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Examination of the Action of 3,4-Methylenedioxymethamphetamine on Rat A10 Dopamine Neurons

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ABSTRACT Extracellular single cell recording was used to examine the effect of intravenous administration of (−), (+), and (±)-3,4-methylenedioxymethamphetamine (MDMA) on A10 dopamine (DA) neurons in chloral hydrate anesthetized male rats. Both (±)-MDMA and (+)-MDMA inhibited the firing rate of most (79%) A10 DA cells. By contrast, (−)-MDMA induced either no effect or a slight increase in the firing rate of these cells. Analysis of the effects of (±)-MDMA on the firing pattern of the DA cells revealed an overall decrease in the percentage of spikes in bursts but both increases and decreases were seen in the coefficient of variation of interspike intervals.

To determine the contribution of 5-HT and DA to the (±)-MDMA-induced inhibition of A10 DA cells rats were pretreated either with the 5-HT synthesis inhibitor *p*-chlorophenylalanine (PCPA) or the DA synthesis inhibitor α-methyl-*p*-tyrosine (AMPT). Pretreatment of rats with PCPA did not reduce the ability of (±)-MDMA to inhibit the DA cells. However, in rats pretreated with AMPT, the (±)-MDMA-induced inhibition was blocked and some cells (44%) showed instead an increase in firing rate following administration of (±)-MDMA. The administration of *l*-3,4-dihydroxyphenylalanine (L-DOPA) to AMPT-treated rats rapidly restored the inhibition of cell firing by (±)-MDMA.

In conclusion, the results reported here demonstrate that MDMA has an overall inhibitory effect on A10 DA cells. Despite MDMA's greater potency in releasing 5-HT compared to DA, the inhibitory effect of this drug on A10 DA cells appears to be mediated by the latter transmitter.

INTRODUCTION

Methylenedioxymethamphetamine (MDMA) is a commonly used recreational drug of abuse. Structurally MDMA is similar to amphetamine and in pharmacological studies MDMA, like amphetamine, induces both inhibition of uptake and release of brain monamines (Hekmatpanah and Peroutka, 1990; Hiramatsu and Cho, 1990). In contrast to amphetamine, however, MDMA shows considerably greater potency at the 5-HT transporter compared to its potency at the dopamine (DA) transporter (Johnson et al., 1991; Steele et al., 1987) and it produces a degeneration of 5-HT containing neurons when administered chronically (McKenna and Peroutka, 1990).

Behavioral studies suggest that MDMA has some similarities to amphetamine in its central stimulus effects. In rat drug discrimination tests, amphetamine generalizes to MDMA in rats trained to recognize MDMA from saline (Oberlender and Nichols, 1988). However, MDMA also shows differences from amphetamine in its discriminative stimulus effects. For example, conflicting evidence exists as to whether MDMA can substitute for amphetamine in rats trained to recognize amphetamine from saline (Glennon et al., 1988; Oberlender and Nichols, 1988). Furthermore, whereas the central effects of amphetamine are mediated predominately by DA (Schechter and Boja, 1988; Schechter and Cooke, 1975), in the case of MDMA 5-HT appears to have a greater importance. For example, the MDMA

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discriminative stimulus generalizes to that of the potent serotonin releaser, norfenfluramine (Schechter, 1989) and can be blocked by 5-HT_3 receptor antagonists (Glennon et al., 1992). A direct agonist action on 5-HT_2 receptors may also be important for the central stimulus effects of this drug since MDMA also bears a structural likeness to the hallucinogenic 5-HT agonist mescaline, and rats trained on mescaline show drug-like responding when given MDMA (Callahan and Appel, 1988). In addition to a role in mediating the discriminative stimulus effects of MDMA, 5-HT also appears to be responsible for the locomotor activating effects of this drug (Callaway et al., 1991).

Many drugs of abuse have been found to influence the firing rate of A10 DA cells. For example, systematic administration of morphine and nicotine induces an increase in the firing rate of these cells by an agonist action on mu-opiate and nicotinic receptors, respectively (Gysling and Wang, 1983; Mereu et al., 1987). Phencyclidine also induces a rate increase, via antagonism of NMDA receptors (French and Ceci, 1990). By contrast, amphetamine and cocaine induce a decrease in the firing rate of DA cells (Einhorn et al., 1988; Wang, 1981b). This rate decrease is due to the increased extracellular DA levels produced by these drugs producing an increased stimulation of inhibitory negative feedback pathways and DA autoreceptors (Pitts and Marwah, 1988; Wang, 1981b).

