



The Acute Effects of Amphetamine Derivatives on Extracellular Serotonin and Dopamine Levels in Rat Nucleus Accumbens

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KANKAANPÄÄ, A., E. MERIRINNE, P. LILLSUNDE AND T. SEPPÄLÄ. *The acute effects of amphetamine derivatives on extracellular serotonin and dopamine levels in rat nucleus accumbens.* PHARMACOL BIOCHEM BEHAV 59(4) 1003–1009, 1998.—The acute effects of amphetamine derivatives on extracellular concentration of serotonin (5-HT) and dopamine in the nucleus accumbens were studied with in vivo microdialysis using conscious, freely moving rats. 5-HT, dopamine, and their major metabolites were measured by HPLC with electrochemical detection. Amphetamine (1.0–9.0 mg/kg) elevated dopamine levels considerably, but failed to affect the levels of 5-HT, except at the highest dose administered. 3,4-Methylenedioxyamphetamine (MDA, 1.0–9.0 mg/kg) and 3,4-methylenedioxyamphetamine (MDMA, 1.0–9.0 mg/kg) elevated both 5-HT and dopamine levels dose dependently. The failure of 2,5-dimethoxy-4-methylamphetamine (DOM, 0.5–1.0 mg/kg) to affect the 5-HT levels suggests that extracellular levels of 5-HT play a minor role in hallucinogenic activity. The strong effects of MDA and MDMA on levels of 5-HT indicate that their actions on serotonergic mechanisms are different from those of the hallucinogens. In addition, methylenedioxyamphetamines may act via dopaminergic mechanisms similar to those of amphetamine. © 1998 Elsevier Science Inc.

Serotonin (5-HT) Dopamine DOM MDA MDMA Amphetamine Microdialysis

AMPHETAMINE is considered to be principally stimulatory and 2,5-dimethoxy-4-methylamphetamine (DOM; STP) mainly an hallucinogenic agent. Methylenedioxyamphetamine (MDA; known as “Love”) and its *N*-methylated analogue methylenedioxyamphetamine (MDMA; “Ecstasy”), have both stimulatory and hallucinogenic properties and also produce other central effects (6,7,9). These features unique to methylenedioxyamphetamines have led to the suggestion that they form a distinct category separate from psychomotor stimulants and hallucinogens (16,17).

The hallucinogenic amphetamine-derivative DOM is chemically related to mescaline, and has been shown to produce hallucinogenic effects similar to those produced by classical hallucinogens such as lysergic acid diethylamide (LSD), mescaline, and psilocybin (24). Although hallucinogenic activity is thought

to involve serotonergic mechanisms (8,28), there is in vitro evidence that shows that DOM fails both to release 5-HT (14) and to inhibit the synaptosomal uptake of this transmitter (25).

Psychomotor stimulant drugs, like amphetamine, are known to stimulate dopaminergic activity in mesolimbic brain areas. A variety of techniques, including in vivo microdialysis, have demonstrated that amphetamine strongly elevates extracellular dopamine levels in rat brain (31), particularly in the nucleus accumbens (2).

The acute administration of MDMA is shown to release both dopamine and 5-HT in awake-behaving rat (11,12,30). On the other hand, administration of MDA and MDMA in vitro decreases the concentration of 5-HT and its major metabolite 5-hydroxyindoleacetic acid (5-HIAA) in several regions of the rat forebrain (21–23,26,27).

The aim of this study was to compare the acute effects of hallucinogenic and stimulatory amphetamine derivatives on release of 5-HT and dopamine. We studied the effects of multiple doses of DOM, MDA, MDMA, and amphetamine on extracellular concentrations of 5-HT and dopamine, as well as their metabolites, in rat nucleus accumbens by *in vivo* microdialysis using conscious, freely moving rats.

