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Involvement of γ-aminobutyric acid neurotransmission in phencyclidine-induced dopamine release in the medial prefrontal cortex

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Abstract

The present study was designed to examine the possible involvement of γ-aminobutyric acid (GABA) neurotransmission in the mechanism of phencyclidine (1-(1-phenylcyclohexyl)piperidine; PCP)-induced dopamine release in the medial prefrontal cortex, using in vivo microdialysis in awake, freely moving rats. Local perfusion via the dialysis probe into the medial prefrontal cortex with PCP (100 and 500 μM) and dizocilpine ((+)-5-methyl-10,11-dihydroxy-5-*H*-dibenzo(a,d)cyclo-heptan-5,10-imine; MK-801, 10 and 50 μM), a selective non-competitive NMDA receptor antagonist, was found to increase extracellular dopamine levels. Co-perfusion with NMDA (1 mM) or the $GABA_A$ receptor agonist muscimol (50 μM) attenuated the effects of PCP (500 μM) and MK-801 (50 μM) on extracellular dopamine levels. The dopamine reuptake inhibitor nomifensine (50 μM) also produced an increase in extracellular dopamine levels in the medial prefrontal cortex, but this effect was not affected by co-perfusion with muscimol (50 μM). On the other hand, local perfusion with PCP (100 and 500 μM) and MK-801 (10 and 50 μM), but not nomifensine (50 μM), reduced extracellular GABA levels in the medial prefrontal cortex. Co-perfusion with NMDA (1 mM) reduced the effects of PCP (500 μM) and MK-801 (50 μM) on extracellular GABA levels. These results suggest that PCP may facilitate dopamine release in the medial prefrontal cortex, at least in part, by the inhibition of GABA release via the antagonism of NMDA receptors. © 1998 Elsevier Science B.V.

Keywords: Phencyclidine; Dopamine; GABA (γ-aminobutyric acid); NMDA (*N*-methyl-D-aspartate); Medial prefrontal cortex; Microdialysis

1. Introduction

Since phencyclidine (1-(1-phenylcyclohexyl)piperidine; PCP), a major drug of substance abuse, has been reported to produce a variety of psychotic symptoms that closely resemble the positive and negative symptoms of schizophrenia (Allen and Young, 1978; Javitt and Zukin, 1991), PCP has been suggested to be useful for an experimental animal model of schizophrenia. A number of studies have focused on the physiological and biochemical effects of PCP on the central nervous system. Both systemic and local administration of PCP has been shown to increase the release and metabolism of dopamine preferentially in the medial prefrontal cortex compared to the striatum and the nucleus accumbens (Deutch et al., 1987; Rao et al., 1989; Hondo et al., 1994; Nishijima et al., 1996; Kuroki et al., unpublished data). The preferential activation of prefrontal dopamine neurons by PCP may be the basis for the pathophysiology of PCP-induced psychosis as well as schizophrenia, since the function of the prefrontal dopamine neuron systems has been suggested to be disturbed in schizophrenics (Weinberger, 1987; Deutch, 1992; Dolan et al., 1995). While the in vivo effects of PCP on dopamine release have been extensively studied in the striatum (Carboni et al., 1989; Chapman et al., 1990; Yonezawa et al., 1995) and the nucleus accumbens (Hernandez et al., 1988; McCullough and Salamone, 1992), the mechanism by which PCP preferentially increases prefrontal dopamine release remains to be determined.

Among the various sites of actions of PCP, the most fundamental one is the non-competitive antagonism of NMDA type of excitatory amino acid receptors (Wong et al., 1988; Javitt and Zukin, 1991). We previously suggested that the PCP-induced dopamine release in the medial prefrontal cortex may be attributable, at least in part, to the antagonistic action of PCP on NMDA receptors since dizocilpine ((+)-5-methyl-10,11-dihydroxy-5-*H*-dibenzo(a,d)cyclo-heptan-5,10-imine; MK-801), a more se-

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lective NMDA receptor antagonist than PCP, also increased dopamine release in the medial prefrontal cortex (Hondo et al., 1994; Schmidt and Fadayel, 1996). PCP and MK-801, unlike amphetamines, increased dopamine release in the medial prefrontal cortex in a tetrodotoxin-sensitive manner (Hondo et al., 1994). These data provided, in part, the basis for the so-called second generation glutamatergic hypothesis of schizophrenia in which a disturbed glutamatergic neurotransmission is considered to possibly affect the dopaminergic function in the prefrontal cortex of schizophrenics (Carlsson, 1989; Deutsch et al., 1989; Bunney et al., 1995).

The medial prefrontal cortex receives both dopaminergic projections from the ventral tegmental area (Thierry et al., 1973; Van Eden et al., 1987) and glutamatergic inputs from other cortical regions (Jay et al., 1992). NMDA receptors have been demonstrated to exist over the outer layers in the frontal cortex (Cotman et al., 1987), whereas prefrontal dopamine neurons terminate exclusively in the deep layers of the medial prefrontal cortex (Thierry et al., 1973; Van Eden et al., 1987). These data suggest that glutamatergic terminals may make indirect contacts with dopamine neurons in the prefrontal cortex. Therefore, PCP is unlikely to interact directly with dopamine neurons via NMDA receptors in the medial prefrontal cortex. A number of studies have suggested that γ-aminobutyric acid (GABA) interneurons may play an essential role in the interaction between glutamate and dopamine neurons in the prefrontal cortex. NMDA receptors may regulate cortical GABA release (Drejer et al., 1987; Drejer and Honoré, 1987), and $GABA_A$ receptors, which demonstrate a relatively high density in the prefrontal cortex (Bowery et al., 1987; De Blas et al., 1988), may regulate prefrontal dopamine release (Santiago et al., 1993b). Taken together, although the anatomical nature of these local circuits still remains unclear, a glutamate–GABA–dopamine interaction seems to exist within the medial prefrontal cortex. It is possible to hypothesize that PCP facilitates dopamine release in the medial prefrontal cortex by the inhibition of GABA release via the antagonism of NMDA receptors. To test this hypothesis, we examined the effects of local application of PCP and MK-801 on extracellular GABA levels in the medial prefrontal cortex of awake, freely moving rats, using in vivo microdialysis. Furthermore, we also investigated whether and how NMDA and the $GABA_A$ receptor agonist muscimol affect the PCP- and MK801-induced changes in extracellular levels of dopamine and GABA in the medial prefrontal cortex.

