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ORIGINAL INVESTIGATION

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# 3,4-Methylenedioxymethamphetamine enhances the release of acetylcholine in the prefrontal cortex and dorsal hippocampus of the rat

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**Abstract** *Rationale:* The neurochemical effects produced by acute administration of 3,4-methylenedioxymethamphetamine (MDMA) on the monoaminergic systems in the brain are well documented; however, there has been little consideration of the potential effects of MDMA on other neurotransmitter systems. *Objective:* The present study was designed to investigate the acute effect of MDMA on cholinergic neurons by measuring acetylcholine (ACh) release in the medial prefrontal cortex (PFC) and dorsal hippocampus, terminal regions of cholinergic projection neurons originating in the basal forebrain. *Methods:* In vivo microdialysis and high-performance liquid chromatography with electrochemical detection (HPLC-ED) were used to assess the effects of MDMA on the extracellular concentration of ACh in the PFC and dorsal hippocampus of the rat. *Results:* The systemic administration of MDMA (3–20 mg/kg, i.p.) resulted in an increased extracellular concentration of ACh in the PFC and dorsal hippocampus. Reverse dialysis of MDMA (100 μM) into the PFC and hippocampus also increased ACh release in these brain regions. Treatment with parachlorophenylalanine and α-methyl-*para*-tyrosine, inhibitors of serotonin (5-HT) and dopamine (DA) synthesis, respectively, significantly attenuated the release of ACh stimulated by MDMA in the PFC, but not in the dorsal hippocampus. *Conclusions:* MDMA exerts a stimulatory effect on the release of ACh in the PFC and dorsal hippocampus in vivo, possibly by mechanisms localized within these brain regions. In addition, these results suggest that the MDMA-induced release of ACh in the PFC involves both serotonergic and dopaminergic mechanisms.

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## Introduction

It is well documented that 3,4-methylenedioxymethamphetamine (MDMA) exerts a pronounced stimulatory effect on the release of serotonin (5-HT) in the brain, as evidenced in vitro in synaptosomes and striatal slices (Nichols et al. 1982; Johnson et al. 1986), as well as in vivo (Gough et al. 1991; Gudelsky and Nash 1996). The MDMA-induced release of 5-HT appears to be a carrier-mediated process that involves the interaction of MDMA with the 5-HT uptake site (Rudnick and Wall 1992; Gudelsky and Nash 1996). MDMA has also been shown to increase dopamine (DA) release in vitro (Johnson et al. 1986) and in vivo (Yamamoto and Spanos 1988; Nash and Brodkin 1991). The MDMA-induced release of DA involves both carrier-mediated and impulse-dependent processes (Nash and Brodkin 1991; Yamamoto et al. 1995). The contribution of impulse-dependent processes to MDMA-induced DA release appears to involve 5-HT neuronal systems, as the magnitude of MDMA-induced DA release is modulated by 5-$HT_2$ receptor activation (Nash 1990; Gudelsky et al. 1994; Yamamoto et al. 1995) and the 5-$HT_2$ receptor-linked protein kinase C (Nair and Gudelsky 2004b).

Though the effect of MDMA on the release of 5-HT and DA is relatively well documented, little is known about the influence of MDMA on the release of other neurotransmitters. Recently, MDMA has been reported to have a stimulatory effect on the release of acetylcholine (ACh) in striatal slices in vitro (Fischer et al. 2000) and in the frontal cortex and striatum in vivo (Acquas et al. 2001).

The release of cortical ACh has been shown to be enhanced following novel, arousing, stressful, sensory, and rewarding stimuli (Sarter and Bruno 1999; Pepeu and Giovannini 2004). In addition, many drugs of abuse, e.g., cocaine, amphetamine, ketamine, and nicotine, have been shown to enhance the release of cortical or hippocampal

ACh (Arnold et al. 2001, 2003; Nelson et al. 2002; Imperato et al. 1993). It can be envisioned that the enhanced processing of drug-associated environmental cues that accompany drug dependence involves drug-induced alterations in cholinergic neurotransmission.

The purpose of the present study was to further characterize the stimulatory effect of MDMA on the release of ACh in the prefrontal cortex (PFC), as well as in the hippocampus, and to investigate a potential role of serotonergic and/or dopaminergic mechanisms in the cholinergic response to MDMA.