METHOD

Subjects

Adult male Wistar rats aged 11–12 weeks were used in the study. The rats were delivered from Helsinki University Laboratory Animal Centre, Finland, at least 1 week before the experiments. The total number of individuals was 125, and they were housed two per cage in a temperature-controlled room with a light cycle of 12 h, and free access to food and water.

The experimental setup was approved by the Committee for Animal Experiments of the National Public Health Institute.

Drugs

Amphetamine sulphate (Sigma Chemical Co., St. Louis, MO), MDA hydrochloride and MDMA hydrochloride (supplied by NIDA, USA) were dissolved in saline in concentrations of 1.0, 3.0, and 9.0 mg/ml free base. DOM hydrochloride (supplied by NIDA) was dissolved in saline in concentrations of 0.5 and 1.0 mg/ml free base. These solutions were injected in a volume of 0.1 ml/100 g body weight.

The following treatments ($n = 5-6$ in each group) were administered: saline (0.9% NaCl), amphetamine (1.0, 3.0, and 9.0 mg/kg), MDA (1.0, 3.0, and 9.0 mg/kg), MDMA (1.0, 3.0, and 9.0 mg/kg) and DOM (0.5 and 1.0 mg/kg). All drugs were administered subcutaneously at 2.5 h after starting the perfusion.