MDMA has been reported to have an inhibitory effect on A9 DA cells (Kelland et al., 1989). However, no information is currently available on the action of this drug on A10 DA neurons. Therefore we conducted a study to determine, first, what effect MDMA had on these cells and, second, since the behavioral effects of MDMA have both 5-HT and DA components, whether this effect could be modified by DA or 5-HT synthesis inhibition.

MATERIALS AND METHODS

Materials

MDMA hydrochloride [racemic, (+), and (−)] was obtained from NIDA (Bethesda, MD). *l*-3,4-dihydroxyphenylalanine (L-DOPA), *dl-p*-chlorophenylalanine methyl ester hydrochloride (PCPA), α-methyl-*dl-p*-tyrosine methyl ester hydrochloride (AMPT), and apomorphine hydrochloride were purchased from Sigma Chemical Co. (St. Louis, MO). Haloperidol was purchased from Research Biochemicals Incorporated (Natick, MA). Benserazide (Ro4-4602) was obtained from Hoffman-La Roche.

Animals and surgery

The experiments were performed on male Sprague-Dawley rats (250–350 g; Germantown, NY) anesthetized with 400 mg/kg (i.p.) chloral hydrate. For drug administration, a lateral tail vein was cannulated with a 25 gauge needle. The animals were then mounted in a stereotaxic apparatus and a hole drilled over the VTA (3.0 mm anterior to Lambda, lateral 0.5–1.0 mm, ventral 6.5–8.0 mm) according to the atlas of Paxinos and Watson (1986).

Recording procedure

Single barrel glass electrodes were pulled and their tip broken back under a microscope. The electrodes were filled with a solution of 0.5% sky blue in 0.5 M NaCl and had a impedance of approximately 2–3 Mohms (measured at 135 Hz). Electrodes were lowered through the brain using a hydraulic microdrive.

DA neurons were readily identified by the following characteristics: 1) triphasic waveform with a width of 2–4 ms and usually with an inflection in the initial component; 2) a slow and regular or bursting firing pattern; 3) a firing rate of 2–9 spikes/sec; 4) a characteristic low pitched sound when monitored through an audio amplifier (Bunney et al., 1973; Wang, 1981a).

Drug administration

MDMA, haloperidol, benzerazide and L-DOPA were administered i.v. after allowing 3–4 min to obtain a stable baseline. AMPT (200 mg/kg at 4 and 2 h prior to recording) and PCPA (200 mg/kg at 26 and 24 h prior to recording) were administered i.p. at doses and time intervals chosen to be similar to those previously reported to be effective in producing an approximately 85% depletion of DA (Kelland et al., 1989) or an approximately 70% depletion of 5-HT (Steigrad et al., 1978), respectively.

Data analysis

Spike times were monitored by IBM 486 PC connected to the recording equipment via an interface unit (1401*plus* and Spike2 software; Cambridge Electronic Design) and the data obtained from each cell subsequently analyzed off-line to obtain the firing rate, regularity of firing, and "burstiness." The regularity of firing was measured by the coefficient of variation (i.e., the ratio of the standard deviation in spike intervals to the mean spike interval). "Burstiness" was measured by determining the number of spikes occurring in bursts relative to the total number of spikes. Burst onset was signalled by an interspike interval <80 ms, burst termination by an interval >160 ms (Grace and Bunney, 1984).

RESULTS

Effect of (±), (+), and (−)-MDMA on A10 DA cells

The intravenous administration of (±)-MDMA had an inhibitory effect on most A10 DA cells that was dose-dependent (Fig. 1A). However, some cells (6/29) failed to showed either no or a relatively small (>30% decrease) to this drug (Fig. 1B). Pooling the data for all cells revealed an overall inhibitory effect of (±)-MDMA (Fig. 2). Analysis of the firing pattern of the DA cells showed that (±)-MDMA produced no overall change in