## Materials and methods

### Animals

Adult male rats (200–300 g) of the Sprague–Dawley strain (Harlan Laboratories, Indianapolis, IN) were used in this study. The animals were housed three per cage until guide cannula implantation, after which they were housed one per cage in a temperature- and light-controlled room. Food and water were available ad libitum. Principles of laboratory animal care were followed. All procedures were in strict adherence to NIH guidelines and approved by the Institutional Animal Care and Use Committee.

### In vivo microdialysis

A guide cannula (Scipro Inc., Sanborn, NY, part no. MAB 4.15.IC) was implanted under ketamine/xylazine (70:7 mg/kg, i.m.)-induced anesthesia dorsal to the PFC or hippocampus, according to the stereotaxic atlas of Paxinos and Watson (1986). Twenty-four to forty-eight hours following surgery, a concentric style microdialysis probe (Scipro Inc., part no. MAB 4.15.3.PES for PFC, part no. MAB 4.17.2.PES for hippocampus, outer diameter 0.2 mm) was inserted through the guide cannula into the PFC (AP +3.2 mm, ML +0.7 mm, DV −4.0 mm from the bregma) or dorsal hippocampus (AP −3.6 mm, ML +3.2 mm, DV −4.0 mm from the bregma). The active portions of the membrane for the probes in the PFC and hippocampus were 3.0 and 2.0 mm, respectively. The dialysis probes were connected to an infusion pump set to deliver artificial cerebrospinal fluid containing 136 mM NaCl, 1.7 mM KCl, 1.2 mM $CaCl_2$, 6 mM $Na_2HPO_4$, 5 mM glucose, and 100 nM neostigmine at a constant rate of 1.8 μL/min. After an equilibration period of 2.5 h, dialysis samples were collected every 30 min. At least four baseline samples were obtained prior to any drug treatment.

Following the experiments, the placement of the microdialysis probe in the PFC and hippocampus was verified on frontal sections of the brain. For graphical depiction of probe placement (Fig. 1), coronal sections of the brain were obtained from rats perfused with 4% paraformaldehyde, and the sections were stained with cresyl violet prior to inspection.

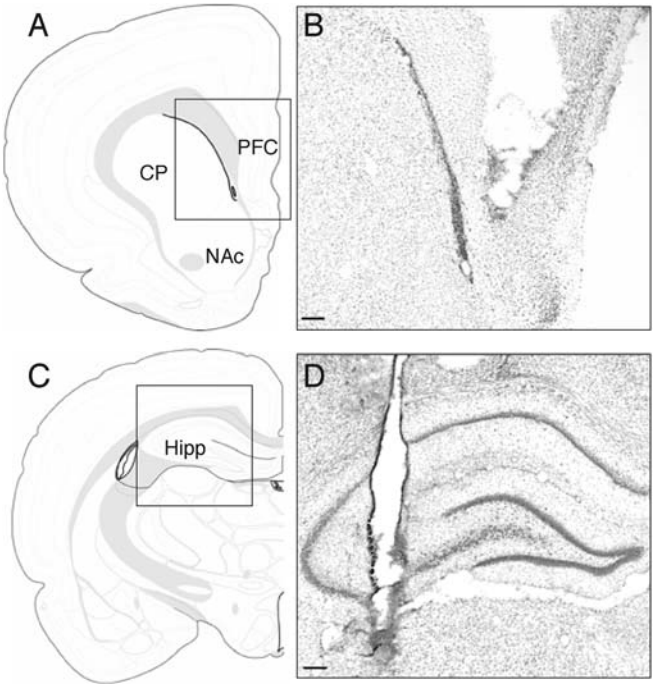


**Fig. 1** Placement of microdialysis probes in the PFC and hippocampus. **a** and **c** are schematic representations of the photomicrographs of dialysis probe placements in **b** and **d**. The *boxes* in **a** and **c** indicate location of the probe placement in **b** and **d**, respectively. *Scale bars* in **b** and **d** indicate 200 μm. *Hipp* Hippocampus, *CP* caudate–putamen, *NAc* nucleus accumbens

### Biochemical measurements

The extracellular concentration of ACh was quantified using HPLC-ED. An aliquot (20 μL) of the dialysate was injected onto a 150×3 mm ACH-3 column (ESA, Inc., Chelmsford, MA) that was connected to a post-column enzyme reactor containing acetylcholinesterase and choline oxidase (ESA). ACh was hydrolyzed to hydrogen peroxide that was detected using a peroxidase-wired glassy carbon target electrode (ESA) with the potential set at −200 mV. The mobile phase for the separation of ACh consisted of 100 mM disodium hydrogen phosphate, 0.5 mM tetramethylammonium chloride, 2 mM octanesulfonic acid sodium salt, 0.005% Reagent MB, a microbicide (ESA), pH 8.0, pumped at a flow rate of 0.33 mL/min. Peak heights were quantified using a Hewlett-Packard integrator. The quantity of ACh was calculated based on a known standard curve. The standard curve was constructed across a concentration range from 0.05 to 1 pmol/20 μL. The curve was linear across this range of concentrations. The lower limit of detection using these assay conditions was approximately 0.01 pmol/20 μL.