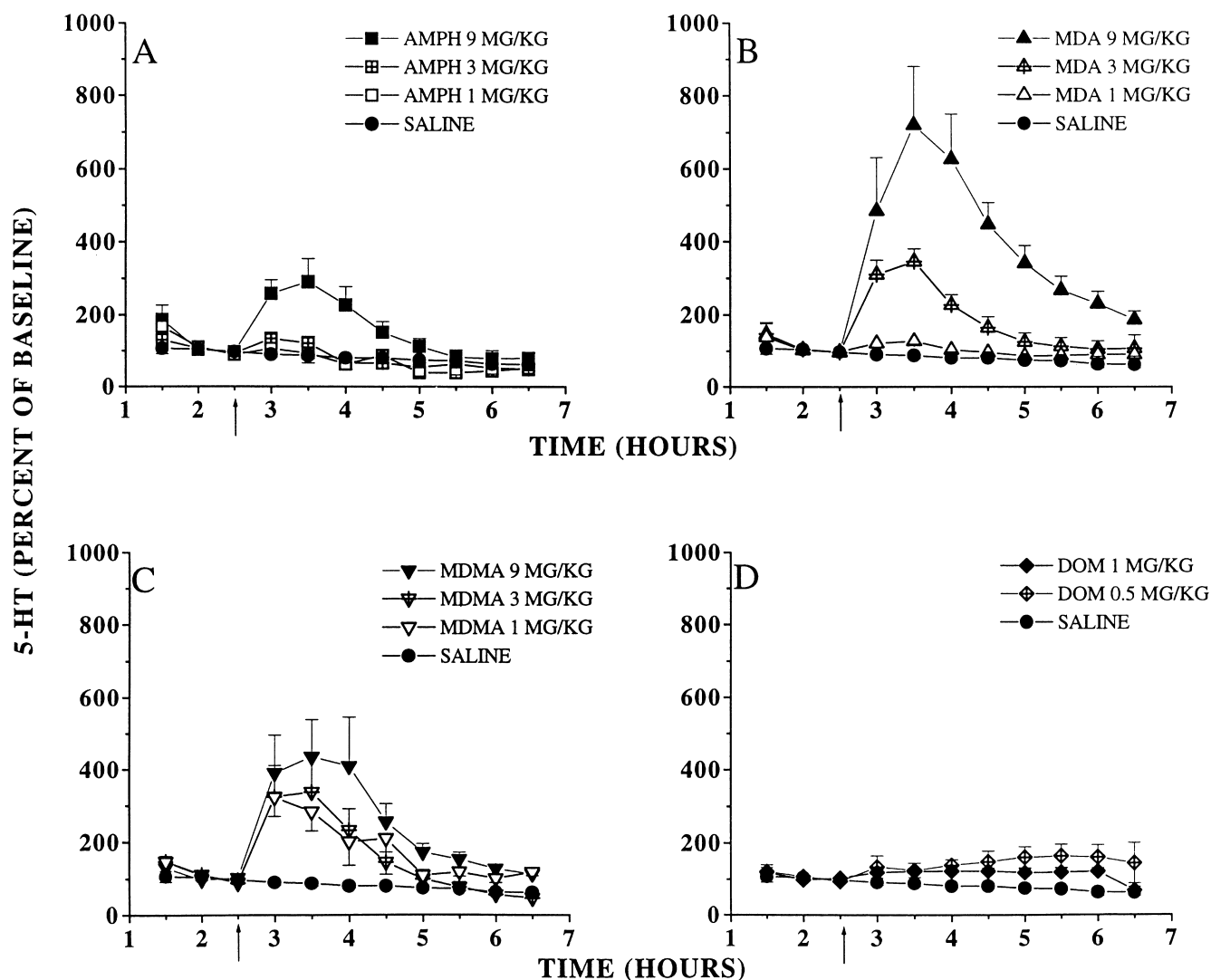


FIG. 1. The effects of the amphetamine derivatives on extracellular 5-HT levels in nucleus accumbens. Amphetamine (1.0, 3.0, and 9.0 mg/kg; A), MDA (1.0, 3.0, and 9.0 mg/kg; B), MDMA (1.0, 3.0, and 9.0 mg/kg; C), and DOM (0.5 and 1.0 mg/kg; D) were administered subcutaneously at 2 h 30 min after starting perfusion, as indicated by the arrows. The data expressed as percentages of the basal release are given as means \pm SE ($n = 5-6$). Error bars are not shown when they are smaller than the symbols.

Surgery and In Vivo Sampling Procedure

The rats were anesthetized using 4% halothane gas (Trothane, I.S.C. Chemicals Ltd, UK). A guide cannula (CMA/12, CMA Microdialysis, Sweden) was implanted stereotaxically into the nucleus accumbens and secured with dental cement (Aqualox, VOCO, Germany) and two small screws. The coordinates of the nucleus accumbens relative to the bregma were A: +2.0, L: -1.2, V: -8.0 as calculated according to Paxinos and Watson (19). During surgery halothane was maintained at 2%. The animals recovered approximately 48 h after surgery.

On the day of the experiment the rats were given a minor dose of halothane (4%, 1–2 min), and a microdialysis probe (CMA/12, CMA Microdialysis, Sweden) of a membrane length of 2 mm was lowered down the guide cannula into the nucleus accumbens and perfused with modified Ringer's solution (147 mM NaCl, 1.2 mM CaCl₂, 2.7 mM KCl, 1.0 mM MgCl₂, pH 6) at a flow rate of 2 µl/min. To determine stable baseline levels, the perfusate was discarded during the first 60 min, after which samples were collected at 30-min intervals. The samples were assayed immediately after the experiment. At the end of the experiment the animals were decapitated, the brain was removed, and then immersed in 10% buffered formalin solution. The correct placement of the microdialysis probe was verified visually, and data were included only from animals with accurately placed probes.

Chemical Assays

The dialysate samples were analyzed for dopamine, 5-HT, and their metabolites by two separate HPLC systems, both using Brownlee ODS 5 µ (100 × 2.1 mm) reverse-phase columns (Applied Biosystems, Inc., USA) and electrochemical amperometric detectors (ANTEC, The Netherlands). One of the detectors was set at +780 mV for dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-HIAA assay, and the other at +600 mV for 5-HT assay. The mobile phases were similar in the two systems (0.1 M NaH₂PO₄ adjusted to pH 3.2 with phosphoric acid, 7% acetonitrile and 0.1 M EDTA), with the exception that the concentration of octanesulphonic acid was 1 mM for the dopamine, DOPAC, HVA, and 5-HIAA assay, and 0.01 mM for the 5-HT assay. The relatively low detection potential (+600 mV) applied in the 5-HT assay eliminated the possible interference of 3-methoxytyramine (3-MT) in detection of 5-HT. The flow rate was 0.60 ml/min in both systems.