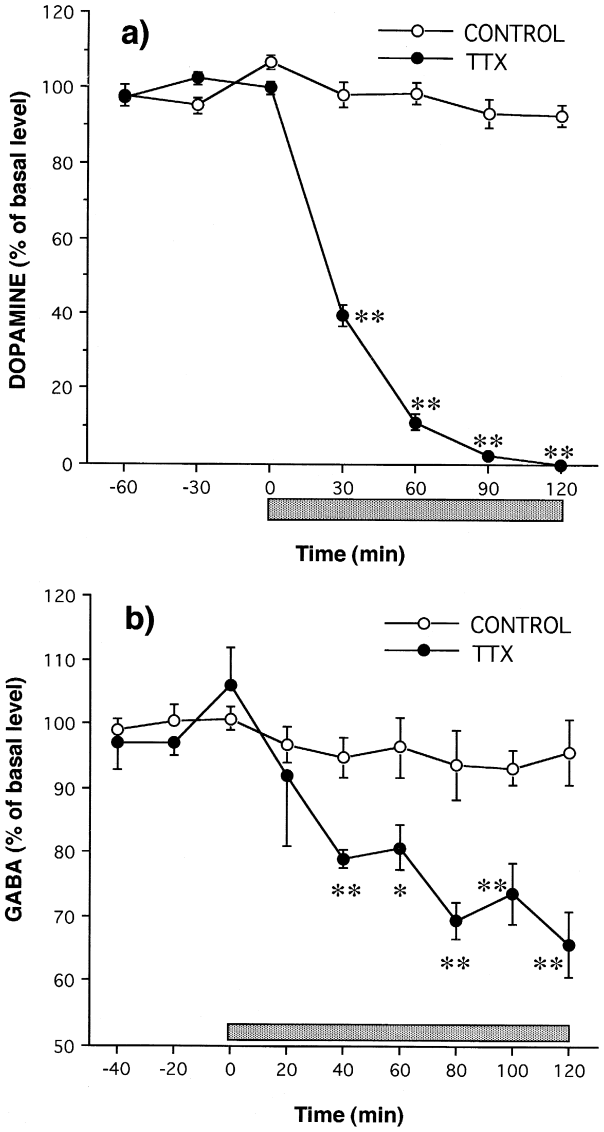


Fig. 1. (a) Effects of tetrodotoxin (TTX) infusion on the basal extracellular dopamine levels in the dialysates of the rat medial prefrontal cortex. The dotted bar indicates the time period of TTX infusion. Each point represents the mean ± S.E.M. (control, $n = 5$; TTX, $n = 15$) expressed as percentages of the pre-drug basal level. $^{*}P < 0.05$, $^{**}P < 0.01$ as compared to the control group. Two-way repeated measures ANOVA indicated a significant effect of treatment ($F(1,18) = 1866.95$, $P < 0.001$) and an interaction between treatment and time ($F(4,72) = 101.72$, $P < 0.001$) on extracellular dopamine levels in the dialysates. One-way ANOVA revealed that TTX significantly decreased extracellular dopamine levels in the dialysates during the 30–120 min after TTX perfusion ($P < 0.001$). (b) Effects of tetrodotoxin (TTX) infusion on the basal extracellular GABA levels in the dialysates of the rat medial prefrontal cortex. The dotted bar indicates the time period of TTX infusion. Each point represents the mean ± S.E.M. (control, $n = 5$; TTX, $n = 5$) expressed as percentages of the pre-drug basal level. $^{*}P < 0.05$, $^{**}P < 0.01$ as compared to the control group. Two-way repeated measures ANOVA indicated a significant effect of treatment ($F(1,8) = 17.77$, $P = 0.003$) and an interaction between treatment and time ($F(6,48) = 3.48$, $P = 0.006$) on extracellular GABA levels in the dialysates. One-way ANOVA revealed that TTX significantly decreased extracellular GABA levels in the dialysates during the 40–120 min after TTX perfusion ($P < 0.03$).

2. Materials and methods

2.1. Animals and surgery

Male Wistar rats weighing 250–350 g were housed three or four per cage at constant room temperature (22°C)

and relative humidity (50%) under a 12 h light–dark cycle (light: 8.00–20.00), and were provided with food and water ad libitum. The rats were anesthetized intraperitoneally (i.p.) with chloral hydrate (300 mg/kg), and the concentric dialysis probe (regenerated cellulose membrane, 3.0 mm in length, 0.22 mm in outer diameter, cut-off molecular weight 50,000; Eicom, Kyoto) was implanted into the left medial prefrontal cortex (coordinates: A +2.7 mm, L 0.7 mm from bregma, 4.2 mm below the dura surface) according to the stereotaxic atlas of Paxinos and Watson (1982). The rats were monitored until full recovery from the anesthesia for at least 20 h, after which the extracellular dopamine and GABA levels in the dialysates were then observed to be stabilized (no more than 10% variation; Yonezawa et al., unpublished data).

