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ENANTIOMERIC DIFFERENCES IN THE EFFECTS OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE ON EXTRACELLULAR MONOAMINES AND METABOLITES IN THE STRIATUM OF FREELY-MOVING RATS: AN *IN VIVO* MICRODIALYSIS STUDY

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Summary—The effects of (+) and (−) 3,4-methylenedioxymethamphetamine (MDMA) and racemic *p*-chloroamphetamine (PCA) on extracellular dopamine and its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), as well as the metabolite of 5-hydroxytryptamine (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), were determined in dialysates of the striatum conscious rats by using intracerebral dialysis and high performance liquid chromatography with electrochemical detection (HPLC-EC). The (+) and (−)MDMA isomers (5, 10 mg/kg, s.c.) and PCA (2.5, 5 mg/kg, s.c.) caused a rapid increase of extracellular levels of dopamine and decreased extracellular levels of DOPAC and HVA immediately after administration in dialysates of striatum. The order of potency for this effect was PCA > (+)MDMA > (−)MDMA. The levels of 5-HIAA also decreased after the administration of drugs, but the effect had a slower time course than DOPAC and HVA and did not exhibit an enantiomeric difference. The data indicate that, although these drugs are thought to affect the 5-HT neuronal system preferentially, they also affect dopamine systems and by a mechanism in which the (+) isomer was more potent than the (−).

Key words—3,4-methylenedioxymethamphetamine (MDMA), *p*-chloroamphetamine, dopamine release, *in vivo* microdialysis, enantiomers.

3,4-Methylenedioxymethamphetamine (MDMA), a ring substituted derivative of methamphetamine, has received a great deal of attention recently as it represents one of a number of 'designer drugs' being abused: it has been reported to produce both stimulant- and hallucinogen-like effects in man (Shulgin, 1986). In experimental animals, MDMA produces a variety of behavioral effects, such as stereotypy, disruption of operant behavior and stimulus generalization with amphetamine and hyperthermia (Anderson, Braun, Braun, Nichols and Shulgin, 1978; Glennon, Little, Rosecrans and Yousif, 1987; Hiramatsu, Nabeshima, Kameyama, Maeda and Cho, 1989a; Schechter, 1987; Glennon, Yousif and Patrick, 1988). Neurochemical studies in rodents after *in vivo* administration of MDMA (Battaglia, Yeh, O'Hearn, Molliver, Kuhar and de Souza, 1987; Johnson, Letter, Merchant, Hanson and Gibb, 1988a; Schmidt, 1987; Stone, Stahl, Hanson and Gibb, 1986) have demonstrated effects on serotonergic (5-HT) systems in brain, including a blockade of active uptake and decreases in the levels of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) and a reduction in the activity of tryptophan hydroxylase.

Analysis of the effects of the optical isomers of MDMA revealed that they affect 5-HT and dopamine (DA) systems in brain with different potencies. Comparison of the effects of the stereoisomers of MDMA on the release and uptake of [^{3}H]5-HT and [^{3}H]DA *in vitro* showed that the (+)isomer of MDMA was a more potent agent (Johnson, Hoffman and Nichols, 1986; Kalix, Yousif and Glennon, 1988; Nichols, Lloyd, Hoffman, Nichols and Yim, 1982; Schmidt, Levin and Lovenberg, 1987; Steele, Nichols and Yim, 1987). Behavioral studies with rodents have shown that (+)MDMA is also more potent than (−)MDMA in causing stereotyped behavior in rats (Hiramatsu *et al.*, 1989a), the disruption of operant responding in mice (Rosecrans and Glennon, 1987) and in mimicking the discriminative stimulus produced by racemic MDMA (Battaglia, Brooks, Kulsakdinun and de Souza, 1988; Schechter 1987). On the other hand, (−)MDMA is more potent than (+)MDMA in binding to central 5-HT binding sites (Lyon, Glennon and Titeler, 1986), suggesting that the (−)isomer is more active at postsynaptic sites.

