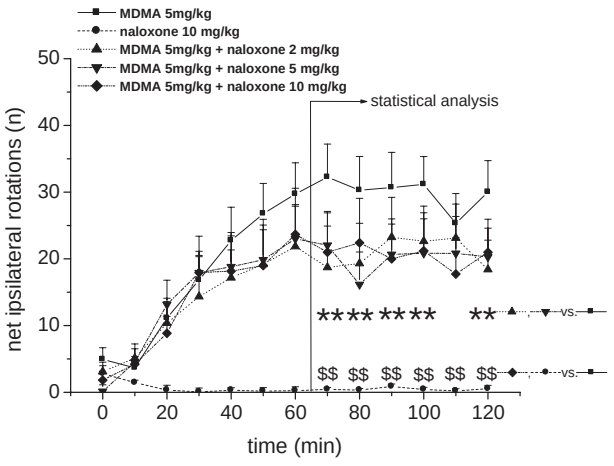


Fig. 1. Naloxone administration (2, 5, or 10 mg/kg) decreases MDMA (5 mg/kg)-induced ipsilateral rotations in unilaterally 6-OHDA medial forebrain bundle lesioned rats (means±S.E.M., $n=12$), ($F(4,55)=6.179$, $P=0.0004$). Naloxone did not induce rotations on its own. Rats were treated with the respective drugs after 10 min of baseline recording. **, $$ indicates $P<0.01$ (Fisher's LSD protected *t*-test for multiple pair wise comparisons) versus respective group.

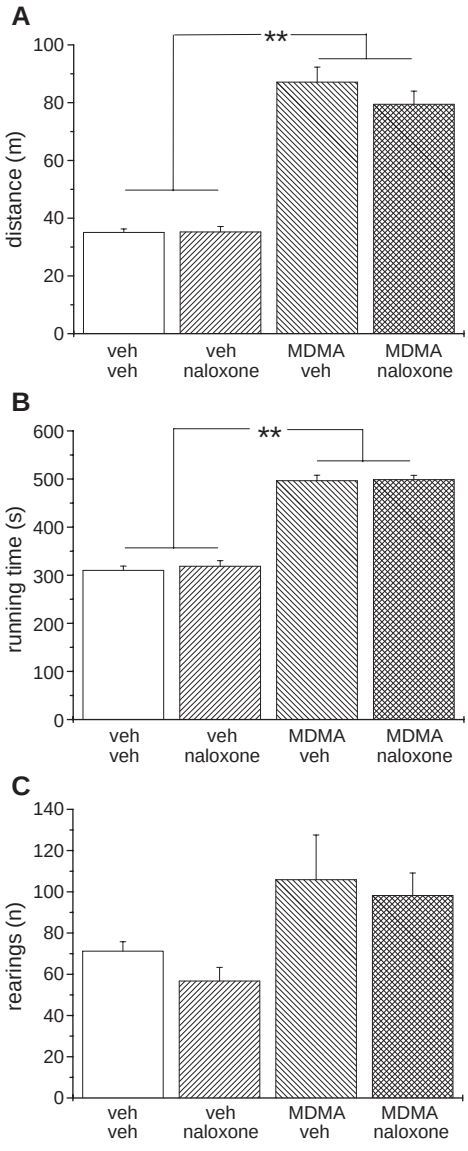


Fig. 2. Naloxone administration (10 mg/kg) does not influence MDMA (5 mg/kg)-induced hyperlocomotion in rat open field behaviour (means± S.E.M., $n=10$). Naloxone did not induce hyperlocomotion on its own. (A) MDMA treatment augmented the total distance travelled ($F(1,36)=175.860$, $P<0.0001$). (B) Running time in MDMA treated animals was also significantly augmented ($F(1,36)=318.129$, $P<0.0001$). (C) The number of rearings only showed a tendency to be increased by MDMA. ** indicates $P<0.01$ post hoc comparisons with Tukey/Kramer Procedure versus respective group.

The levels of significance of the individual treatments are shown in Fig. 2.

## 4. Discussion

In the current experiments, administration of racemic MDMA (5 mg/kg) produced ipsilateral rotations in unilaterally 6-OHDA lesioned rats. This is consistent with our previous reports (Lebsanft et al., 2003). Naloxone in dosages 2, 5, and 10 mg/kg did not produce rotations on

its own but partly reduced the number of MDMA-induced ipsilateral rotations. In contrast to this effect on rotation and to reports on mice (Compan et al., 2003), naloxone did not block MDMA-induced hyperactivity in an open field in our experiment with unlesioned rats. We found that naloxone treatment itself alone did not induce hyperactivity or rearings in male Sprague–Dawley rats. This is in accordance with Kuzmin et al. (2000) and with Compan et al. (2003) who reported no hyperactivity or increased rearing in mice treated with naloxone.

The locomotor stimulating effect of MDMA assessed as increase of distance travelled and running time has been reported several times before. In our experiment, the number of rearings only showed a tendency to be increased by MDMA, rearings have been reported to be increased or decreased inconsistently.

Our results regarding MDMA and naloxone in unlesioned rats differ from the results gained in unilateral dopamine lesioned rats. Only rotational behaviour in unilaterally lesioned rats induced by MDMA was diminished by naloxone whereas naloxone had no effect on simple MDMA-induced locomotion in unlesioned rats. MDMA's anti-parkinsonian effect may therefore not simply resemble its locomotor stimulating properties.