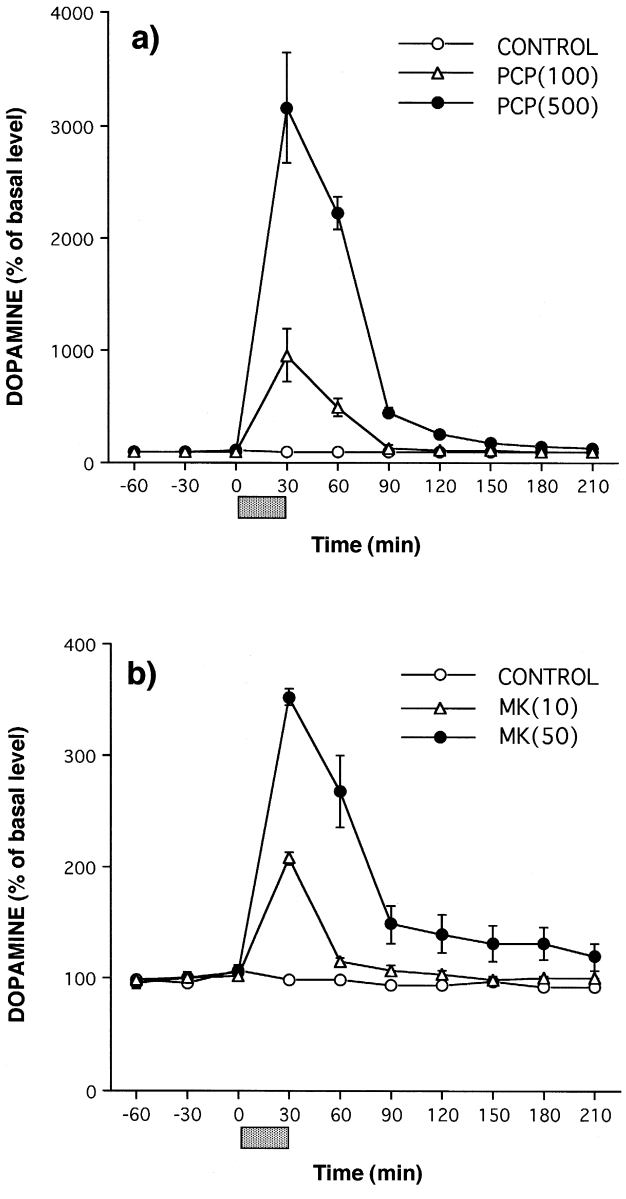


Fig. 2. (a) Effects of local perfusion with phencyclidine (PCP; 100 and 500 μM) via the dialysis probe into the rat medial prefrontal cortex on the basal extracellular dopamine levels in the dialysates of this region. The dotted bar indicates the time period of PCP perfusion for 30 min. Each point represents the mean ± S.E.M. of 5 rats in each group, expressed as percentages of the pre-drug basal level. Two-way repeated measures ANOVA revealed a significant effect of dose ($F(2,12) = 81.65$, $P < 0.001$) and an interaction between dose and time ($F(14,84) = 28.42$, $P < 0.001$) on extracellular dopamine levels in the dialysates. One-way ANOVA with post-hoc comparison, at each time point, indicated that 500 μM PCP significantly increased extracellular dopamine levels in the dialysates during the 30–210 min after PCP administration ($P < 0.003$). (b) Effects of local perfusion with dizocilpine (MK-801; 10 and 50 μM) via the dialysis probe into the rat medial prefrontal cortex on the basal extracellular dopamine levels in the dialysates of this region. The dotted bar indicates the time period of MK-801 perfusion for 30 min. Each point represents the mean ± S.E.M. of 5 rats in each group, expressed as percentages of the pre-drug basal level. Two-way repeated measures ANOVA revealed a significant effect of dose ($F(2,12) = 24.87$, $P < 0.001$) and an interaction between dose and time ($F(14,84) = 46.76$, $P < 0.001$) on extracellular dopamine levels in the dialysates. One-way ANOVA with post-hoc comparison, at each time point, indicated that 50 μM MK-801 significantly increased extracellular dopamine levels in the dialysates during the 30–120 min after MK-801 administration ($P < 0.02$).

2.2. Microdialysis

One day following the surgery, the implanted probe was perfused with an artificial cerebrospinal fluid (140 mM NaCl, 3.35 mM KCl, 1.15 mM $MgCl_2$, 1.26 mM $CaCl_2$, 1.2 mM Na_2HPO_4, and 0.3 mM NaH_2PO_4, at pH 7.3) at a flow rate of 1.5 μl/min and 1.8 μl/min for the assay of extracellular levels of dopamine and GABA in the dialysates, respectively. Extracellular dopamine and GABA levels in the dialysates were measured in separate experiments under the different experimental conditions, since basal extracellular dopamine levels in the dialysates of the medial prefrontal cortex were very low. After a 2 h period of equilibration, dialysis samples were collected every 30 min and every 20 min for the assay of extracellular levels of dopamine and GABA in the dialysates, respectively. After three consecutive samples were collected to determine the basal extracellular levels of dopamine and GABA in the dialysates, the drugs were administered locally into the medial prefrontal cortex via the dialysis probe. The in vitro recovery by the probe at 37°C were approximately 7.8 ± 0.1% for dopamine and 9.0 ± 0.1% for GABA, respectively. After the completion of each experiment, the rats were sacrificed with an overdose of chloral hydrate. The brains were removed and cut coronally along the puncture created by the probe using a cryostat. The location of the tip was then verified macroscopically. All experiments were carried out between 9.00 and 17.00. The procedures performed in this study were approved by the Committee of Ethics on Animal Experiments of the Faculty of Medicine, Kyushu University and were in strict accordance with the Guidelines for Animal Experiments of the Faculty of Medicine, Kyushu University and The Law

(No. 105) and Notification (No. 6) of the Japanese Government.