## Drugs

MDMA hydrochloride was generously provided by the National Institute on Drug Abuse (Bethesda, MD). D-Amphetamine sulfate, α-methyl-*para*-tyrosine (AMPT), and parachlorophenylalanine (pCPA) were purchased from Sigma Chemical Co. (St. Louis, MO). All drugs were dissolved in 0.9% NaCl with the exception of AMPT, which was dissolved in water, and injected in volumes of 1 ml/kg. Doses of MDMA (3, 10, and 20 mg/kg, i.p.) were chosen based on the behavioral and neurochemical effects of the drug reported previously (Yamamoto and Spanos 1988; Gudelsky and Nash 1996; Darvesh et al. 2002; Green et al. 2004). In addition, interspecies scaling studies suggest that MDMA doses of 5 and 10 mg/kg in the rat result in plasma concentrations of MDMA typically found in recreational users of the drug (O'Shea et al. 1998; Ricaurte et al. 2000). The doses for AMPT and pCPA were based on previous reports in which similar dosage regimens produced significant DA and 5-HT depletion, respectively (Nash et al. 1988; Peters and Michael 2000; Lebsanft et al. 2003), and attenuation of MDMA-induced DA and 5-HT release, respectively (Brodkin et al. 1993).

## Statistical analyses

Student's *t* test was used to analyze differences in absolute values for baseline ACh concentrations between vehicle- and MDMA-, vehicle- and pCPA-, and vehicle- and AMPT-treated groups. For experiments in which there was a single treatment, dialysis values for ACh in microdialysis samples were converted to a percent of mean baseline value and analyzed using a two-way repeated-measures ANOVA (Sigma Stat, Jandel Scientific). Values

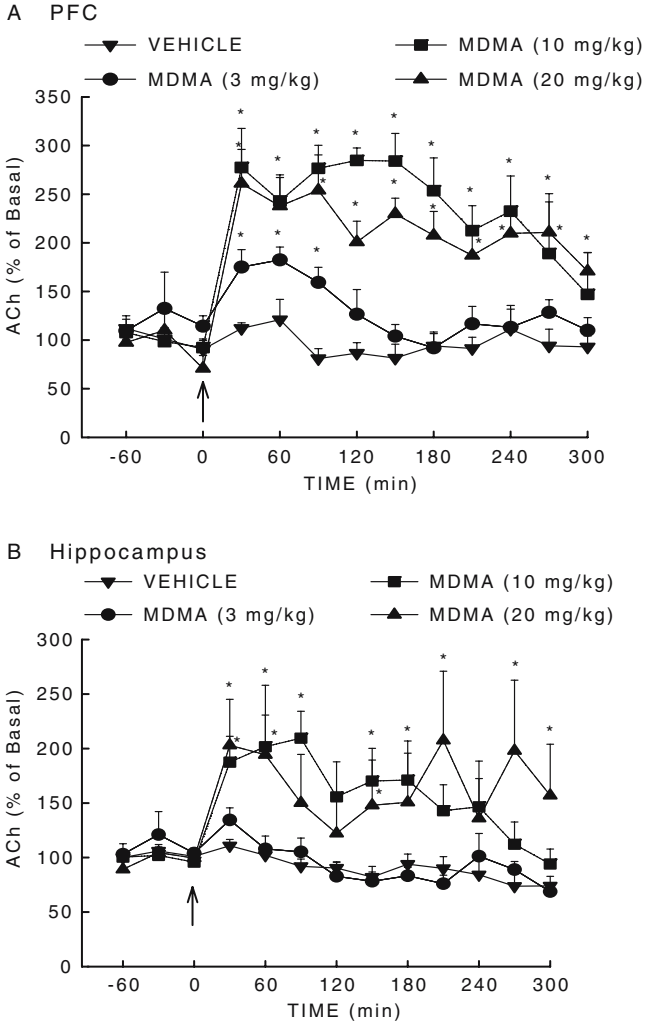


**Fig. 2** Effect of MDMA on ACh release in the PFC (**a**) and hippocampus (**b**). Rats received intraperitoneal injections of either vehicle or MDMA (3, 10, or 20 mg/kg, i.p.) at time 0. *N*=6–12 rats/group. *Asterisk* indicates values that are significantly (*P*<0.05) greater than those for animals given vehicle