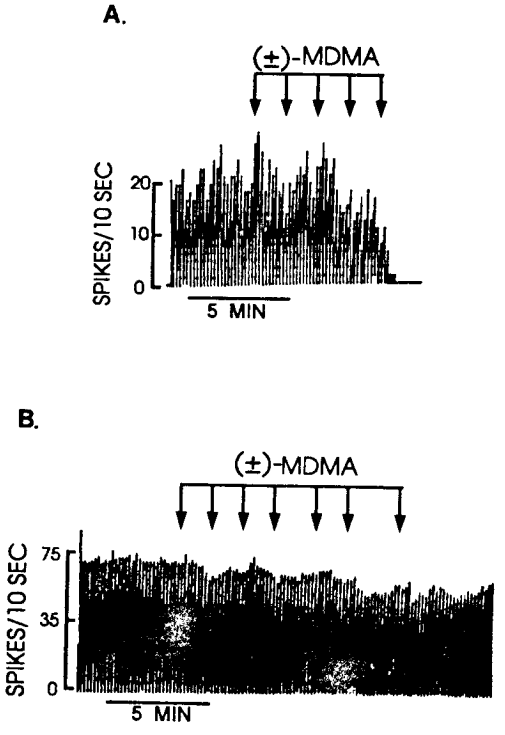

Fig. 1. Rate histograms to show the response of A10 DA cells to (±)-MDMA. **A:** Example of a cell inhibited by (±)-MDMA. Arrows represent i.v. injections of 0.25, 0.25, 0.5, 1, and 2 mg/kg (±)-MDMA respectively. **B:** Example of a cell relatively unaffected by (±)-MDMA. Arrows represent i.v. injections of 0.25, 0.25, 0.5, 1, 2, 4, and 8 mg/kg (±)-MDMA.

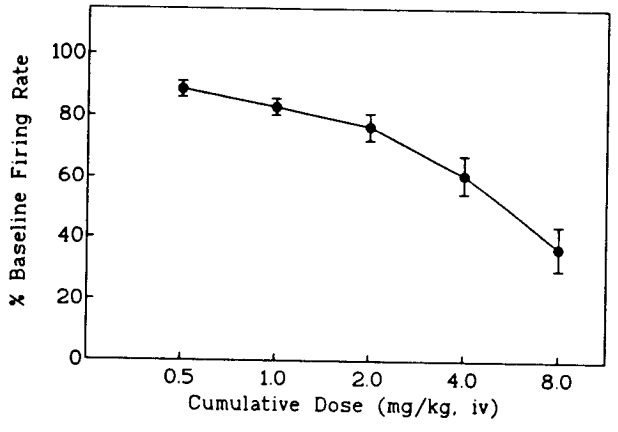

Fig. 2. Dose-response curve for the effect of (±)-MDMA on A10 DA cells. Data are expressed as the percentage of baseline firing rate and are the mean (± SEM) of 29 cells.

the coefficient of variation in the spike intervals (Table I). However, individual cells showed a wide variability in response to their response to (±)-MDMA in this parameter (increase >50% in 4/16 cells; decrease >50% in 1/16 cells). The percentage of spikes as bursts showed a moderate decrease following (±)-MDMA administration (Table II).

The D_2 antagonist, haloperidol (0.05 or 0.1 mg/kg, i.v.), was effective in reversing the (±)-MDMA induced inhibition of firing rate of A10 DA cells in 5/8 cells. No reversal was produced by the selective D_1 antagonist SCH 39166 (n = 3; data not shown).

Analysis of the effect of individual isomers of MDMA on A10 DA cells revealed that only the (+) isomer produced a suppression of cell firing (decrease >30% in 9/11 cells). The (−) isomer either had no effect or produced a slight increase in firing rate in all cells tested (Fig. 3 and Fig. 4).

Effect of AMPT or PCPA pretreatment on the inhibition of A10 DA cells by (±)-MDMA

To determine whether DA release or 5-HT release was responsible for the effects of (±)-MDMA on DA cells, rats were pretreated with either the DA synthesis inhibitor, AMPT, or the 5-HT synthesis inhibitor, PCPA. In rats pretreated with AMPT (±)-MDMA failed to inhibit any of the cells tested (Fig. 5A and Fig. 6). Instead, a moderate increase in firing rate was observed in some cells (increase of >30% in 8/18 cells). Administration of the peripheral DOPA decarboxylase inhibitor, benserazide (5 mg/kg, i.v.), followed by L-DOPA (cumulative dose of 40 mg/kg, i.v.), rapidly restored the inhibition of cell firing by (±)-MDMA in 4/4 cells. By contrast, benserazide followed by L-DOPA had no inhibitory effect in 3/3 control rats, which had not been treated with AMPT or (±)-MDMA (Fig. 5B).

In contrast to the effects of AMPT, pretreatment with the 5-HT synthesis inhibitor, PCPA, did not affect the ability of (±)-MDMA to inhibit the DA cells (Fig. 5C and Fig. 6).