2.3. Assay of dopamine and GABA levels in dialysates

2.3.1. Assay of dopamine levels in dialysates

Extracellular dopamine levels in the dialysates were assayed by high performance liquid chromatography with electrochemical detection (HPLC-ECD). Each sample was automatically injected into the HPLC-ECD system by an on-line injector (CMA/160; Carnegie Medicin, Stockholm). The HPLC-ECD system consisted of an EP-10 pump (Eicom, Kyoto) set at a flow rate of 1.0 ml/min, a LC-4B electrochemical detector (Bioanalytical Systems, West Lafayette, IN) with a graphite carbon electrode set at +500 mV vs. an Ag/AgCl reference electrode (Eicom). Dopamine was separated by a reverse-phase column (Eicompak CA-sODS, 4.6 × 150 mm, Eicom). The mobile phase was 0.1 M phosphate buffer (pH 6.0) containing 500 mg/l sodium octanesulphonate, 50 mg/l Na_2EDTA and 25% (v/v) methanol.

2.3.2. Assay of GABA levels in dialysates

Extracellular GABA levels in the dialysates were analyzed using precolumn *o*-phthaldialdehyde derivertization followed by HPLC coupled with fluorometric detection, as described previously in detail (Hondo et al., 1995).

2.4. Drug treatments

Phencyclidine (1-(1-phenylcyclohexyl)piperidine hydrochloride; PCP) was synthesized according to the method of Maddox et al. (1965), then identified and examined for its purity by nuclear magnetic resonance imaging, mass spectroscopy and elementary analysis. Dizocilpine ((+)-5-methyl-10,11-dihydroxy-5-*H*-dibenzo(a,d)cyclo-heptan-5, 10-imine hydrogen maleate; MK801), nomifensine (Research Biochemicals, Natick, MA), *N*-methyl-D-aspartate (NMDA), muscimol (Sigma Chemical, St. Louis, MO) and tetrodotoxin (Wako Pure Chemical, Osaka) were all commercially obtained. All these drugs were dissolved in the artificial cerebrospinal fluid and were then locally administered into the rat medial prefrontal cortex via the dialysis probe. The pH of the solution of NMDA was adjusted to 7.3 with 1 N NaOH. The effect of the drugs was followed for another 120–180 min. The doses of PCP and MK-801 were chosen based on the findings of our previous study which showed them to produce significant increases in extracellular dopamine levels in the dialysates of the medial prefrontal cortex (Hondo et al., 1994). The doses of MK-801 were justified according to the in vitro data which indicated that the potency of MK-801 to NMDA receptors