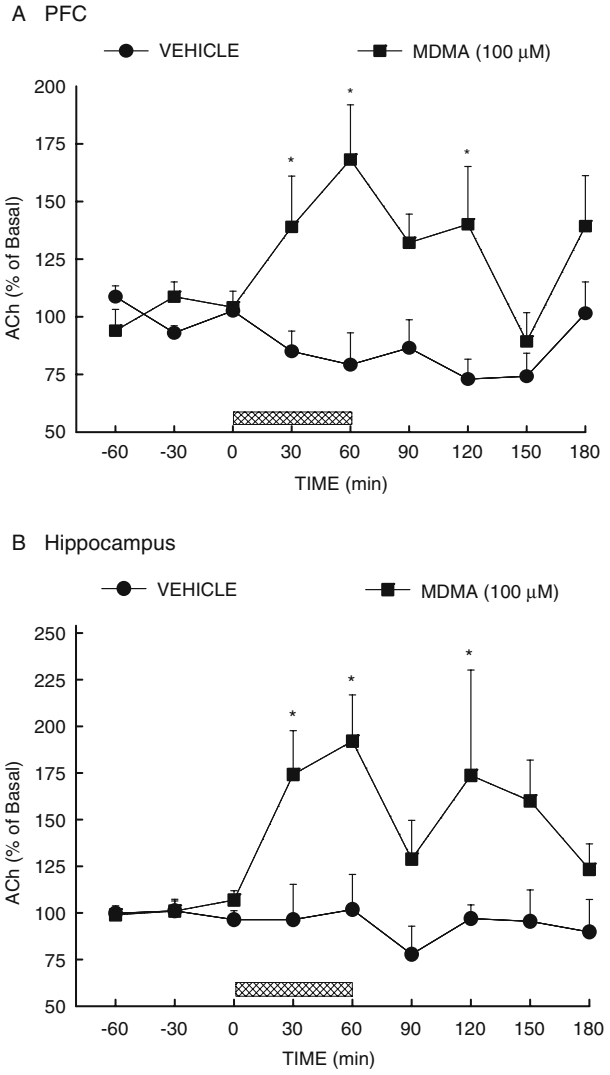


**Fig. 3** Effect of intracortical (**a**) or intrahippocampal (**b**) administration of MDMA by reverse dialysis on ACh release in the PFC and hippocampus, respectively. Rats received intracortical or intrahippocampal infusion of vehicle or MDMA (100 μM) for a 60-min period (indicated by the *hatched bar*). *N*=7–10 rats/group. *Asterisk* indicates values that are significantly (*P*<0.05) greater than animals that were treated with vehicle

for ACh obtained from experiments in which there were multiple drug treatments were analyzed by SAS (SAS Institute, Inc.), with consideration for factors of pretreatment, treatment, and time with repeated measures. ANOVAs were constructed using three baseline values and all values following drug administration. Subsequent multiple comparisons between treatment groups were conducted by post hoc analysis with Student–Newman–Keuls test. Treatment differences were considered statistically significant at $P<0.05$.

## Results

The basal concentrations of ACh in the PFC and dorsal hippocampus were 0.41±0.03 and 0.15±0.02 pmol/20 μL, respectively (mean±SEM). Treatment with pCPA or AMPT did not significantly alter basal dialysate concentrations of ACh in either brain region.

The effects of systemic administration of MDMA on extracellular concentrations of ACh in the PFC and hippocampus are depicted in Fig. 2. A two-way repeated-measures ANOVA revealed significant effects of drug [$F(3,21)=16.71$, $P<0.001$], time [$F(12,229)=13.09$, $P<0.001$], and a drug × time interaction [$F(36,229)=3.95$, $P<0.001$] for MDMA-induced increases in extracellular ACh in the PFC. Subsequent analysis of the main effect of drug indicated that extracellular concentrations of ACh in the PFC were increased significantly ($P<0.001$) by 10 and 20 mg/kg, but not by 3 mg/kg, and that there was no difference in the stimulatory effect of 10 and 20 mg/kg.