DISCUSSION

In the present study (±)-MDMA was found to produce a dose-dependent inhibition of the majority of A10 DA cells tested. The (±)-MDMA-induced decrease in firing rate was accompanied by a relatively small decrease in the burst firing and both increases and decreases in the coefficient of variation.

Examination of the effects of the (+) and (−) isomers of MDMA on A10 dopamine cells showed that only the (+) isomer produced an inhibition of the A10 DA cells whereas the (−) isomer was either inactive or produced a slight excitation of these cells. Biochemical studies on synaptosomes have determined that whereas both the (+) and (−) isomers of MDMA are active at producing inhibition of uptake and release of 5-HT, only the (+) isomer shows any significant activity in producing inhibition of uptake and release of DA (Johnson et al., 1986; Steele et al., 1987). Since only the (+) isomer was active in the present study these findings suggest that, despite MDMA's approximately 10-fold greater potency in inducing 5-HT release compared to DA release, the inhibition in DA cell firing was due to the DA-releasing effects of this drug.

TABLE I. Effect of (±)-MDMA on the coefficient of variation of A10 DA cells

	Change from basal after (±)-MDMA				
Basal	0.5 mg/kg	1 mg/kg	2 mg/kg	4 mg/kg	8 mg/kg
64% ± 9% (16)	−1% ± 3% (16)	0% ± 3% (16)	0% ± 2% (15)	+14% ± 12% (13)	+9% ± 16% (10)

Values are means ± SEM of the number of cells shown in brackets. At doses of 2 mg/kg and above the coefficient of variation could not be measured in all cells due to complete or almost complete inhibition of firing rate by (±)-MDMA.

TABLE II. Effect of (±)-MDMA on the percentage of spikes in bursts in A10 dopamine cells

	Change from basal after (±)-MDMA				
Basal	0.5 mg/kg	1 mg/kg	2 mg/kg	4 mg/kg	8 mg/kg
8.9% (0, +90%)	−0.9% (−28, +10%)	−0.5% (−18, +10%)	−2.6% (−43, +4%)	−3.4% (−47, +4%)	−3.5% (−90, +10%)

Data are medians from 16 cells. Minimum and maximum values are shown in brackets. The percentage of spikes in bursts was taken as zero where cells were fully inhibited by (±)-MDMA.

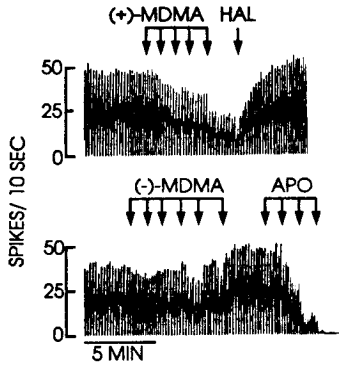

Fig. 3. Rate histograms showing the response of A10 DA cells to (+)-MDMA and (−)-MDMA. The first sets of arrows represent MDMA doses of 0.5, 0.5, 1, 2, and 4 mg/kg i.v. for (+)-MDMA and doses of 0.5, 0.5, 1, 2, 4, and 8 mg/kg i.v. for (−)-MDMA. The second sets of arrows represent either a haloperidol dose of 0.05 mg/kg i.v. or apomorphine doses of 1, 2, 4, and 8 μg/kg i.v.

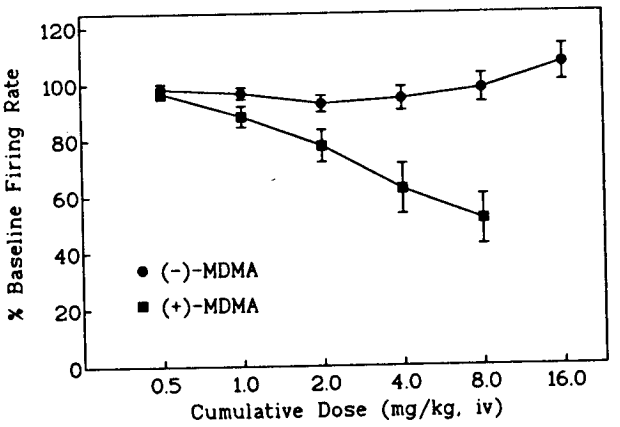

Fig. 4. Dose-response curve for the effect of (+)-MDMA and (−)-MDMA on A10 DA cells. Data are means (± SEM) of eleven and eight cells respectively.