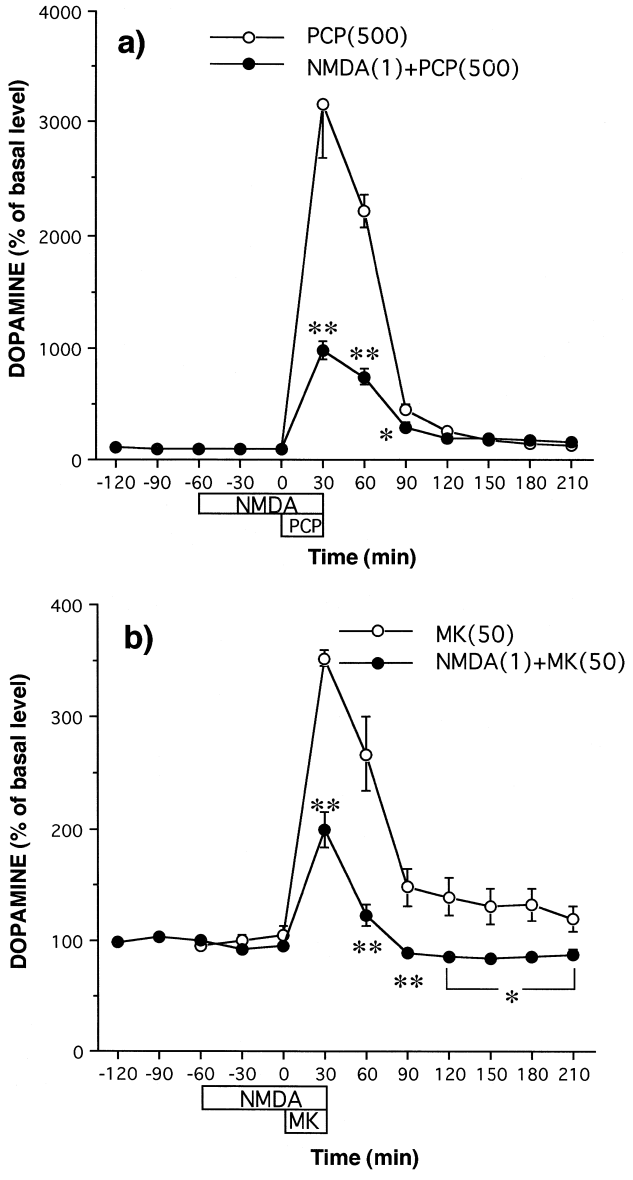


Fig. 3. (a) Effects of local perfusion with *N*-methyl-D-aspartate (NMDA; 1 mM) on the phencyclidine (PCP; 500 μM)-induced increases in extracellular dopamine levels in the dialysates of the rat medial prefrontal cortex. The bar indicates the time period of each drug treatment. Each point represents the mean ± S.E.M. of 5 rats in each group, expressed as percentages of the pre-drug basal level. $^{*}P < 0.05$, $^{**}P < 0.01$ as compared to the PCP-treated group. Two-way repeated measures ANOVA revealed a significant effect of treatment ($F(1,8) = 52.84$, $P < 0.001$) and an interaction between treatment and time ($F(7,56) = 21.82$, $P < 0.001$) on the extracellular dopamine levels in the dialysates. One-way ANOVA indicated that NMDA significantly attenuated the PCP-induced increases in extracellular dopamine levels in the dialysates during the 30–90 min after PCP administration ($P < 0.02$). (b) Effects of local perfusion with *N*-methyl-D-aspartate (NMDA; 1 mM) on the dizocilpine (MK-801; 50 μM)-induced increases in extracellular dopamine levels in the dialysates of the rat medial prefrontal cortex. The bar indicates the time period of each drug treatment. Each point represents the mean ± S.E.M. of 5 rats in each group, expressed as percentages of the pre-drug basal level. $^{*}P < 0.05$, $^{**}P < 0.01$ as compared to the MK-801-treated group. Two-way repeated measures ANOVA revealed a significant effect of treatment ($F(1,8) = 22.91$, $P = 0.001$) and an interaction between treatment and time ($F(7,56) = 16.8$, $P < 0.001$) on extracellular dopamine levels in the dialysates. One-way ANOVA indicated that NMDA significantly attenuated the MK-801-induced increases in extracellular dopamine levels in the dialysates during the 30–210 min after MK-801 administration ($P < 0.03$).

is approximately 10-fold higher than that of PCP ($K_i = 3$ nM for MK-801 vs. $K_i = 42$ nM for PCP; Wong et al., 1988). The dose of nomifensine was chosen based on the in vitro data which showed that the affinity of nomifensine for the dopamine transporters is approximately 10-fold higher than that of PCP ($K_i = 60$ nM for nomifensine vs. $K_i = 677$ nM for PCP; Giros et al., 1992).

2.5. Statistical analysis

The data were analyzed statistically using the two-way repeated measures analysis of variance (ANOVA) followed by Fisher's protected least significant difference post-hoc comparison. Treatment or dose was treated as a between-subject, and time was treated as a repeated measures variable. When the treatment or dose × time interaction term was statistically significant, one-way ANOVA followed by Scheffe *F*-test was done at each time point. All data are presented as the percentages of the pre-drug basal levels (calculated as the mean of three consecutive samples before drug administration). A probability (P) of less than 0.05 was considered to be significant in the present study.

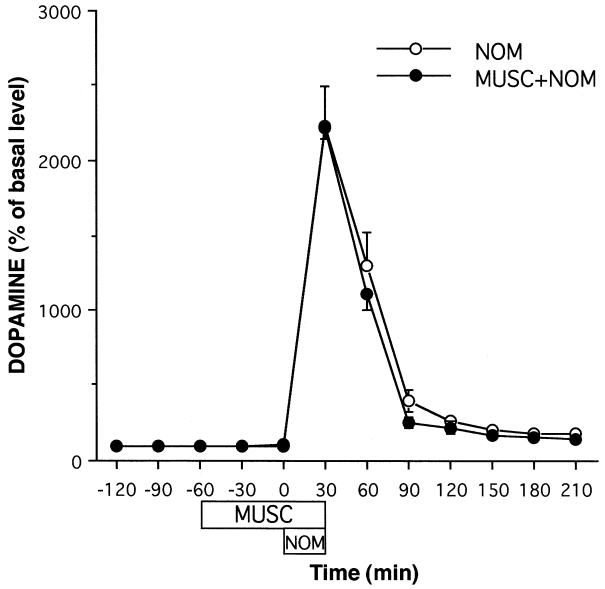


Fig. 5. Effects of local perfusion with muscimol (MUSC; 50 μM) on the nomifensine (NOM; 50 μM)-induced increases in extracellular dopamine levels in the dialysates of the rat medial prefrontal cortex. The bar indicates the time period of each drug treatment. Each point represents the mean ± S.E.M. of 5 rats in each group, expressed as percentages of the pre-drug basal level. Two-way repeated measures ANOVA failed to indicate that muscimol did affect the nomifensine-induced increases in extracellular dopamine levels in the dialysates.