Extracellular concentrations of ACh in the hippocampus were also increased following MDMA administration. The main effects of drug [$F(3,20)=4.77$, $P<0.01$] and time [$F(12,230)=4.67$, $P<0.001$], as well as the drug × time interaction [$F(36,230)=3.15$, $P<0.001$], were all significant. As in the PFC, dialysate concentrations of ACh were significantly ($P<0.05$) increased by 10 and 20 mg/kg, but not by 3 mg/kg.

The intracortical and intrahippocampal infusions of MDMA (100 μM) by reverse dialysis for 1 h resulted in a significant increase in extracellular concentrations of ACh in both brain regions. ANOVAs indicated a significant main effect of drug in both the PFC [$F(1,12)=12.25$, $P=0.004$] and hippocampus [$F(1,15)=10.33$, $P=0.006$] and a significant drug × time interaction [$F(8,91)=3.25$, $P=0.003$] only in the PFC. There was no significant effect of time in either the PFC or the hippocampus (Fig. 3a and b).

The MDMA-induced increase in ACh release in the PFC and hippocampus was also examined in rats treated with

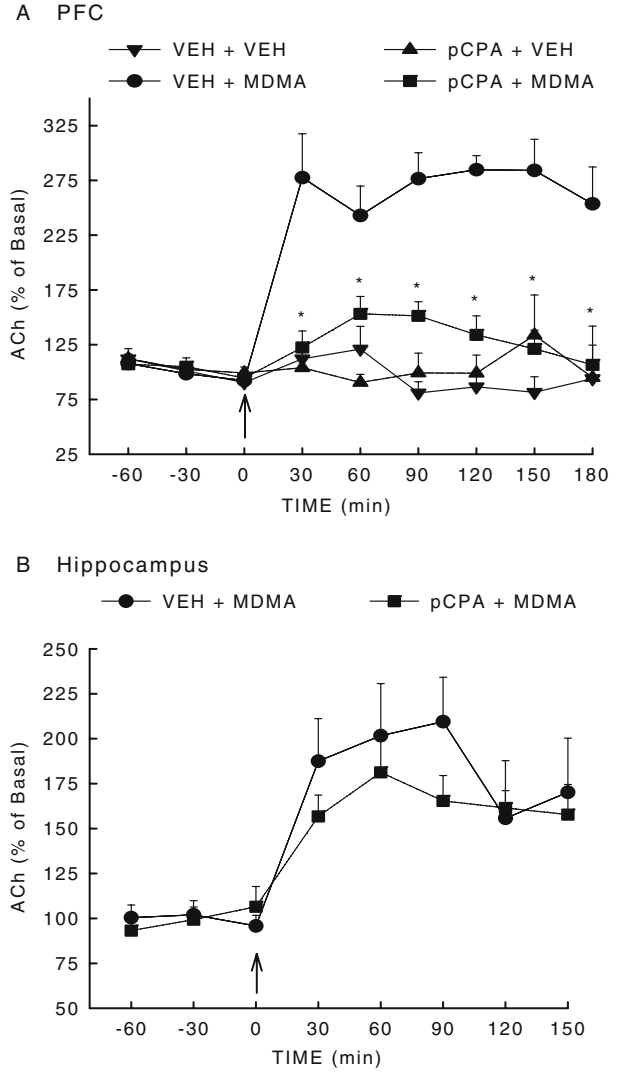


**Fig. 4** Effect of pCPA on MDMA-induced ACh release in the PFC (**a**) and hippocampus (**b**). Rats were treated with vehicle or pCPA (150 mg/kg, i.p.) for three consecutive days. MDMA (10 mg/kg, i.p.) or vehicle was administered 24 h following the last pCPA or vehicle injection. $N$=6–10 rats/group. *Asterisk* indicates values that are significantly ($P<0.05$) less than those for animals that received vehicle and MDMA

