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Methylenedioxymethamphetamine induces spontaneous tail-flicks in the rat via 5-HT_{1A} receptors

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In rats lightly restrained in horizontal cylinders, (±)-3,4-methylenedioxymethamphetamine (MDMA) dose dependently (0.16-10.0 mg/kg, s.c.) elicited spontaneous tail-flicks; that is, tail-flicks in the absence of extraneous stimulation. In contrast, amphetamine over a similar dose-range was inactive. Selective inhibitors of 5-hydroxytryptamine (5-HT) uptake and carrier-mediated 5-HT release, paroxetine and citalopram, did not induce spontaneous tail-flicks themselves and blocked those induced by MDMA. In distinction, maprotiline and bupropion, selective inhibitors of noradrenaline and dopamine uptake, respectively, failed to modify the action of MDMA. Spontaneous tail-flicks elicited by MDMA were unaffected by the selective 5-HT_3 receptor antagonists, ICS 205,930 and GR 38032F. They were attenuated by the mixed 5-HT_1/5-HT_2 receptor antagonist, methiotepin, the mixed 5-HT_{1A}/5-HT_{1B} receptor antagonist, (−)-alprenolol and the mixed 5-HT_{1A}/5-HT_2 receptor antagonist, spiperone, but not by the selective 5-HT_{1C}/5-HT_2 receptor antagonists, ritanserin, ICI 169,369 and ketanserin. The novel 5-HT_{1A} receptor antagonists, BMY 7378 and NAN-190, each abolished MDMA-evoked spontaneous tail-flicks. Selective D_1, D_2, α_1, α_2, β_1 and β_2 antagonists had little influence upon induction of spontaneous tail-flicks by MDMA. These data indicate that MDMA evokes spontaneous tail-flicks in the rat via a release of 5-HT which acts at 5-HT_{1A} receptors. Thus, 5-HT_{1A} receptors appear to be involved in the acute functional actions of MDMA.

MDMA (3,4-methylenedioxymethamphetamine); 5-HT (5-hydroxytryptamine, serotonin); 5-HT_{1A} receptors; BMY 7378; NAN-190

1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA; 'ecstasy'), a phenylisopropylamine structurally related both to the CNS stimulant, amphetamine, and to the hallucinogen, mescaline, induces a state of empathy and increased self-awareness in man; it is attracting increasing interest in view of its proposed employment as an adjunct in psychotherapy and its recreational use as a drug of abuse (Gold et al., 1988; Greer and Tolbert, 1986; see McKenna and Peroutka, 1990 for review). The use of MDMA in man is a source of concern since it may possess neurotoxic properties; these are primarily expressed on serotonergic pathways and are observed both in rodents and in monkeys (Battaglia et al., 1988b; McKenna and Peroutka, 1990; Schmidt, 1987; Insel et al., 1989). Whereas the acute administration of amphetamine elicits a rapid release of dopamine (DA) and noradrenaline (NA), MDMA inhibits the uptake of serotonin (5-HT) and induces its rapid release together with, to a lesser extent, DA and NA (Hekmatpanah and Peroutka, 1990; Schechter, 1988; Schmidt et al., 1987; Schmidt and Taylor, 1988; Stone et al., 1988; Yamamoto and Spanos, 1988). The release of 5-HT reflects an action of MDMA in the CNS and is induced at the level of serotonergic terminals. Although it is still under debate whether release of 5-HT requires entry of MDMA into the neurone (Wang et al., 1987; Zaczek et al., 1990), it can be prevented by drugs such as citalopram or paroxetine which interfere with mechanisms for 5-HT reuptake and its carrier-mediated release (McKenna and Peroutka, 1990; Schmidt et al., 1987). MDMA has very low affinity for 5-HT receptors and an induction of 5-HT and/or DA release is thought to largely underlie its acute behavioural actions and, possibly, its abuse potential in man (Battaglia et al., 1988a; Lyon et al., 1986; McKenna and Peroutka, 1990; Schmidt et al., 1987).