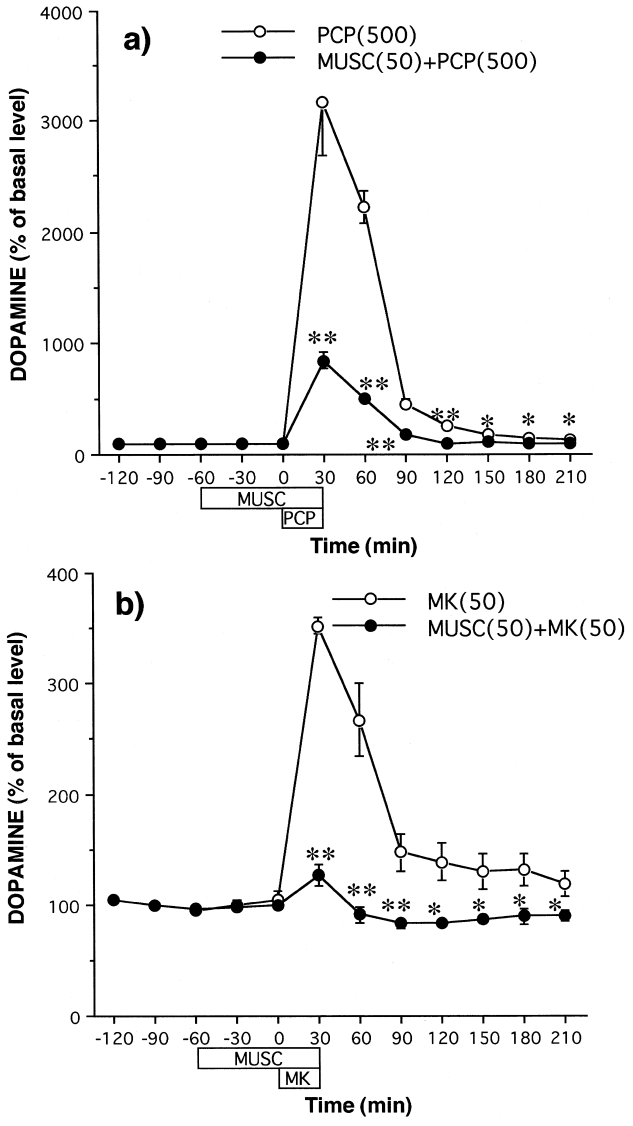


Fig. 4. (a) Effects of local perfusion with muscimol (MUSC; 50 μM) on the phencyclidine (PCP; 500 μM)-induced increases in extracellular dopamine levels in the dialysates of the rat medial prefrontal cortex. The bar indicates the time period of each drug treatment. Each point represents the mean ± S.E.M. of 5 rats in each group, expressed as percentages of the pre-drug basal level. $^{*}P < 0.05$, $^{**}P < 0.01$ as compared to the PCP-treated group. Two-way repeated measures ANOVA revealed a significant effect of treatment ($F(1,8) = 85.96$, $P < 0.001$) and an interaction between treatment and time ($F(7,56) = 24.67$, $P < 0.001$) on extracellular dopamine levels in the dialysates. One-way ANOVA indicated that muscimol significantly attenuated the PCP-induced increases in extracellular dopamine levels in the dialysates during the 30–210 min after PCP administration ($P < 0.03$). (b) Effects of local perfusion with muscimol (MUSC; 50 μM) on the dizocilpine (MK-801; 50 μM)-induced increases in extracellular dopamine levels in the dialysates of the rat medial prefrontal cortex. The bar indicates the time period of each drug treatment. Each point represents the mean ± S.E.M. of 5 rats in each group, expressed as percentages of the pre-drug basal level. $^{*}P < 0.05$, $^{**}P < 0.01$ as compared to the MK-801-treated group. Two-way repeated measures ANOVA revealed a significant effect of treatment ($F(1,8) = 32.75$, $P < 0.001$) and an interaction between treatment and time ($F(7,56) = 43.03$, $P < 0.001$) on extracellular dopamine levels in the dialysates. One-way ANOVA indicated that muscimol significantly attenuated the MK-801-induced increases in extracellular dopamine levels in the dialysates during the 30–210 min after MK-801 administration ($P < 0.048$).

3. Results

3.1. Characterization of basal extracellular levels of dopamine and GABA

The basal extracellular levels of dopamine and GABA in the dialysates of the medial prefrontal cortex were 13.1 ± 0.8 fmol/45 μl/30 min and 418.4 ± 14.5 fmol/36 μl/20 min (mean ± S.E.M., not corrected for in vitro recovery; $n = 80$ and $n = 48$), respectively.

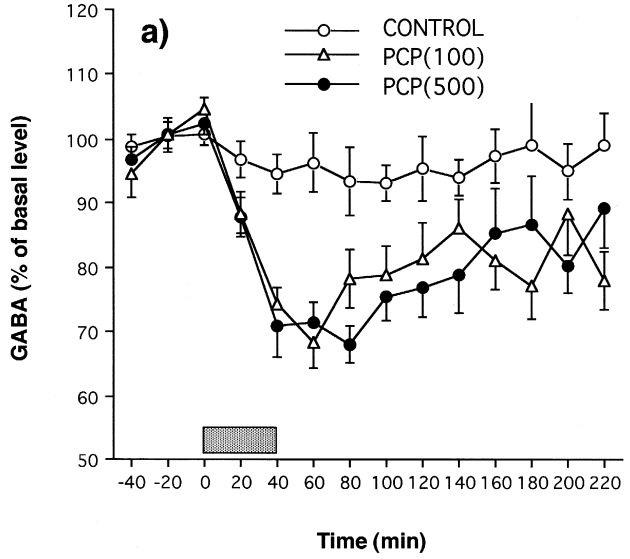
In the control group of rats, extracellular levels of both dopamine and GABA in the dialysates fluctuated by no more than 10% of the baseline values during the period of the experiment, and either time itself or syringe-switching procedures had no significant effect on extracellular dopamine and GABA levels (Figs. 1, 2, 6 and 7). Continuous infusion of tetrodotoxin (10 μM) into the medial prefrontal cortex via the dialysis probe, completely abolished dopamine levels in the dialysates (Fig. 1a) and also significantly decreased GABA levels in the dialysates from the control levels (Fig. 1b).

3.2. Effects of NMDA and muscimol on the PCP- and MK-801- induced increases in extracellular dopamine levels

Local administration of PCP (100 and 500 μM) into the medial prefrontal cortex for 30 min significantly increased extracellular dopamine levels in the dialysates of this region (Fig. 2a). Local perfusion with MK-801 (10 and 50 μM) for 30 min also significantly increased extracellular dopamine levels in the dialysates of the medial prefrontal cortex (Fig. 2b).