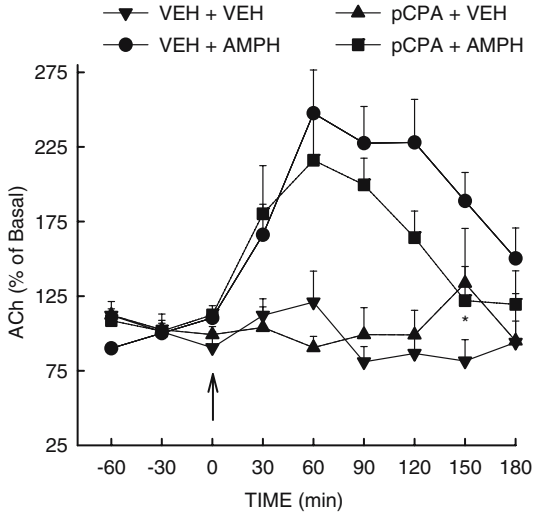


**Fig. 5** Effect of pCPA on amphetamine-induced ACh release in the PFC. Rats were treated with vehicle or pCPA (150 mg/kg, i.p.) for three consecutive days. Amphetamine (*AMPH*, 2 mg/kg, i.p.) or vehicle was administered 24 h following the last pCPA or vehicle injection. $N$=6–10 rats/group. *Asterisk* indicates a value that is significantly ($P<0.05$) less than that for animals treated with vehicle and MDMA

the tryptophan hydroxylase inhibitor pCPA (150 mg/kg, i.p., daily) or vehicle for 3 days; dialysis samples were obtained 24 h following the last injection of pCPA or vehicle. The MDMA-induced increase in ACh release in the PFC was significantly less in rats treated with pCPA than in control rats (Fig. 4a). The ANOVA revealed significant main effects of pretreatment [$F(1,22)=8.18$, $P=0.009$], treatment [$F(1,22)=29.88$, $P<0.001$], and time [$F(8,176)=15.16$, $P<0.001$]. Moreover, the interaction of pretreatment × treatment also was significant [$F(1,22)=12.46$, $P=0.002$], as were all other interactions, i.e., pretreatment × time [$F(8,176)=6.44$, $P<0.0005$], treatment × time [$F(8,176)=18.32$, $P<0.0001$], and pretreatment × treatment × time [$F(8,176)=9.49$, $P<0.0001$]. In contrast to the attenuated response to MDMA in the PFC of pCPA-treated rats, the MDMA-induced increase in extracellular concentration of ACh in the hippocampus was unaltered by pCPA treatment (Fig. 4b).

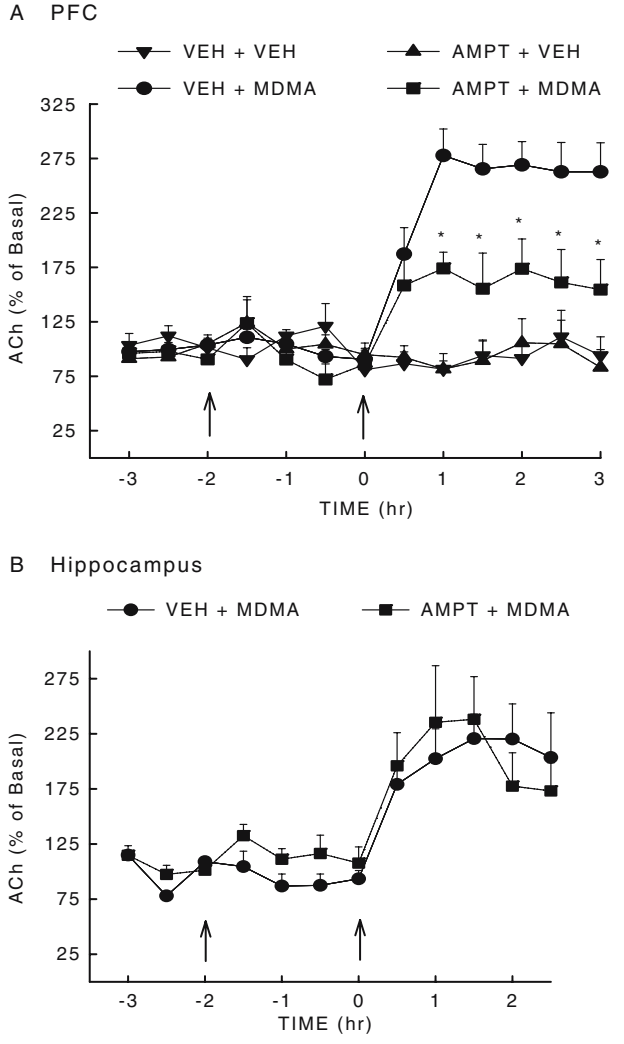


**Fig. 6** Effect of AMPT on MDMA-induced ACh release in the PFC (**a**) and hippocampus (**b**). Rats received intraperitoneal injections of vehicle or AMPT (250 mg/kg) 120 min prior to the administration of either vehicle or MDMA (10 mg/kg, i.p.). $N=5–14$ rats/group. *Asterisk* indicates values that are significantly ($P<0.05$) less than those for animals given vehicle and MDMA