Multiple 5-HT receptors exist (see Glennon, 1987; Hoyer, 1988; Tricklebank, 1987) and, currently, a major task is the attribution of functional roles to these various receptor types and the determinination of their

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pathophysiological significance. 5-HT receptors have been provisionally divided into the following major classes: 5-HT_1, 5-HT_2, 5-HT_3 and 5-HT_4 (Glennon, 1987; Hoyer, 1988; Richardson and Engel, 1987). While subtypes of 5-HT_2 and 5-HT_3 receptors may well exist, several subtypes of 5-HT_1 receptors have already been distinguished. These have been termed 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C} and 5-HT_{1D} (Conn and Sanders-Bush, 1987a; Hoyer, 1988). Clearly, an important question concerns the receptor type underlying the behavioural effects of MDMA. In this respect, surprisingly little information is available. Nevertheless, 5-HT_2 receptors have been proposed to mediate its influence upon nigro-striatal dopaminergic transmission and upon both prolactin and corticosterone secretion in the rat (Nash et al., 1988; 1990). It is of interest whether other 5-HT receptor types are involved in the acute effects of MDMA.

In recent studies, we have identified and pharmacologically characterized a novel behavioural response in the rat, the induction of 'spontaneous tail-flicks'; that is, tail-flicks in the absence of extraneous stimulation (Millan et al., 1989; in press). Spontaneous tail-flicks can be elicited by the highly selective 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT; Hoyer, 1988), and also by other high efficacy 5-HT_{1A} receptor agonists but not by agonists at other 5-HT receptor types. This behaviour appeared useful for an evaluation of the possible mediation by 5-HT_{1A} receptors of some of the acute behavioural effects of MDMA. In this paper, we demonstrate that MDMA evokes spontaneous tail-flicks via a 5-HT_{1A} receptor-mediated mechanism in the rat.

2. Materials and methods

2.1. Animals

Male Wistar rats of 200-220 g (Iffa Credo, Ills-kirchen, France) were housed in sawdust-lined cages in groups of three with free access to rat chow and water. Lights were on from 07:30 a.m. to 07:30 p.m. Laboratory temperature was maintained at 21 ± 1°C and relative humidity at 60 ± 5%. Experiments were performed between 01.00 and 05.00 p.m. Rats were used once only.

2.2. Evaluation of spontaneous tail-flicks

As described previously (Millan et al., 1989), rats were introduced into horizontal, opaque, plastic cylinders placed close to the edge of the laboratory bench such that the tail, which emerged from a slit at the rear, hung freely. A spontaneous tail-flick was defined as the raising of the tail to a level higher than that of the body axis. One spontaneous tail-flick was regarded as complete upon the lowering of the tail to a level below this axis. Spontaneous tail-flicks were recorded over 5 min following a 5 min adaptation period to the cylinders. The observer was unaware as to treatment of individual rats.

2.3. Induction of spontaneous tail-flicks by MDMA and their inhibition by antagonists

The ability of MDMA and amphetamine to evoke spontaneous tail-flicks was evaluated 30 min following their administration. For antagonist studies, a dose of 10 mg/kg of MDMA was selected since this dose robustly induced a response comparable to that seen with 0.63 mg/kg of the selective 5-HT_{1A} agonist, 8-OH-DPAT, the actions of which we have previously characterized (Millan et al., 1989; in press). Rats were pretreated with antagonists 10 min prior to MDMA: that is, 40 min prior to commencement of testing. In the time intervening between injections and recording, rats remained in their home cages.

2.4. Drugs

All drugs were dissolved in sterile distilled water. If necessary, a few drops of lactic acid were added and the pH readjusted to > 6.0 with dilute NaOH. The only exception was maprotiline which was suspended in distilled water plus a few dops of Tween 80. All drugs were injected s.c. with the exception of maprotiline which was given i.p. Drug doses are in terms of the base. Drug salts and sources are as follows. Haloperidol and (+)-SCH 23390 HCl (Research Biochemicals, Natick, MA, USA), (−)-alprenolol d-tartrate (Sigma, Chesnes, France), d-amphetamine (Cooperation Pharmaceutique Francaise, Melun, France), maprotiline HCl (Ciba-Geigy, Reuil-Malmaison, France), betaxolol HCl (Synthelabo, Bagneux, France), bupropion HCl (Wellcome, Research Triangle Park, USA), citalopram HBr (Lundbeck, Copenhagen, Denmark), ketanserin (Janssen Pharmaceutica, Beerse, Belgium), ICI 118,551 HCl and ICI 169,369 (ICI, Macclesfield, UK), ICS 205,930 (Sandoz, Basle, Switzerland), methiotepin maleate (Hoffman-La Roche, Basle, Switzerland) and paroxetine HCl (Beecham Pharmaceuticals, Epsom, UK). BMY 7378, GR 38032F, MDMA, ritanserin and NAN-190 were synthesized by Servier chemists.