Neurochemical experiments have shown that MDMA caused a dramatic decrease in concentrations of both 5-HT and 5-HIAA in the striatum 3 hr after a single dose (Schmidt, 1987; Stone, Stahl, Hanson and Gibb, 1986). In contrast, the

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dopaminergic system in the striatum was much less affected by MDMA (Schmidt *et al.*, 1987). In the present study, the effects of MDMA and PCA on the DA and 5-HT system were monitored continuously with *in vivo* microdialysis and HPLC-EC procedures to determine the temporal changes in neurochemical activity. Responses at early times after administration were of interest because of the rapidity of behavioral changes (Hiramatsu *et al.*, 1989a). *p*-Chloroamphetamine was used as a typical DA-serotonergic agent as it has (Gal and Sherman, 1978) long-lasting effects on the 5-HT system.

The results showed differences in the time course of changes in the two systems and support the idea that the actions on DA and on 5-HT have different stereoselectivities.

METHODS

Animals

Male Sprague–Dawley rats (250–350 g) were housed in a room with controlled lighting (12 hr light/dark cycle) and temperature (23°C) and access to food and water *ad libitum*.

Construction of the dialysis probes

The dialysis probes were constructed in the laboratory by a modification of the procedure originally described by Nakahara, Ozaki, Kaneda and Nagatsu (1988). These probes are easily and inexpensively fabricated from an intravenous catheter (Angiocath, Deseret Medical Inc., Utah) and injection needle (B-D IM-1, Becton Dickinson, New Jersey). The guide cannula and a dummy probe were made from the intravenous catheter. The infusion and effluent tubes were made from fused silica tubing (o.d., 170-μm, i.d., 120-μm, Scientific Instrument Services Inc., New Jersey), which were attached to short lengths of stainless steel tubing. These tubes were fixed with epoxy resin glue. Dialysis membrane (cellulose acetate, 5000 molecular cut off, i.d., 230-μm, wall thickness, 10-μm, Bioresearch Center, Nagoya, Japan) was then attached to the needle and trimmed to 4 mm. The tip of the dialysis membrane and its junction with the needle were sealed with epoxy cement.

Recovery

Individual probes were immersed in buffered saline solutions of the monitored compounds, perfusion solution passed through the probes and the effluent monitored for levels of compound. Recovery, calculated from the levels in the solution and the effluent, ranged from 9–15% at 37°C and was determined for each probe before use. The experimental data are presented as a percentage of the baseline for each animal to avoid large differences in recovery and in the differences in recovery that might occur between tissue and aqueous media.

Surgical procedure

Rats were anesthetized with pentobarbital (40 mg/kg, i.p.) and placed in a stereotaxic frame. Using coordinates chosen according to the stereotaxic atlas of Paxinos and Watson (1986), guide cannula were implanted so that the tips were just above the striatum (A: 1.0, L: 3.0, V: 4.0 relative to the bregma). The animals were allowed to recover from the procedure for one week prior to experimentation. In the experiment, the dialysis probe was inserted through the guide cannula and the 4 mm length of dialysis membrane entered the striatum.

Sampling procedure

The dialysis probe was perfused with physiological Ringer solution (composition in mM: NaCl 147; KCl 4; $CaCl_2$ 2.3) at 2 μl/min, using microbore tubing (Cole-Palmer Instrument Company, Illinois, with an i.d. of 0.19 mm and an o.d. of 2 mm), connected to a microinfusion pump (Syringe Infusion Pump 22, Harvard Apparatus, Massachusetts) via a single-channel liquid swivel. The infusion and effluent cannulae were passed through or attached to a tether, which was attached to the animal by a rodent jacket (Harvard Apparatus). This arrangement allowed the animal to move freely within the cage. The rats were placed in individual cages (18 × 29 × 31 cm) and the dummy cannulae replaced with dialysis probes, which were fixed to the guide cannulae with wax. The animals were allowed to adapt for at least 60 min before the experiment was started. The perfusate was collected in a small (250 μl) disposable microcentrifuge tube which was secured to the middle of the tether. The collecting tube contained 10 μl 0.4 N perchloric acid and internal standard (3,4-dihydroxyhydrocinnamic acid, 1.2 ng). The total dead volume from the tip of the probe to the collection tube was usually 10 μl but was always measured in order to adjust the delay to collect samples after administration of drugs. Samples (30 μl) were collected at 15 min intervals and at least four control samples were taken before administration of drugs. Perfusate samples from brain were taken up to 240 min after treatment with drugs or saline.