The specificity of the inhibitory effect of MDMA on stimulated ACh release in the PFC was evaluated by examining amphetamine-stimulated ACh release in vehicle- and pCPA-treated animals. Administration of amphetamine (2 mg/kg, i.p.) resulted in extracellular concentrations of ACh that were approximately 230% of baseline values in the PFC. However, in contrast to the suppression by pCPA treatment of the ACh response to MDMA in the PFC, 5-HT depletion by pCPA had little, if any, effect on the amphetamine-induced increase in the extracellular concentration of ACh in the PFC (Fig. 5). The ANOVA indicated a significant effect of treatment [$F(1,18)=27.12$, $P<0.0001$] and time [$F(8,144)=10.81$, $P<0.0001$]. However, the factor of pretreatment and the pretreatment × treatment interaction were not significant, and the pretreatment × treatment × time interaction was marginally significant [$F(8,144)=2.74$, $P=0.034$].

The effect of inhibition of DA synthesis with AMPT on MDMA-induced ACh release is depicted in Fig. 6. The MDMA-induced increase in the extracellular concentration of ACh in the PFC was reduced by approximately 65% in rats treated with AMPT (Fig. 6a). There was a significant main effect of treatment [$F(1,23)=24.29$, $P<0.0001$], pretreatment [$F(1,23)=4.93$, $P=0.04$], and time [$F(12,276)=18.32$, $P<0.001$]. In addition, the pretreatment × treatment interaction was significant [$F(1,23)=5.24$, $P=0.032$], as were the interactions of treatment × time [$F(12,276)=23.67$, $P<0.0001$], pretreatment × time [$F(12,276)=3,46$, $P<0.01$], and pretreatment × treatment × time [$F(12,276)=3.39$, $P<0.01$]. In contrast to the PFC, there was no significant difference in the MDMA-induced increase in extracellular concentration of ACh in the hippocampus of AMPT- and vehicle-treated animals (Fig 6b).

## Discussion

In the present study, acute administration of MDMA enhanced ACh release in the PFC and dorsal hippocampus. Intracortical and intrahippocampal infusions of MDMA also increased ACh release in these brain regions. The increase in extracellular concentration of ACh evoked by MDMA was attenuated by 5-HT and DA synthesis inhibiting drugs pCPA and AMPT, respectively, in the PFC, but not in the dorsal hippocampus. These results indicate that MDMA enhances the release of ACh in the PFC and hippocampus, possibly by mechanisms localized to these brain regions. Furthermore, it also appears that cortical, but not hippocampal, ACh release induced by MDMA is mediated by serotonergic and dopaminergic mechanisms.

The finding that MDMA enhances ACh release is consistent with an earlier report by Acquas et al. (2001). These investigators demonstrated a stimulatory effect of MDMA on ACh release in the frontal cortex and striatum following intravenous administration. Other psychostimulants (e.g., amphetamine, cocaine, nicotine, methamphetamine, methylphenidate) have also been reported to stimulate the release of ACh in various brain regions in vivo (Day and Fibiger 1992; Imperato et al. 1993, Reid et al. 1999; Acquas and Fibiger 1996; Day et al. 1997, Taguchi et al. 1998;

Arnold et al. 2001, 2003). In addition, the repeated administration of nicotine or amphetamine has been shown to result in a sensitization of cortical ACh release (Nelson et al. 2003; Arnold et al. 2003). Inasmuch as it is generally hypothesized that cortical ACh release functions in attentional processing (Sarter et al. 2003), it can be envisioned that the alterations in cholingergic neurotransmission underlies the processing of drug-associated environmental stimuli.

Administration of MDMA locally into the PFC and hippocampus enhanced ACh release in these brain regions. In addition, MDMA perfused into the nucleus basalis magnocellularis, a region that provides the major source of cholinergic innervation to the cerebral cortex (Lehmann et al. 1980), also stimulated ACh release in the PFC (unpublished observation). Thus, MDMA appears to enhance ACh release, at least in part, by mechanisms localized to the PFC, basal nucleus, and hippocampus. However, this does not exclude the possibility that other brain regions might be involved in the ACh-releasing effect of MDMA.