After perfusing with NMDA (1 mM) alone for 60 min, PCP (500 μM) or MK-801 (50 μM) was added to the perfusion buffer for 30 min. Co-perfusion with NMDA (1 mM) significantly reduced the PCP- and MK-801-induced increases in extracellular dopamine levels in the dialysates (Fig. 3a and b). Local perfusion with NMDA (1 mM) alone for 90 min, had no effect on extracellular dopamine levels in the dialysates of the medial prefrontal cortex (data not shown).

After perfusing muscimol (50 μM) alone for 60 min, PCP (500 μM) or MK-801 (50 μM) was added to the perfusion buffer for 30 min. Co-perfusion with muscimol (50 μM) significantly reduced the PCP- and MK-801-induced increases in extracellular dopamine levels in the dialysates of the medial prefrontal cortex (Fig. 4a and b). However, local perfusion with muscimol (50 μM) alone had no effect on extracellular dopamine levels in the dialysates (data not shown).



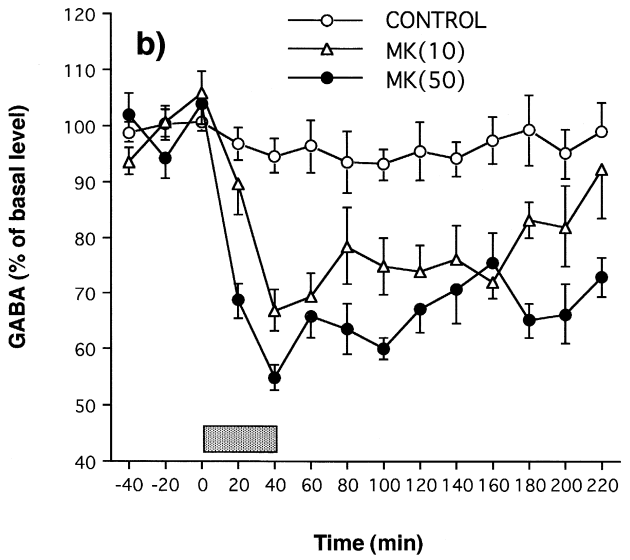


Fig. 6. (a) Effects of local perfusion with phencyclidine (PCP; 100 and 500 μM) via the dialysis probe into the rat medial prefrontal cortex on the basal extracellular GAB213A levels in the dialysates of this region. The dotted bar indicates the time period of PCP perfusion for 40 min. Each point represents the mean ± S.E.M. of 5 rats in each group, expressed as percentages of the pre-drug basal level. Two-way repeated measures ANOVA revealed a significant effect of dose ($F(2,12) = 8.21$, $P = 0.005$) and an interaction between dose and time ($F(22,132) = 2.38$, $P = 0.001$) on extracellular GABA levels in the dialysates. One-way ANOVA with post-hoc comparison, at each time point, indicated that 500 μM PCP significantly decreased extracellular GABA levels in the dialysates during the 20–100 min after PCP administration ($P < 0.01$). (b) Effects of local perfusion with dizocilpine (MK-801; 10 and 50 μM) via the dialysis probe into the rat medial prefrontal cortex on the basal extracellular GABA levels in the dialysates of this region. The dotted bar indicates the time period of MK-801 perfusion for 40 min. Each point represents the mean ± S.E.M. of 5 rats in each group, expressed as percentages of the pre-drug basal level. Two-way repeated measures ANOVA revealed a significant effect of dose ($F(2,12) = 23.35$, $P < 0.001$) and an interaction between dose and time ($F(22,132) = 2.96$, $P < 0.001$) on extracellular GABA levels in the dialysates. One-way ANOVA with post-hoc comparison, at each time point, indicated that 50 μM MK-801 significantly decreased extracellular GABA levels in the dialysates during the 20–220 min after MK-801 administration ($P < 0.03$).

3.3. Effects of muscimol on the nomifensine-induced changes in extracellular dopamine levels

Local perfusion of nomifensine (50 μM) into the medial prefrontal cortex for 30 min significantly increased extracellular dopamine levels in the dialysates of this region (Fig. 5). After perfusing muscimol (50 μM) alone for 60 min, nomifensine (50 μM) was added to the perfusion buffer for 30 min. Co-perfusion with muscimol (50 μM) did not affect the nomifensine-induced increases in extracellular dopamine levels in the dialysates of the medial prefrontal cortex (Fig. 5).

3.4. Effects of NMDA on the PCP- and MK-801-induced changes in extracellular GABA levels

Local perfusion with PCP (100 and 500 μM) into the medial prefrontal cortex for 40 min significantly decreased extracellular GABA levels in the dialysates of this region (Fig. 6a). Local perfusion with MK-801 (10 and 50 μM) for 40 min also significantly decreased extracellular GABA levels in the dialysates of the medial prefrontal cortex (Fig. 6b).

After perfusing NMDA (1 mM) alone was perfused for 40 min, PCP (500 μM) or MK-801 (50 μM) was added to the perfusion buffer for 40 min. Co-perfusion with NMDA (1 mM) significantly attenuated the PCP- and MK801-induced decreases in extracellular GABA levels in the dialysates (Fig. 7a and b). When perfused alone for 80 min, NMDA (1 mM) produced a modest increase by 15% of the baseline in extracellular GABA levels in the dialysates during the first 40 min period of the perfusion, but this effect was not statistically significant.