Calculations

The mean of the two samples before drug treatments was considered the baseline level and was defined as 100%. The statistical evaluation was carried out by two-way ANOVA followed by Tukey's test.

RESULTS

The means of basal concentrations in dialysate were as follows (±SE; *n* = 25): dopamine 157 ± 21 fmol/60 µl, 5-HT 73 ± 11 fmol/60 µl, DOPAC 24.8 ± 2.8 pmol/60 µl, HVA 10.0 ± 1.2 pmol/60 µl, and 5-HIAA 6.5 ± 0.4 pmol/60 µl. The baseline levels remained unaltered in saline-treated rats.

The Acute Effects of the Drugs on Extracellular Levels of 5-HT and 5-HIAA in the Nucleus Accumbens

The effects of the amphetamine derivatives on 5-HT levels in nucleus accumbens are shown in Fig. 1. MDA and MDMA elevated the extracellular levels of 5-HT dose dependently,

but amphetamine had a significant effect on 5-HT only at the highest dose (9 mg/kg). MDA, at doses of 3.0 and 9.0 mg/kg, elevated the 5-HT levels to 350%, $F(10, 110) = 8.94$, $p < 0.001$, and 700%, $F(10, 107) = 7.11$, $p < 0.001$, of the baseline level, respectively (Fig. 1B). The elevations of 5-HT levels following the administration of MDMA at doses of 1.0, 3.0, and 9.0 mg/kg were 300%, $F(10, 101) = 2.70$, $p < 0.01$, 350%, $F(10, 108) = 4.81$, $p < 0.001$, and 450%, $F(10, 110) = 4.31$, $p < 0.001$, of the baseline levels, respectively (Fig. 1C). DOM failed to affect the 5-HT levels significantly (Fig. 1D).

MDA and MDMA, unlike amphetamine or DOM, affected the extracellular levels of the 5-HT metabolite 5-HIAA. The levels of 5-HIAA decreased gradually after the administration of the drugs towards the end of the sample collection period. MDA, at doses of 3.0 and 9.0 mg/kg, reduced the levels of 5-HIAA to 70%, $F(10, 106) = 3.10$, $p < 0.01$, and 40%, $F(10, 106) = 5.17$, $p < 0.001$, of the baseline, respectively. MDMA, at doses of 3.0 and 9.0 mg/kg, reduced the levels of 5-HIAA to 60%, $F(10, 104) = 2.37$, $p < 0.05$, and 50%, $F(10, 106) = 3.31$, $p < 0.01$, of the baseline levels, respectively.

The Acute Effects of the Drugs on Extracellular Levels of Dopamine, DOPAC, and HVA in the Nucleus Accumbens

Figure 2 shows the effects of the drugs on dopamine levels in nucleus accumbens. Amphetamine, MDA, and MDMA elevated the extracellular dopamine levels dose dependently. Amphetamine, at doses of 1.0, 3.0, and 9.0 mg/kg, elevated the extracellular dopamine levels to 700%, $F(10, 109) = 20.13$, $p < 0.001$, 800%, $F(10, 101) = 9.33$, $p < 0.001$, and 1300%, $F(10, 104) = 2.24$, $p < 0.05$, of the baseline levels, respectively (Fig. 2A). MDA elevated the dopamine levels only at doses of 3.0 and 9.0 mg/kg, to 270%, $F(10, 107) = 2.05$, $p < 0.05$, and 450%, $F(10, 105) = 5.64$, $p < 0.001$, of the baseline level, respectively (Fig. 2B). MDMA, at doses of 1.0, 3.0, and 9.0 mg/kg, elevated the dopamine levels to 300%, $F(10, 109) = 2.38$, $p < 0.05$, 350%, $F(10, 105) = 2.69$, $p < 0.01$, and 450%, $F(10, 104) = 2.70$, $p < 0.01$, of the baseline levels, respectively (Fig. 2C). DOM failed to affect the dopamine levels significantly at either of the doses used (0.5 and 1.0 mg/kg; Fig. 2D).