Drug chemical structures are as follows. BMY 7378 (8-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-8-aza-spirol-[4]-decane-7,9-dione 2HCl), GR 38032F (1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-l-yl)methyl]-4H-carbazol-4-one HCl), ICI 118,551 (erythro-d,l-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol 0l), ICI 169,369 (2-(2-dimethylaminoethylthio)-3-phenylquinoline), ICS 205,930 (3α-tropanyl) 1H-indol-3-carboxylic acid ester), NAN-190 (1-(2-methoxyphenyl)-4-[4-(2-phtalimmido) butyl]-8-azaspiro (4,5) decane-

7,9-dione) and SCH 23390 (R(+)-7-chloro-8-hydroxy-3-methyl-l-phenyl-2,3,4,5,tetrahydro-1H-3-benzazepine HCl).

2.5. Statistics

Data were initially analysed by 1-way analysis of variance (ANOVA) followed by Newman-Keuls test employing procedure 36 of the pharmacological calculations system of Tallarida and Murray (1987): the limit of significance was < 0.05. F values and significance are given in the legends to the tables and figures. The inhibitory dose 50 (dose reducing the action of MDMA to 50% of maximal) plus its 95% confidence limits was calculated according to the method of Finney (1964). The slopes and regression coefficients of dose-response curves were calculated and compared using procedure 6 of Tallarida and Murray (1987).

3. Results

3.1. Induction of spontaneous tail-flicks by MDMA

Figure 1 shows that MDMA dose dependently induced spontaneous tail-flicks, with a minimum (significantly) effective dose of 5 mg/kg. In distinction, over a dose-range of 0.16-10.0 mg/kg, the selective inhibitors of 5-HT uptake, paroxetine and citalopram, failed to induce spontaneous tail-flicks (not shown). In contrast to MDMA, amphetamine failed to induce spontaneous tail-flicks at doses of up to 10.0 mg/kg. Each of the drugs evaluated for its ability to block MDMA-induced spontaneous tail-flicks (see below) was tested alone. None of the drugs elicited a level of spontaneous tail-flicks differing significantly from vehicle-treated animals (data not shown).

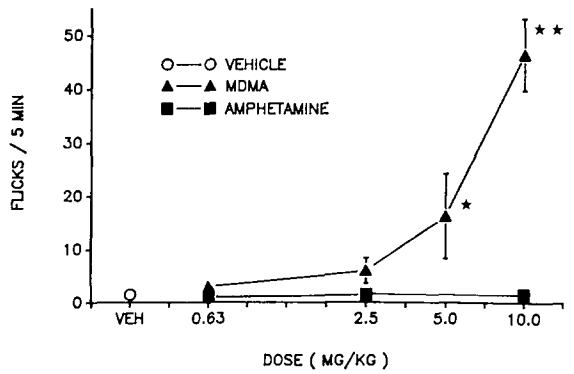

Fig. 1. Induction of spontaneous tail-flicks by MDMA but not amphetamine in the rat. Mean ± S.E.M. is shown. N = 5-10 per value. Asterisks indicate significance of MDMA vs. vehicle values. * $P < 0.05$ and ** $P < 0.01$ (Newman-Keuls test). ANOVA as follows: MDMA: $F(4, 36) = 13.21$, $P < 0.01$. Amphetamine: $F(3, 28) = 0.92$, $P > 0.05$.