The locomotor stimulating effects of MDMA in the open field may be mediated mainly by dopamine release. MDMA is known to increase serotonin release but also to enhance dopamine efflux (Bradberry et al., 1991; Sprouse et al., 1990; Johnson et al., 1986; Schmidt et al., 1987; Yamamoto and Spanos, 1988; McKenna and Peroutka, 1990; Stone et al., 1986; Stone et al., 1988; Koch and Galloway, 1997). In vivo dopamine release time course (Nash, 1990; Nash and Yamamoto, 1992; Gough et al., 1991) in the striatum corresponds with the time course of rotation in 6-OHDA hemilesioned MDMA treated rats in this experiment and in earlier reports (Lebsanft et al., 2003). This enhancement of release and blockade of the metabolism of dopamine and serotonin resembles the mechanism of amphetamine (Gough et al., 1991). Zetterström et al. (1986) have demonstrated that ipsilateral rotation in response to amphetamine in unilaterally 6-OHDA denervated rats correlated well with the time-course of dopamine release in the striatum contralateral to the lesion. But naloxone did not alter amphetamine-induced rotational behaviour or striatal dopamine levels of unilaterally lesioned rats (Kimmel et al., 1998). It was postulated earlier that MDMA's effect on the striatal dopamine function in vivo is partially dependent on endogenous serotonin because when serotonin's effect was blocked by pre-treatment with fluoxetine, the ability of MDMA to increase extracellular dopamine was significantly attenuated (Bradberry, 1994; Koch and Galloway, 1997) and depletion of serotonin with parachlorophenylalanine attenuated the increase of extracellular striatal dopamine produced by MDMA (Brodkin et al., 1993). We have reported that blocking serotonin release by treatment with citalopram or depletion of serotonin with parachlorophenylalanine also attenuates rotational behaviour in 6-OHDA lesioned rats elicited by MDMA (Lebsanft et al., 2003). The facilitating effect of serotonin release on dopamine release is dependent on intact serotonergic—and perhaps other transmitter systems since it is not evident in striatal slices (Koch and Galloway, 1997).

MDMA is a dirty drug interacting with many different receptors and transporters, at the postsynaptic side. There may also be a convergence of different neurotransmitter systems at the level of G proteins. MDMA binds to different brain recognition sites including serotonin reuptake sites, serotonin receptors, histamine receptors, muscarinic receptors, dopamine receptors, NMDA receptors (Battaglia et al., 1988; Battaglia and De Souza, 1989; Fischer et al., 2001), to induce acetylcholine release (Fischer et al., 2001; Acquas et al., 2001). Furthermore, MDMA has been shown to act as agonist at the rat trace amine receptor (Bunzow et al., 2001).

In our experiment, we further investigated the role of endogenous opioids in MDMA-induced locomotion and rotational behaviour in rats. Behaviour is susceptible to manipulation at various transmitter systems including dopamine or endogenous opioids. Opioids play a role in these behaviour changes as μ- and δ-opioid antagonists have been shown to reduce dyskinesia in parkinsonian primates (Henry et al., 2001).

Thus, MDMA-induced elevated dopamine level is not only due to direct release but also to an indirect influence by other transmitter systems.

The in vitro pharmacological profile for MDMA by Battaglia and colleagues (Battaglia et al., 1988; Battaglia and De Souza, 1989) revealed only low affinities (>500 μM) at μ-, δ-, and κ-opioid receptors but it has been shown that opioids modulate MDMA's reinforcing properties (Bilsky et al., 1991; Bradberry et al., 1991; Reid et al., 1996) and it has been shown recently that enkephalin contributes to the locomotor stimulating effects of MDMA in mice (Compan et al., 2003). MDMA combined treatment with the opioid antagonist naloxone failed to induce hyperactivity in wild-type mice (Compan et al., 2003). As we cannot confirm these results in the open field for rats, we suppose that MDMA has rather different effects on the endogenous opioids in rats and mice. However, for the stimulating properties of MDMA that induce rotational behaviour in 6-OHDA hemilesioned rats, the modulating effects of opioids seem to be comparable to the effects seen on hyperactivity in mice.

Axon terminals of striatal efferent neurons contain metenkephalin and gamma-amino-butyric acid (GABA) in the globus pallidus; substance P, dynorphin, and GABA in the substantia nigra. Decreased GABA release by striatopallidal neurons is related to hyperlocomotion (Graybiel, 1990; Parent and Hazrati, 1995; Compan et al., 2003), increased release to catalepsy (Scheel-Krüger et al., 1980; Scheel-Krüger, 1984, 1986). μ- and δ-opioid receptor agonists have been shown to increase extracellular dopamine levels in the nucleus accumbens and striatum (Spanagel,

1995). Furthermore, it has been shown that selective opioid agonists increase locomotion in mice possibly via the striatopallidal neurons (Mickley et al., 1990; Kuzmin et al., 2000, Compan et al., 2003). Therefore, it is possible that MDMA exerts its locomotor stimulating effects partly via the endogenous opioids. However, in our experiment, this effect was not evident in an open field in normal rats but only became evident in 6-OHDA hemilesioned rats.

There are further possibilities where endogenous opioids may interfere in combination with GABA on locomotor behaviour. MDMA administration decreased metenkephalin levels in the globus pallidus, in wild-type but not in 5-$HT_{1B}$ knockout mice (Compan et al., 2003), suggesting that the effects of MDMA on metenkephalin metabolism are mediated via activation of 5-$HT_{1B}$ receptors. These effects could be antagonised by application of the opioid antagonist naloxone resulting in decreased hyperlocomotion. It could be possible that these effects on the opioidergic system are especially important in animals with disturbed dopaminergic transmission such as 6-OHDA hemilesioned rats. Opioid receptor-agonism could therefore be involved in MDMA-induced anti-parkinsonian effects.

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