Amphetamine reduced extracellular levels of DOPAC by more than 50% of the baseline level at doses of 1.0, $F(10, 96) = 3.45$, $p < 0.01$, 3.0, $F(10, 106) = 5.79$, $p < 0.001$, and 9.0 mg/kg, $F(10, 104) = 8.00$, $p < 0.001$ (Fig. 3A). MDA, at a dose of 9.0 mg/kg, reduced the concentration of DOPAC to 50%, $F(10, 105) = 6.19$, $p < 0.001$, of the baseline level (Fig. 3B). The decreases in the concentration of DOPAC following administration of 1.0, 3.0, and 9.0 mg/kg of MDMA were by 75%, $F(10, 107) = 2.30$, $p < 0.05$, 80% (not significant), and 50%, $F(10, 105) = 6.75$, $p < 0.001$, respectively (Fig. 3C). DOM seemed to elevate rather than reduce the extracellular concentration of DOPAC, but this effect was not statistically significant (Fig. 3D).

Amphetamine reduced the concentration of HVA to some 50% of the baseline level at doses of 1.0, $F(10, 107) = 3.05$, $p < 0.01$, 3.0, $F(10, 105) = 4.22$, $p < 0.001$, and 9.0 mg/kg, $F(10, 105) = 4.02$, $p < 0.001$, but MDA and MDMA affected the HVA concentration first at the dose of 9.0 mg/kg, $F(10, 105) = 3.62$, $p < 0.001$, and $F(10, 104) = 5.21$, $p < 0.001$, respectively. DOM seemed to elevate the concentration of HVA as well, but this effect was not significant.

DISCUSSION

As measured by this in vivo microdialysis study, the amphetamine derivatives elevated the extracellular 5-HT levels

in nucleus accumbens in the following order of magnitude: MDMA > MDA > amphetamine > DOM. For elevation of the dopamine levels the corresponding order is: amphetamine > MDMA = MDA > DOM. Thus, amphetamine predominantly elevated the dopamine levels, while MDA and MDMA elevated both the 5-HT and dopamine levels, and DOM failed to affect either of the compounds markedly. These results are consistent with *in vitro* comparison studies that show that MDMA and MDA induce the release, or inhibit the uptake, of both 5-HT and dopamine, but that DOM has no effect on either of the transmitters (13,14,18,25). Our results also agree with the *in vivo* microdialysis studies of Yamamoto and Spanos (30), Hiramatsu and Cho (12), Gough et al. (11), and Nash and Nichols (15), in which the acute administration of MDMA and MDA elevate extracellular 5-HT and dopamine levels and reduce the levels of DOPAC and HVA, as well as with the studies of Zetterström et al. (31) and Carboni

et al. (2), in which amphetamine elevated extracellular dopamine and decreased the levels of DOPAC and HVA.

The doses of DOM, which are lower than those of the other drugs, were chosen on the basis of the potency of the drug; the ED₅₀ value (determined from drug discrimination studies) for DOM is 0.44 mg/kg in the rat (8), compared, for example, to 0.97 mg/kg reported for MDA (17). Furthermore, in humans DOM produces hallucinogenic effects in total doses of 5–10 mg (24), while the doses of MDMA reported for recreational use are in the range of 60–250 mg (1–4 mg/kg) (20). Thus, the ineffectiveness of DOM in releasing 5-HT and dopamine in our study is unlikely to be due to inadequate dosage.