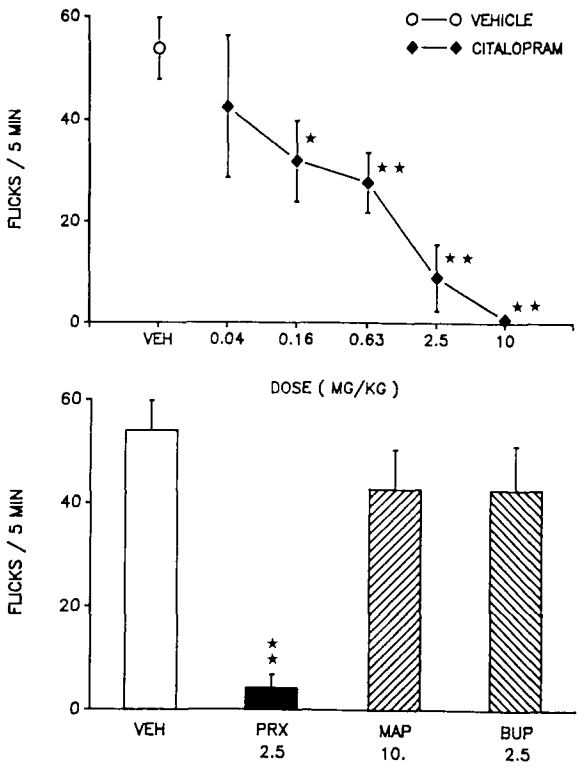

Fig. 2. The influence of 5-HT uptake inhibitors upon MDMA-induced spontaneous tail-flicks in the rat. Upper panel: dose-dependent antagonism by citalopram. Lower panel: selective blockade by paroxetine (PRX) as compared to maprotiline (MAP) and bupropion (BUP). Doses indicated in mg/kg. All rats received MDMA at a dose of 10.0 mg/kg. Mean ± S.E.M. is shown. N = 5-8 per value. * $P < 0.05$, ** $P < 0.01$ (Newman-Keuls test). For analysis of dose-response curve with citalopram, see Results. ANOVA for lower panel: $F(3, 26) = 7.38$, $P < 0.01$.

3.2. Antagonism of MDMA-induced spontaneous tail-flicks by 5-HT uptake inhibitors

Pretreatment with the selective 5-HT uptake inhibitor, paroxetine, almost completely abolished the spontaneous tail-flicks induced by MDMA (fig. 2). In contrast, neither the selective inhibitor of NA uptake, maprotiline, nor the selective inhibitor of DA uptake, bupropion, significantly influenced the action of MDMA (fig. 2). A further selective 5-HT uptake inhibitor, citalopram dose dependently attenuated MDMA-induced spontaneous tail-flicks (fig. 2). The ID_{50} (95% confidence limits) was 1.9 (0.6-6.1) mg/kg. The slope of the dose-response curve was -27.9 and the linear regression coefficient, -0.97. At the highest dose tested, the action of MDMA was blocked completely.

3.3. Attenuation of MDMA-induced spontaneous tail-flicks by 5-HT antagonists

Figure 3 shows that MDMA-induced spontaneous tail-flicks were not significantly affected by administration of the selective 5-HT_3 receptor antagonists, GR

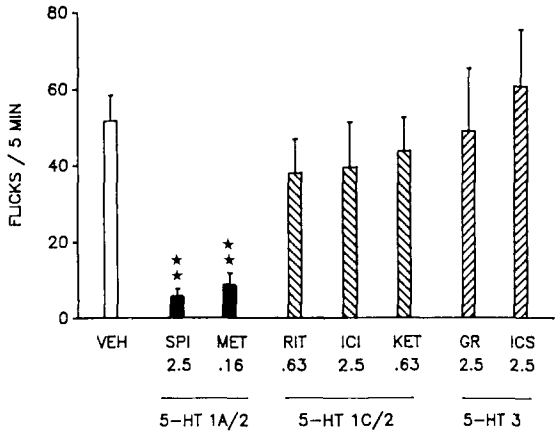

Fig. 3. The influence of 5-HT antagonists upon MDMA-induced spontaneous tail-flicks in the rat. Doses indicated in mg/kg. All rats received MDMA at a dose of 10.0 mg/kg. Mean ± S.E.M. is shown. N = 5-8 per column. VEH (vehicle), SPI (spiperone), MET (methiotepin), RIT (ritanserin), ICI (ICI 169, 369), KET (ketanserin), GR (GR 38032F) and ICS (ICS 205, 930). ** $P < 0.01$ (Newman-Keuls test). ANOVA, $F(7,43) = 12.81$, $P < 0.001$.