Rats treated with a dosage regimen of pCPA known to attenuate MDMA-induced 5-HT release (Brodkin et al. 1993) exhibited a diminished ACh response in the PFC to MDMA, but not to amphetamine. Thus, the inhibitory effect of pCPA on MDMA-induced ACh release is likely due to a diminished release of 5-HT rather than a nonspecific inhibitory effect of the drug on cholinergic neurons in the PFC. Moreover, the differential effect of pCPA on MDMA- and amphetamine-induced ACh release illustrates the differences in the mechanisms by which these two amphetamines stimulate ACh release in the PFC.

Considerable evidence supports a stimulatory role for 5-HT in the regulation of ACh release in various brain regions. Selective 5-HT uptake inhibitors, releasing agents and 5-HT itself, have been reported to increase the extracellular concentration of ACh (Ohue et al. 1992; Hirano et al. 1995; Consolo et al. 1996), and receptors of the 5-$HT_{2A/C}$, 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_3$, and 5-$HT_4$ subtypes have been purported to exert a stimulatory influence on ACh release in the PFC and/or the hippocampus (Hirano et al. 1995; Consolo et al. 1996; Yamaguchi et al. 1997; Giovannini et al. 1998; Koyama et al. 1999; Nair and Gudelsky 2004a). Furthermore, receptors of the 5-$HT_2$ and 5-$HT_4$ subtypes are known to be present on cholinergic and noncholinergic neurons in the PFC (Quirion et al. 1985; Saito et al. 1996; Barnes and Sharp 1999; Svenningsson et al. 2002). Also, 5-HT terminals are found in the vicinity of basal forebrain cholinergic neurons, although direct synaptic contacts have not yet been confirmed at the electron microscopic level (Jones and Cuello 1989; Zaborszky 1989) in this brain region or in the cortex or hippocampus. Additional studies are required to elucidate the 5-HT receptor subtype(s) involved in the stimulatory effect of MDMA on ACh release in the PFC.

The MDMA-induced increase in the extracellular concentration of ACh in the PFC was also significantly diminished in rats in which catecholamine synthesis was inhibited by AMPT. Although AMPT inhibits the synthesis of both DA and norepinephrine, it is likely that it is a dopaminergic mechanism that contributes to the cortical ACh response to MDMA. Systemic administration of the prominent DA releaser amphetamine, as well as MDMA, stimulates ACh release in the PFC (Acquas et al. 2001; Day et al. 1994; Arnold et al. 2001). Moreover, amphetamine-induced ACh release in rats is suppressed in rats with 6-hydroxydopamine-induced lesions of the mesotelencephalic DA system or in rats treated with the $D_1$ antagonist SCH 23390 (Day and Fibiger 1992; Day et al. 1994). On an anatomical basis, the PFC and the basal nucleus receive dopaminergic projections from the midbrain (Jones and Cuello 1989; Zaborszky 1989). Finally, noradrenergic mechanisms appear to be inhibitory, not stimulatory, to cortical ACh release (Beani et al. 1978; Bianchi et al. 1979; Vizi 1980). However, considering the extensive noradrenergic innervation of the cortex (Scheinin et al. 1994), it is conceivable that a noradrenergic component mediates the effects of MDMA on cortical ACh release.

The present studies have utilized the acetylcholinesterase inhibitor neostigmine to measure detectable levels of ACh in the dialysate. The artificial increase in extracellular ACh levels due to the presence of neostigmine may influence the activity of cortical nicotinic and muscarinic receptors. Since nicotinic receptor activation is known to enhance 5-HT and DA release (Marshall et al. 1997; Singer et al. 2004), the presence of neostigmine may result in a greater release of 5-HT and/or DA than under physiological conditions that could modify the effect of MDMA. Alternatively, activation of presynaptic cholinergic autoreceptors by elevated ACh concentrations could also alter the cholinergic response to MDMA.

Although treatment with pCPA and AMPT attenuated the MDMA-induced elevation of the extracellular ACh concentration in the PFC, the ACh response in the hippocampus was unaffected by either agent. Although serotonergic and dopaminergic agents have been shown to enhance hippocampal ACh release (Consolo et al. 1994; Day and Fibiger 1994; Hersi et al. 1995), it appears that the MDMA-induced release of ACh in the hippocampus involves nondopaminergic and nonserotonergic mechanisms. Further studies are required to identify the neurochemical substrates involved in the stimulatory effect of MDMA on hippocampal ACh release.

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