It is well established that hallucinogenic activity involves a serotonergic (in particular, 5-HT₂ receptor-mediated) mechanism (8,10,28). Nevertheless, in our study DOM failed to affect the extracellular levels of 5-HT in the nucleus accumbens; the slight increase in 5-HT may instead result from the down-

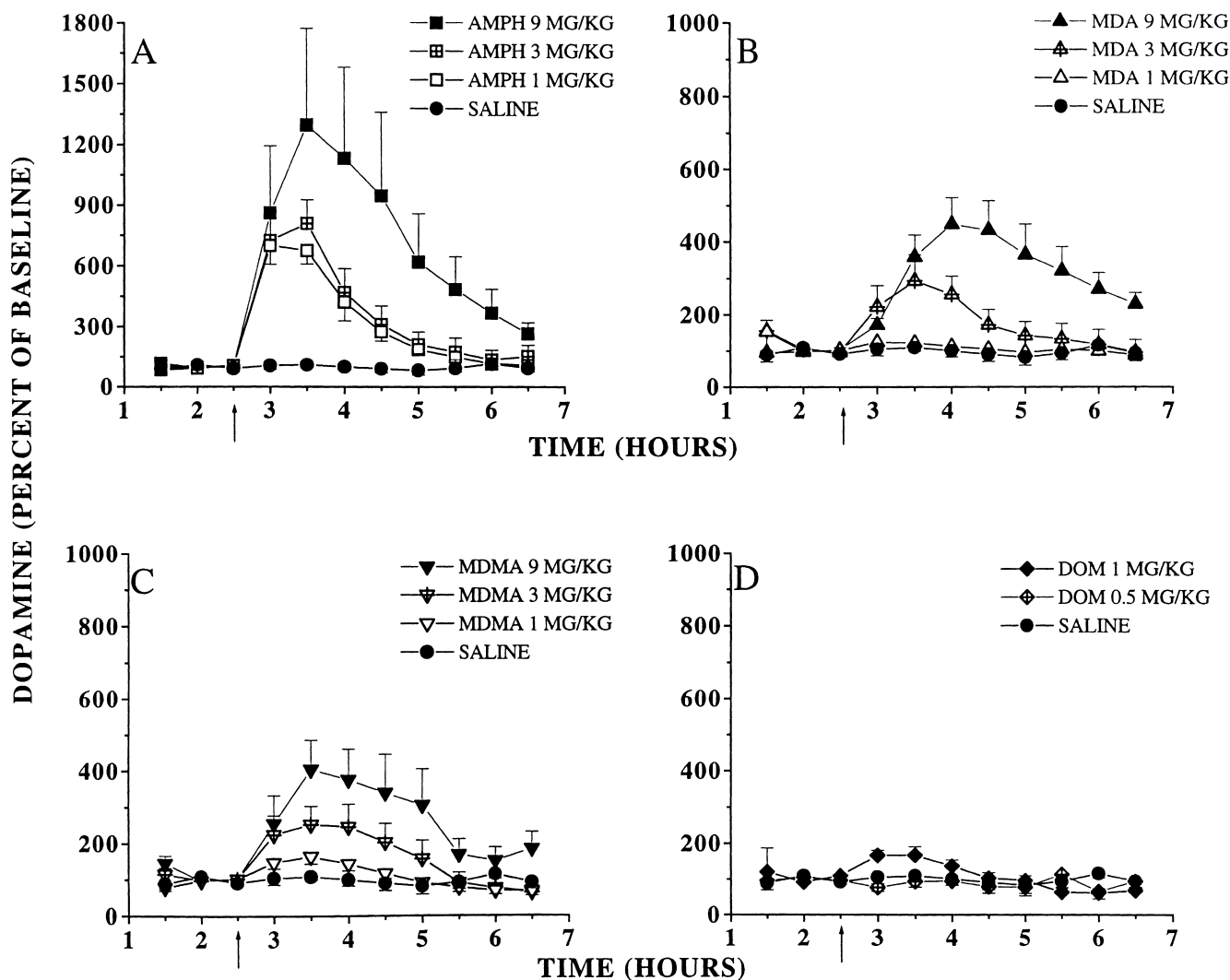


FIG. 2. The effects of the amphetamine derivatives on extracellular dopamine levels in nucleus accumbens. Amphetamine (1.0, 3.0, and 9.0 mg/kg; A), MDA (1.0, 3.0, and 9.0 mg/kg; B), MDMA (1.0, 3.0, and 9.0 mg/kg; C), and DOM (0.5 and 1.0 mg/kg; D) were administered subcutaneously at 2 h 30 min after starting perfusion, as indicated by the arrows. The data expressed as percentages of the basal release are given as means \pm SE ($n = 5-6$). Error bars are not shown when they are smaller than the symbols.