38032F and ICS 205,930. Further, the selective 5-$HT_{1C/2}$ receptor antagonists, ritanserin, ICI 169,369 and ketanserin only tended to diminish the effect of MDMA and this action failed to attain statistical significance. In contrast, spiperone and methiotepin, each of which possess potent 5-HT_{1A} receptor antagonist properties, exerted an almost complete inhibition of the action of MDMA.

In addition, the mixed 5-HT_{1A} /5-HT_{1B} receptor antagonist, (−)-alprenolol, dose dependently and potently blocked the action of MDMA (fig. 4). In distinction, combined treatment with the selective β_1 blocker, betaxolol, and the selective β_2 blocker, ICI 118,551, in each case at a dose of 2.5 mg/kg, failed to significantly modify the action of MDMA. Vehicle (n = 10), 50.9 ± 9.8 vs. betaxalol/ICI 118,551 (n = 6), 43.8 ± 8.3 spontaneous tail-flicks/5 min; ($P > 0.05$, Student's two-tailed t-test). In fig. 5, it is shown that the selective

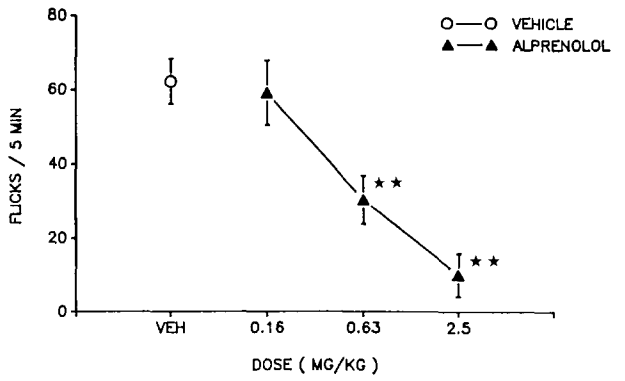

Fig. 4. The influence of (−)-alprenolol against MDMA-induced spontaneous tail-flicks in the rat. All rats received MDMA at a dose of 10.0 mg/kg. Mean ± S.E.M. is shown. N = 5-8 per value. ** $P < 0.01$ (Newman-Keuls test). For analysis of dose-response curve see table 1.

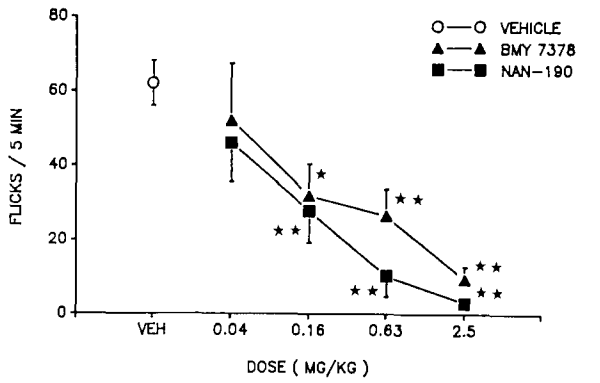

Fig. 5. The influence of BMY 7378 and NAN-190 upon MDMA-induced spontaneous tail-flicks in the rat. All rats received MDMA at a dose of 10.0 mg/kg. Mean ± S.E.M. is shown. N = 5-10 per value. * $P < 0.05$, ** $P < 0.01$ (Newman-Keuls test). For statistical analysis of dose-response curve see table 1.

5-HT_{1A} receptor antagonists, BMY 7378 and NAN-190 each dose dependently and completely blocked the action of MDMA. The results of the statistical analyses of the dose-response curves against MDMA indicated a relative order of potency of NAN-190 > BMY 7378 > (−)-alprenolol, (table 1). Further, there was no significant difference ($P > 0.05$) between the slopes of the dose-response curves for the various drugs.

3.4. Influence of DA antagonists and adrenoceptor antagonists upon MDMA-induced spontaneous tail-flicks

The selective D_1 receptor antagonist, SCH 23390, failed to modify the action of MDMA (table 2). The D_2

TABLE 1

Results of statistical analyses of the antagonism of MDMA-induced spontaneous tail-flicks by (−)-alprenolol, BMY 7378 and NAN-190. The data are presented in figs. 4 and 5. ID_{50}s are given in mg/kg.