HPLC analysis

The perfusates were assayed for DA, DOPAC, HVA and 5-HIAA by high performance liquid chromatography (HPLC) with electrochemical detection. These compounds were separated by reverse phase chromatography using Biophase ODS 5 μm (4.6 × 250 mm, Bioanalytical Systems, Inc., Indiana) and 0.075 M citrate buffer, pH 3.5 (adjust pH 3.5 using acetic acid), containing 10% methanol, 1% tetrahydrofran and 50 mg/l ethylene diamine tetra-ammonium (EDTA), 55 mg/l sodium octylsulfate at 0.7 ml/min flow rate. Electrochemical measurements were made using a glassy carbon working electrode set at +0.7 V vs Ag/AgCl reference electrode (LC-4,

Bioanalytical Systems, Inc., Indiana). The perfusate samples were injected directly onto the HPLC column without any preparation. Signals were recorded with a Hewlett Packard 3390A recording integrator and the peak height of each compound/internal standard determined, by comparison with the control sample from each animal before treatment.

Under the HPLC conditions employed, the retention time for DA was 5.3 min, for DOPAC, 6.3 min, for 5-HT, 7.8 min, for 5-HIAA, 8.8 min, for internal standard, 9.9 min and for HVA, 11.5 min. Baseline resolution of all compounds was achieved and a chromatographic run consumed 14 min. As a result, by selecting dialysate collection times of 15 min, the collection, addition of internal standard and HPLC analysis could be conducted continuously with the autosampler. The concentrations of the neurotransmitters in the dialysate were very small compared to their metabolites and as the concentration of 5-HT was at the borderline of the sensitivity of the assay, it was not monitored. Average basal concentrations of samples of dialysate were: DA, 7.5 nM; DOPAC, 1420 nM; HVA, 780 nM and 5-HIAA, 320 nM. Levels of 5-HT in the dialysate were below detection limits in most cases. The basal levels of the amines and metabolites were stable over the 6 hr sampling period.

The drugs were dissolved in saline and injected subcutaneously. Each rat received only one injection of drug. The (+) or (−)MDMA was obtained from the Research Technology Branch of the National Institute on Drug Abuse (Rockville, Maryland). *p*-Chloroamphetamine (PCA) was purchased from Sigma Chemical Co. (St Louis, Missouri). 3,4-Dihydroxyhydrocinnamic acid (as an internal standard) was obtained from Aldrich Chemical Co. (Milwaukee, Wisconsin). All HPLC assay reagents were of analytical grade.

Data analysis

Statistical analysis of the data was carried out using the Mann–Whitney *U*-test (two-tailed). The area under the curve from each treatment was calculated using trapezoidal rules.

RESULTS

Both (+)MDMA and (±)PCA caused an increase in dialysate levels of DA in a dose-dependent manner (Fig. 1). The effects were maximum at about 60 min after administration and, after the larger doses, persisted for almost 4 hr. The efflux of DA after the larger doses of (+)MDMA and PCA was about 600–700% of control levels. On the other hand, (−)MDMA showed very little effect at either of the two doses used. Levels of the DA metabolites declined after all of these compounds, with a similar time course, the minimum occurring at about 60 min. In contrast to the amine, the decline in metabolites DOPAC and HVA (Fig. 2) after the larger dose of MDMA persisted beyond the 4 hr experiment, whereas after the smaller dose, levels had recovered at 4 hr. The effects of (+)MDMA (10 mg) and PCA (2.5 or 5 mg/kg) on the degree of decline in metabolites were comparable. Levels of 5-HIAA in the dialysate (Fig. 3) also fell, but with a different time course compared with levels of DOPAC or HVA. At the larger doses, a slow decline that was maximum at 120–150 min, continued beyond the 4 hr experiment.

To compare the total effect of the drugs over the period of time studied, the areas under the time–effect curve were determined (Table 1). As shown in the legends for each figure, the values for area under the curve paralleled dose and showed the order (±)PCA > (+)MDMA > (−)MDMA.