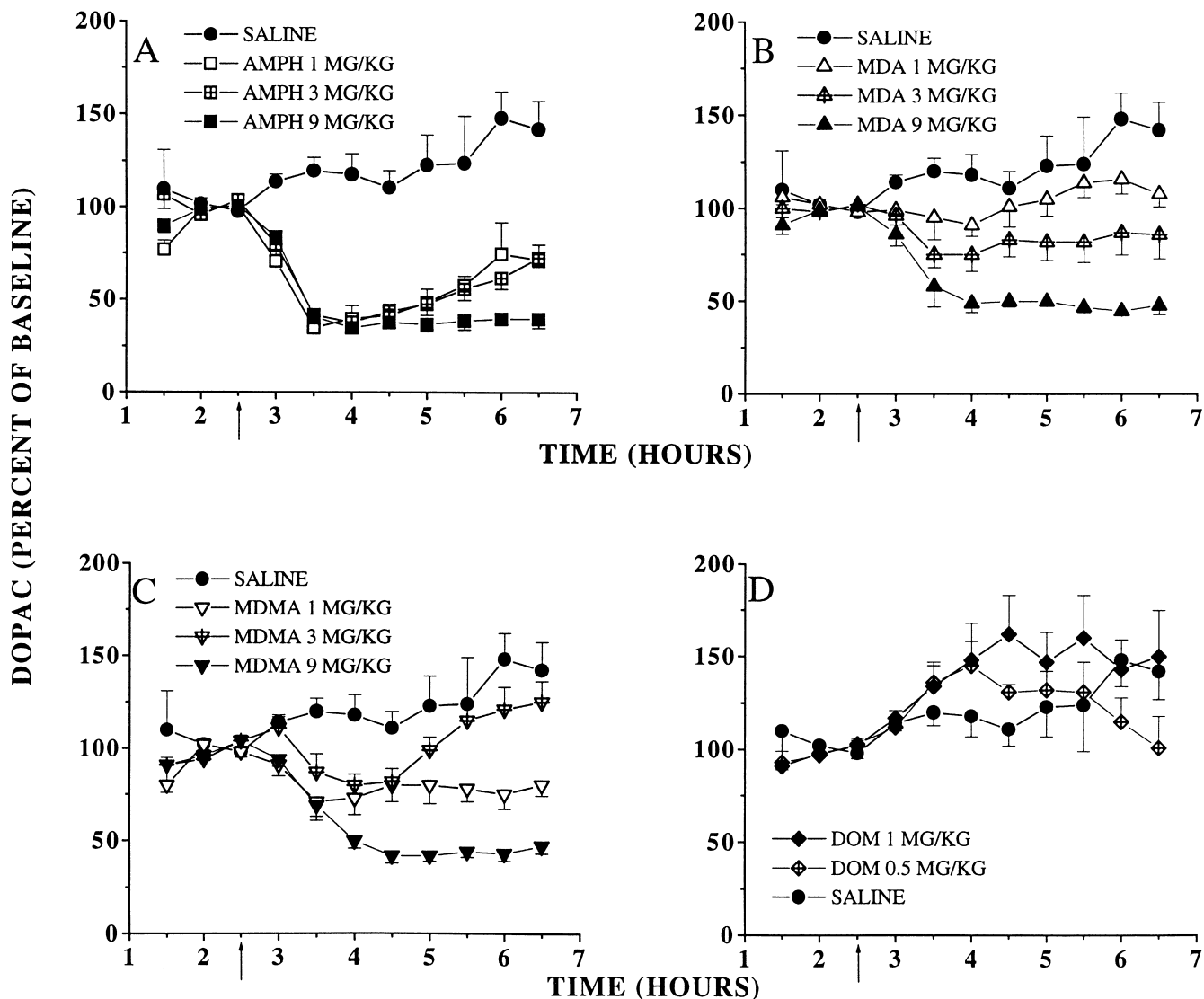


FIG. 3. The effects of the amphetamine derivatives on extracellular DOPAC levels in nucleus accumbens. Amphetamine (1.0, 3.0, and 9.0 mg/kg; A), MDA (1.0, 3.0, and 9.0 mg/kg; B), MDMA (1.0, 3.0, and 9.0 mg/kg; C), and DOM (0.5 and 1.0 mg/kg; D) were administered subcutaneously at 2 h 30 min after starting perfusion, as indicated by the arrows. The data expressed as percentages of the basal release are given as means \pm SE ($n = 5-6$). Error bars are not shown when they are smaller than the symbols.

wards drifting of baseline values. Thus, it seems that changes in the concentration of extracellular 5-HT cannot be considered to reflect acute hallucinogenic activity. However, substances like DOM may instead have other effects on serotonergic neurons, for example, at receptor level.

MDA and MDMA are considered to possess hallucinogenic properties in addition to other central effects (6,7,9). The strong effects of MDA and MDMA on 5-HT levels, compared to the ineffectiveness of DOM, indicates that the methylenedioxyamphetamines act via serotonergic mechanisms other than those of the hallucinogens, and thereby supports their classification separately from the hallucinogens.

According to our results, the levels of 5-HIAA following the administration of MDA or MDMA decreased gradually towards the end of the sample collection period without recovering or reaching a plateau. These results agree with in

vitro studies in which the administration of MDA or MDMA have decreased the concentration of 5-HIAA in several regions in rat forebrain (21-23,26,27). However, in those studies MDA or MDMA also decreased the concentration of 5-HT, but as the time scale used differs from that of ours, these results do not necessarily conflict with ours. It is thought that the depletion of 5-HT