The effect of DA and 5-HT synthesis inhibitors was used to further elucidate the mechanism by which (±)-MDMA inhibited A10 DA cells. It has been long established that the dopamine synthesis inhibitor, AMPT, effectively blocks the dopamine release produced by amphetamine both *in vitro* (Parker and Cubeddu, 1986) and *in vivo* (Scheel-Krüger, 1971). This appears to be due to the fact that the intraneuronal dopamine pool from which amphetamine releases dopamine is primarily the newly synthesized cytoplasmic pool. This dopamine store is rapidly depleted by inhibition of tyrosine hydroxylase by AMPT, thus preventing the amphetamine-induced release of dopamine (Bönish and Trendelenburg, 1988; McMillen, 1983). In the present study AMPT fully blocked the MDMA-induced inhibition of A10 DA cells whereas pretreatment PCPA, which depletes 5-HT stores by inhibition of tryptophan hydroxylase (Gál et al., 1970), failed to affect the (±)-MDMA induced inhibition of A10 DA neurons. These findings thus suggest that the inhibition of DA neuron firing was the result of dopamine rather than 5-HT release. Further evidence for a role of dopamine was provided by the fact that the blockade of the MDMA's inhibition of DA cells by AMPT could be overcome by administration of L-DOPA. L-DOPA acts as a dopamine precursor downstream of the block in the dopamine biosynthetic pathway produced by AMPT and thus restores dopamine levels in AMPT-treated rats (Moore and Rech, 1967).

Previous studies have also indicated that A10 dopamine neurons are inhibited by dopamine uptake inhibitors and releasers. Einhorn et al. (1988) reported that A10 dopamine cells were inhibited by nomifensine, cocaine, and GBR 12909 and Wang (1981b) reported that A10 dopamine cells could be potently inhibited by (+)-amphetamine (IC_{50} of 0.57 mg/kg, i.v.). Haloperidol was effective in reversing the inhibition of A10 DA cells by these compounds (Einhorn et al., 1988; Wang, 1981b). In the present study haloperidol also reversed the

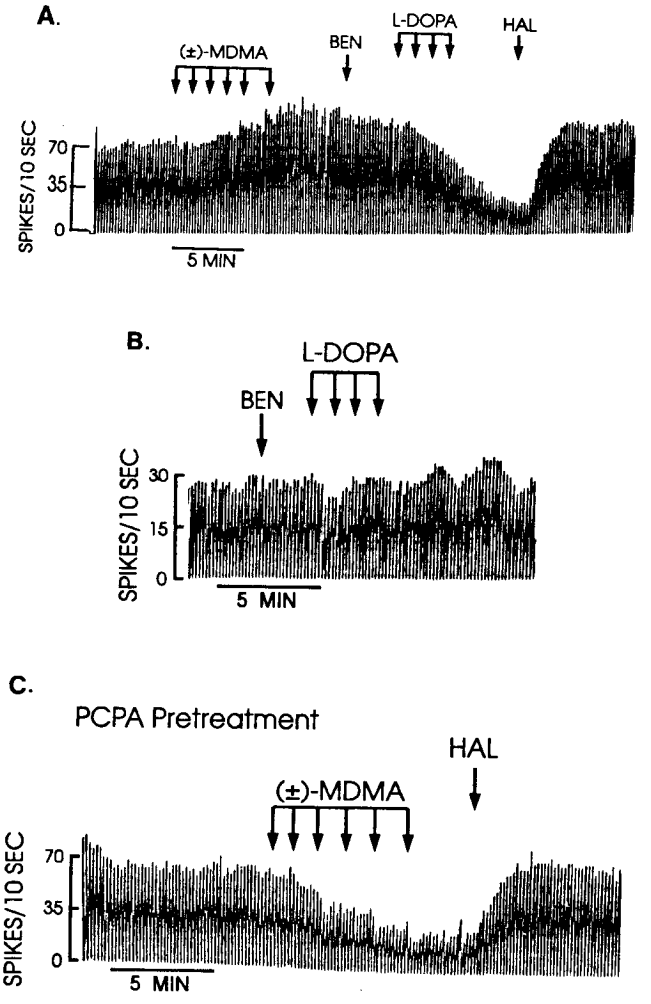

Fig. 5. Rate histograms showing effect of AMPT or PCPA pretreatment on the response of A10 dopamine cells to (±)-MDMA. **A:** Rate histogram from a rat pretreated with AMPT. The animal was administered (±)-MDMA, benserazide, L-DOPA, and haloperidol respectively. **B:** Rate histogram showing the lack of effect of L-DOPA in an untreated rat. The animal was administered benzerazide followed by L-DOPA. **C:** Rate histogram from a rat pretreated with PCPA. The animal was administered (±)-MDMA followed by haloperidol. Drug doses in all three histograms were 0.25, 0.25, 0.5, 1, 2, and 4 mg/kg i.v. of (±)-MDMA, 5 mg/kg i.v. of benserazide, 5, 5, 10, and 20 mg/kg i.v. of L-DOPA, and 0.05 mg/kg i.v. of haloperidol.