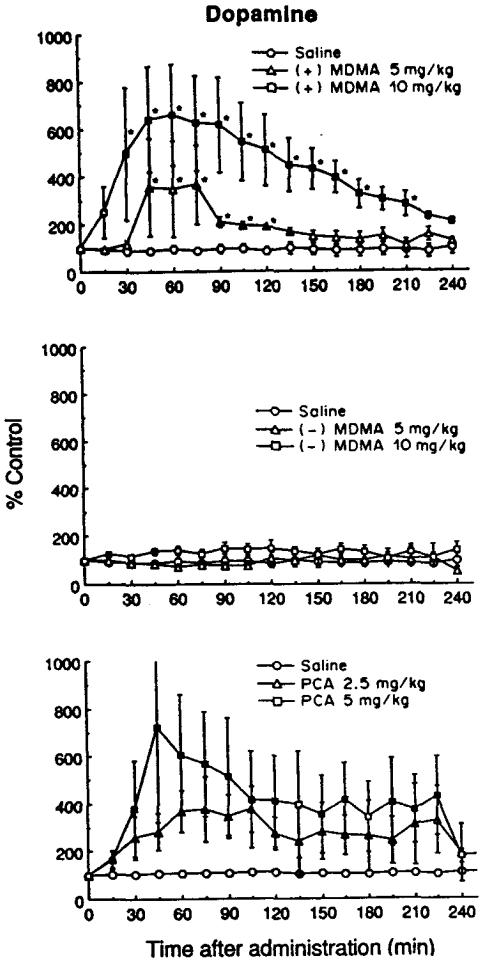

Fig. 1. Effects of (+)-, (−)MDMA and (±)PCA on the efflux of DA in dialysates collected from the striatum of rat. Results are expressed as a percentage of control for each rat. Thirty microliters of each sample of dialysate was injected into the HPLC-EC and the results are the mean of 4–5 independent experiments. Closed symbols indicate significant difference ($P < 0.05$) from the levels of saline-treated rats. *$P < 0.05$ vs corresponding dosage of (−)MDMA. Mean values of areas (in percentage × min × 10^3) under the time–response curve for DA are as follows: Saline; −2.3, PCA 2.5 mg/kg; 41.3, PCA 5 mg/kg; 69.2, (+)MDMA 5 mg/kg; 20.9, (+)MDMA 10 mg/kg; 60.7, (−)MDMA 5 mg/kg; −1.3, (−)MDMA 10 mg/kg; 7.8.

backpedalling behavior that is thought to be mediated by both DA and 5-HT systems (Hiramatsu *et al.*, 1989). At larger doses, MDMA causes a 5-HT-dependent syndrome, characterized by hindlimb abduction and forepaw treading (Yamamoto and Spanos, 1988), which is also induced by 5-methoxy-*N*,*N*-dimethyltryptamine, a direct 5-HT receptor agonist. Thus, in contrast to amphetamine, which is much more selective for DA systems, (+)MDMA appears to induce 5-HT-mediated responses as well, so that the behavioral response is mixed and resembles that produced by the serotonergic agent, PCA (Hiramatsu *et al.*, 1989). The interaction of MDMA with 5-HT systems, as monitored by changes in levels of 5-HIAA, did not exhibit stereochemical differences (Fig. 2; Schmidt, 1987; Schmidt and Taylor, 1988). Furthermore, since the time course of the behavioral response to MDMA was more similar to the changes in DA, it appears that both DA and 5-HT systems are required for the response and the low potency of (−)MDMA on the efflux of DA is reflected in the nature of its behavioral effects. It should also be noted, however, that (+)3,4-methylenedioxyamphetamine [(+)MDA], a major metabolite of (+)MDMA (Hiramatsu, unpublished), is more potent than MDMA in these effects (Hiramatsu *et al.*, 1989), so that its role in the pharmacology of MDMA must be considered as well.

The relationship between the stereochemical differences observed here for the acute effects of MDMA on DA but not 5-HT systems and for the long-term toxicity of MDMA is not clear but, as DA antagonists protect against the neurotoxicity, the involvement of DA is likely (Johnson *et al.*, 1988b; Stone *et al.*, 1988). The stereoselectivity does not appear to be due to pharmacokinetic differences in the availability of MDMA as levels of plasma after intravenous doses of the two isomers are very similar (Hiramatsu *et al.*, unpublished observations). However, levels of MDA after the (+) isomer are much higher (Hiramatsu *et al.*, unpublished observations) and, since MDA also causes neurotoxicity (Ricuarte, Bryan, Strauss, Seiden and Schuster, 1986), its contribution must be considered as well.

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