and 5-HIAA results from a massive release of 5-HT from presynaptic vesicles, which is probably responsible for the increase in 5-HT-levels seen in our results. This release of 5-HT leading to 5-HT and 5-HIAA depletion supports the theory of a neurotoxic effect of the chronically administered methylenedioxyamphetamines on rat serotonergic pathways.

The stimulation of extracellular dopamine release in mesolimbic areas like the nucleus accumbens is related to general activation of motor output and to the reinforcing properties of

drugs of abuse (3,29). Amphetamine, indeed, is a model compound of an addictive psychomotor stimulant drug. The increase in dopamine levels and the decreases in DOPAC and HVA levels observed after the administration of the methylenedioxyamphetamines suggest that they may act via dopaminergic mechanisms similar to those of amphetamine, including displacement of dopamine from storage vesicles (5), inhibition of monoamine oxidase (1,4), and blockade of the reuptake of catecholamines. The ineffectivity of DOM in releasing dopamine suggests that DOM lacks dopaminergic properties, including reinforcement.

In conclusion, the failure of DOM to affect 5-HT levels suggests that extracellular levels of 5-HT do not reflect hallucinogenic activity. DOM seems to affect the serotonergic neu-

rones in a way that is not detectable with *in vivo* microdialysis technique, and it seems to lack the dopaminergic properties of the stimulatory amphetamine derivatives. The strong effects of MDA and MDMA on both extracellular 5-HT and dopamine levels provides evidence that their mechanisms of action on serotonergic neurones are clearly different from those of the hallucinogenic substances, but they may act via dopaminergic mechanisms similar to amphetamine.

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