Drug	ID_{50} (95% C.L.)	Slope	r
NAN-190	0.13 (0.08-0.38)	−26.1	+0.99
BMY 7378	0.29 (0.09-0.94)	−17.3	+0.97
(−)-Alprenolol	0.76 (0.35-1.65)	−44.3	+1.00

TABLE 2

The influence of DA antagonists upon MDMA-induced spontaneous tail-flicks in the rat. The dose is given in mg/kg. All rats received MDMA (10 mg/kg s.c.), 30 min pre-testing and the antagonists (or vehicle), 40 min pre-testing. Mean ± S.E.M. is shown.

Drug	Dose	N	Flicks/5 min
Vehicle	-	13	48.5 ± 7.4
SCH 23390	0.63	8	54.0 ± 14.7
Raclopride	0.63	4	36.8 ± 10.1
Raclopride	2.50	9	31.8 ± 7.3
Raclopride	10.00	6	11.0 ± 5.8 [b]
Haloperidol	0.63	8	20.4 ± 5.3 [a]
Haloperidol	2.50	5	2.2 ± 0.8 [b]

[a] $P < 0.05$ and [b] $P < 0.01$ to vehicle (Newman-Keuls test). ANOVA: $F(5, 41) = 3.7$, $P < 0.01$.

TABLE 3
The influence of adrenoceptor antagonists upon MDMA-induced spontaneous tail-flicks in the rat. The dose is given in mg/kg. All rats received MDMA (10 mg/kg s.c.), 30 min pre-testing and the antagonists (or vehicle), 40 min pre-testing. Mean ± S.E.M. is shown.

Drug	Dose	N	Flicks/5 min
Vehicle	-	9	56.0 ± 8.1
Rauwolscine	10.0	4	56.0 ± 8.8
Prazosin	0.16	11	46.9 ± 11.0
Prazosin	0.63	12	18.3 ± 5.1 [a]
Corynanthine	10.0	5	39.6 ± 11.9

[a] $P < 0.01$ to vehicle (Newman-Keuls test). ANOVA: $F(3, 43) = 3.0$, $P < 0.05$.

receptor antagonists, raclopride and haloperidol, reduced the action of MDMA only at very high doses (table 2).

The selective α_2 receptor antagonist, rauwolscine, did not modify the action of MDMA (table 3). Only at a high dose (0.63 mg/kg) did the selective α_1 receptor antagonist, prazosin, attenuate the action of MDMA. A further selective α_1 receptor antagonist, corynanthine, had no significant effect (table 3).

4. Discussion

The present study demonstrates that MDMA elicits spontaneous tail-flicks in the rat. This property is shared with 8-OH-DPAT and other high efficacy 5-HT_{1A} receptor agonists, but not agonists at other 5-HT receptor types (Millan et al., 1990; in press). Thus, it is reasonable to hypothesize that the induction of spontaneous tail-flicks by MDMA is mediated by a release of a 5-HT which interacts with 5-HT_{1A} receptors, for which MDMA itself has only negligible affinity (Battaglia et al., 1988a; Lyon et al., 1986; McKenna and Peroutka, 1990). The following arguments support this hypothesis.