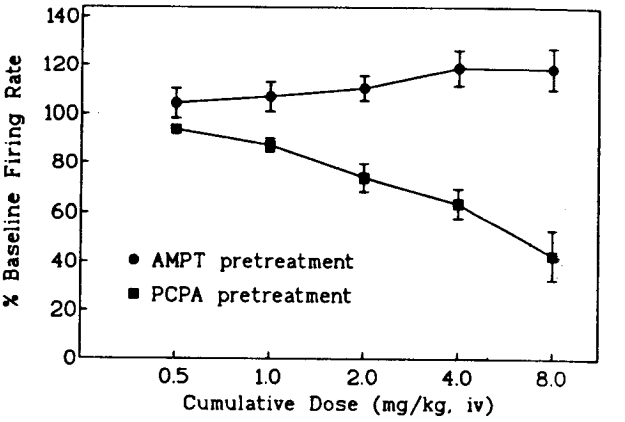

Fig. 6. Dose-response curve for the effect of AMPT or PCPA pretreatment on the response of A10 DA cells to (±)-MDMA. Data are means (± SEM) of 18 and nine cells respectively.

(±)-MDMA-induced inhibition of A10 DA cell firing in most, although not all, cells.

Interestingly, in AMPT pretreated animals, MDMA produced a moderate excitation of some cells. This may be due to the effects of 5-HT release on these cells by MDMA, this being unmasked after removal of the stronger inhibitory DA effect by AMPT. Several studies have shown that the ventral tegmental area, containing the A10 DA neurons, receives a 5-HT input from the dorsal raphe (Parent et al., 1981; Phillipson, 1979; Simon et al., 1979). However, currently the effects of 5-HT release on A10 dopamine cells is unclear. Kelland et al. (1993) reported that electrical stimulation of the 5-HT neurons projecting to the A10 dopamine cells from the dorsal raphe led to a decrease in firing rate of all A10 DA neurons tested, suggesting an inhibitory effect of 5-HT on these cells. However, Guan and McBride (1989) reported that 5-HT microinfusion in the VTA increased the extracellular levels of DA in the nucleus accumbens, suggesting an excitatory effect on DA neurons. An excitatory effect of 5-HT on DA cells is also suggested by the fact that 5-HT has a predominately depolarizing action on A10 DA cells in vitro (Pessia et al., 1994).

The effect of MDMA on A9 DA cells was not examined in the present study. However, a previous report by Kelland et al. (1989) indicated that MDMA has a inhibitory effect on these cells similar to that observed in the A10 area in the present study. However, these investigators reported that MDMA was still able to inhibit the A9 DA cells in AMPT pretreated rats, although with an approximately threefold lower potency. These observations thus contrast with those in the present study in which AMPT completely prevented the effect on MDMA on A10 cells. A second difference between the findings of Kelland et al. (1989) and those in the present study was the observations that PCPA produced a twofold reduction in the potency of MDMA to inhibit A9 DA cells in the study by Kelland et al. (1989) whereas in the present study PCPA did not produce any reduction in the ability of MDMA to inhibit A10 DA cells. The findings of Kelland et al. (1989) thus suggest that both DA and 5-HT contribute to the inhibitory effects of MDMA in the A9 area whereas the present study suggests that in the A10 area DA alone is responsible for the inhibitory effects of MDMA.

In addition to a high affinity for 5-HT uptake and a relatively weak affinity for DA uptake, MDMA also has a high affinity for noradrenaline uptake (Steele et al., 1987). However, noradrenaline release does not appear to have an inhibitory effect on DA neurons (Andén and

Grabowska, 1976; Grenhoff and Svensson, 1989; Hervé et al., 1982) and is thus unlikely to account to the effects on MDMA observed in the present study.

In conclusion, the results reported here demonstrate that MDMA has an overall inhibitory effect on A10 DA cells. Despite MDMAs potent 5-HT releasing action the inhibitory effect of this drug on A10 DA cells appears to be mediated the weaker DA releasing properties of this compound.

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