First, MDMA initiates a rapid release of 5-HT upon its acute administration to rats (McKenna and Peroutka, 1990; Schmidt et al., 1987; Schmidt and Taylor, 1988). Direct evidence for an involvement of this mechanism in the mediation of spontaneous tail-flicks is provided by the ability of citalopram and paroxetine to block the action of MDMA. This observation is similar to their inhibition of MDMA-elicted 5-HT release and neurotoxicity (Hekmatpanah and Peroutka, 1990; Johnson et al., 1986; McKenna and Peroutka, 1990; Schmidt et al., 1987). Each of these drugs acts as a highly selective inhibitor of uptake into serotonergic neurones and also of the carrier-mediated release of 5-HT: in contrast, they exert very little effect on dopaminergic or adrenergic neurones (Fuller and Wong, 1987). Further, maprotiline and bupropion, selective inhibitors of uptake of NA and DA, respectively (Barbaccia et al., 1986; Cooper et al., 1980), failed to modify the action of MDMA (fig. 2). The lack of a key role for a release of DA or NA is also indicated by the inability of amphetamine (fig. 1) or two other stimulants with a similar catecholaminergic mechanism of action (cocaine and methylphenidate) to elicit spontaneous tail-flicks (not shown). Since citalopram and paroxetine when applied alone did not elicit spontaneous tail-flicks, inhibition of 5-HT uptake per se by MDMA cannot underlie spontaneous tail-flicks. Clearly, the carrier-mediated release of 5-HT is required. Further support for the argument that release of 5-HT leads to the induction of spontaneous tail-flicks is provided by the observation that para-chloroamphetamine, which, like MDMA, preferentially liberates 5-HT (Adell et al., 1989), similarly elicits spontaneous tail-flicks (Millan et al., in press). A key question is as to the 5-HT receptor type via which the 5-HT released by MDMA initiates spontaneous tail-flicks.

The highly selective 5-HT_3 receptor antagonists, GR 38032F and ICS 205,930 (Butler et al., 1988; Richardson and Engel, 1986; Tricklebank, 1987), failed to modify the action of MDMA suggesting that 5-HT_3 receptors are not involved in their mediation. In contrast, methiotepin, a mixed 5-HT_1/5-HT_2 receptor antagonist (Glennon, 1987; Hoyer, 1988; Tricklebank et al., 1987), resulted in a pronounced blockade of spontaneous tail-flicks. Similarly, spiperone, an in vivo antagonist of 5-HT_{1A} and 5-HT_2 receptors (Glennon, 1987; Hoyer, 1988; Tricklebank et al., 1987), blocked the action of MDMA. Since by the use of these drugs, an involvement of 5-HT_{1C} or 5-HT_2 receptors could not be excluded, the actions of three 5-HT_1C/5-HT_2 receptor antagonists, ritanserin, ketanserin and ICI 169,369, were evaluated (Conn and Sander-Bush, 1987b; Hoyer, 1988; Blackburn et al., 1988). Each of these drugs, even at the high doses tested, did not significantly attenuate MDMA-induced spontaneous tail-flicks. These data suggest that a major role of 5HT_{1C}/5-HT_2 receptors can be discounted.

(−)-Alprenolol is a β-blocker with high affinity for 5-HT_{1A} receptors rendering it useful in the identification of 5-HT_{1A} receptor-mediated effects in vivo (Hoyer, 1988; Tricklebank et al., 1987). Indeed, it dose dependently attenuated the action of MDMA. Since combined treatment with betaxolol and ICI 118,551, selective blockers of β_1 and β_2 receptors (Tricklebank, 1987), respectively, did not attenuate the action of MDMA, the action of (−)-alprenolol is unlikely to reflect blockade of β receptors. However, (−)-alprenolol is equipotent at 5-HT_{1A} and 5-HT_{1B} receptors. Thus, in addition, we employed two novel 5-HT_{1A} receptor antagonists with only very low affinity at 5-HT_{1B} and other 5-HT receptors types, i.e. BMY 7378 and NAN-190 (Glennon et al., 1988; Yocca et al., 1987). Each of these potently blocked the action of MDMA. Notably, the relative potency and ID_{50}s of (−)-alprenolol, BMY

7378 and NAN-190 for antagonism of MDMA-induced spontaneous tail-flicks (table 1) are remarkably close to the values obtained for the antagonism of spontaneous tail-flicks induced by 8-OH-DPAT: these are 0.1, 0.3 and 0.5 mg/kg for NAN-190, BMY 7378 and (−)-alprenolol, respectively (Millan et al., in press). This finding reinforces the hypothesis that 5-HT_{1A} receptors mediate MDMA-induced spontaneous tail-flicks in the rat: this conclusion is consistent with our previous studies of selective 5-HT agonists which indicate that only 5-HT_{1A} receptor agonists can induce spontaneous tail-flicks in the rat (Millan et al., 1989; in press).

Indeed, neither direct activation of D_1, D_2, α_1, α_2, β_1 nor β_2 receptors by their respective selective agonists (Millan et al., in press) nor administration of amphetamine (fig. 1) induces spontaneous tail-flicks. Together with the lack of influence of bupropion and maprotiline upon the action of MDMA (fig. 2), these findings suggest that a MDMA-effected release of DA or NA to act upon adrenoceptors or dopamine receptors is not responsible for the induction of spontaneous tail-flicks. In addition, we evaluated the influence of selective DA receptor and adrenoceptor antagonists upon the action of MDMA. The selective D_1 receptor antagonist, SCH 23390 (Arnt, 1987; Hess and Creese, 1987) failed to modify induction of spontaneous tail-flicks by MDMA. The selective D_2 receptor antagonist, raclopride (Ögren et al., 1986) only affected the action of MDMA at a very high dose (10.0 mg/kg) and, even at this dose, its action was only partial. The neuroleptic, haloperidol (Arnt, 1987), did, in fact, strongly inhibit spontaneous tail-flicks elicited by MDMA. This greater efficacy of haloperidol possibly relates to the fact that, though it is a preferential D_2 antagonist, it retains some D_1 antagonist properties (Arnt, 1987). Indeed, in studies with 8-OH-DPAT, we found that only *combined* D_1 and D_2 receptor antagonism can inhibit the induction of spontaneous tail-flicks. Nevertheless, a 2.5 mg/kg dose of haloperidol is very high and it cannot be excluded that the reduction in MDMA-induced spontaneous tail-flicks reflects a disruption of motor control. As concerns adrenergic transmission, the selective α_2 antagonist, rauwolscine (McGrath et al., 1989) did not modify the effect of MDMA. The selective α_1 receptor antagonist, prazosin (McGrath et al., 1989), only attenuated MDMA-elicited spontaneous tail-flicks at the high dose of 0.63 mg/kg. In analogy, high doses of prazosin were reported to attenuate the rate-decreasing effects of MDMA in the pigeon (Nader et al., 1989). However, a further α_1 receptor antagonist, corynanthine (McGrath et al., 1989), was ineffective in the present study.

Overall, these data do *not* suggest a major involvement of DA receptors or adrenoceptors in the mediation of the induction of spontaneous tail-flicks by MDMA. As concerns the action of high doses of haloperidol and prazosin, we have obtained similar effects against spontaneous tail-flicks induced by the selective 5-HT_{1A} agonist, 8-OH-DPAT (Millan, submitted). Thus, it is likely that an involvement, possibly a permissive role, of D_2 and α_1 receptors in the eliciting of spontaneous tail-flicks by MDMA or 8-OH-DPAT occurs *downstream* of 5-HT_{1A} receptor activation. Although it has been suggested previously (Gold et al., 1989) that dopaminergic pathways are involved in mediating the locomotor-activating actions of MDMA, little information is available on the influence of pharmacological modulation of dopaminergic or adrenergic transmission upon the functional actions of MDMA. This question warrants further evaluation.

In conclusion, these data provide strong evidence that MDMA elicits a rapid release of 5-HT which subsequently interacts with 5-HT_{1A} receptors to elicit spontaneous tail-flicks. These data complement previous observations in providing an example of a difference between the behavioural actions of MDMA and a classical psychostimulant such as amphetamine (Gold and Koob, 1989; Gold et al., 1988; 1989; Hiramatsu et al., 1989; Nader et al., 1989). Further, the data bear comparison to prior reports of the induction of stereotyped behaviours such as backpedalling and head weaving by MDMA in the rat, although the receptor type responsible was not determined (Hiramatsu et al., 1989). In fact, MDMA has previously been shown to exert two actions characteristic of an activation of 5-HT_{1A} receptors; firstly, induction of fore-paw treading upon systemic application to rats and, secondly, inhibition of serotonergic transmission via a direct action in the dorsal raphe nucleus upon autoreceptors localized upon serotonergic neurones (Spanos and Yamamoto, 1989; Sprouse et al., 1989; Tricklebank, 1985). Although, in neither case, were antagonist studies undertaken, these data also indicate that MDMA can lead to a stimulation of 5-HT_{1A} receptors. Thus, there is clear evidence that MDMA can elicit functional actions 5-HT_{1A} receptors. The relevance of this effect to its abuse potential in man remains to be elucidated.

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