3.5. Effects of nomifensine on extracellular GABA levels

Local perfusion with nomifensine (50 μM) into the medial prefrontal cortex for 40 min had no effect on extracellular GABA levels in the dialysates of the medial prefrontal cortex (data not shown).

4. Discussion

The major findings of this study were as follows: (1) local administration of PCP and MK-801, a selective non-competitive NMDA receptor antagonist, increased dopamine release but decreased GABA release in the medial prefrontal cortex, (2) co-perfusion with the $GABA_A$

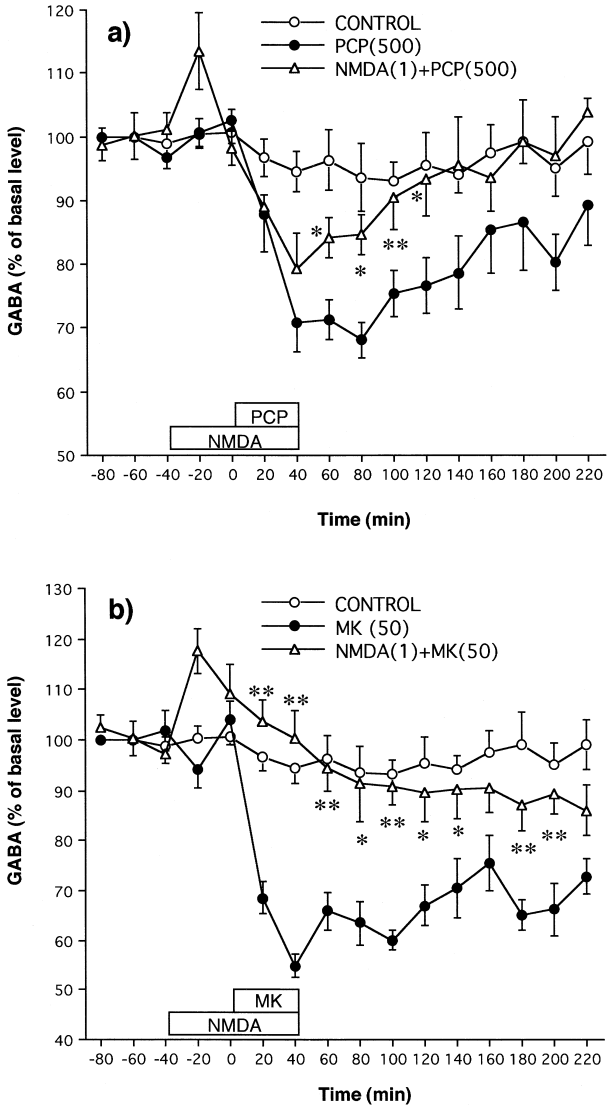


Fig. 7. (a) Effects of local perfusion with *N*-methyl-D-aspartate (NMDA; 1 mM) on the phencyclidine (PCP; 500 μM)-induced decreases in extracellular GABA levels in the dialysates of the rat medial prefrontal cortex. The bar indicates the time period of each drug treatment. Each point represents the mean ± S.E.M. of 4–5 rats in each group, expressed as percentages of the pre-drug basal level. $^{*}P < 0.05$, $^{**}P < 0.01$ as compared to the PCP-treated group. Two-way repeated measures ANOVA revealed a significant effect of treatment ($F(2,11) = 5.31$, $P = 0.02$) and an interaction between treatment and time ($F(22,121) = 2.21$, $P = 0.004$) on extracellular GABA levels in the dialysates. One-way ANOVA indicated that NMDA significantly reduced the PCP-induced decreases in extracellular GABA levels in the dialysates during the 60–120 min after PCP administration ($P < 0.04$). (b) Effects of local perfusion with *N*-methyl-D-aspartate (NMDA; 1 mM) on the dizocilpine (MK-801; 50 μM)-induced decreases in extracellular GABA levels in the dialysates of the rat medial prefrontal cortex. The bar indicates the time period of each drug treatment. Each point represents the mean ± S.E.M. of 5 rats in each group, expressed as percentages of the pre-drug basal level. $^{*}P < 0.05$, $^{**}P < 0.01$ as compared to the MK-801-treated group. Two-way repeated measures ANOVA revealed a significant effect of treatment ($F(2,12) = 18.82$, $P < 0.001$) and an interaction between treatment and time ($F(22,132) = 5.45$, $P < 0.001$) on the extracellular GABA levels in the dialysates. One-way ANOVA indicated that NMDA significantly reduced the MK-801-induced decreases in extracellular GABA levels in the dialysates during the 20–140 min and the 180–200 min after MK-801 administration ($P < 0.04$).

receptor agonist muscimol attenuated the PCP- and MK-801-induced increases in dopamine release, and (3) co-perfusion with NMDA reduced the effects of PCP and MK-801 on dopamine and GABA release, while NMDA alone had no effect on basal release of dopamine and GABA in the medial prefrontal cortex. These results support, at least in part, the hypothesis that PCP may facilitate dopamine release in the medial prefrontal cortex by the inhibition of GABA release via the antagonism of NMDA receptors.

In agreement with in vivo microdialysis studies by others (Moghaddam et al., 1990; Santiago et al., 1993a; Bourdelais and Deutch, 1994; Nishijima et al., 1994), we observed that tetrodotoxin almost completely abolished basal extracellular dopamine levels and partially, but significantly, decreased basal extracellular GABA levels in the medial prefrontal cortex. Basal extracellular levels of dopamine in the rat prefrontal cortex appear to be Ca^{2+}-dependent (Moghaddam et al., 1990; Santiago et al., 1993a; Feenstra et al., 1995). In a preliminary experiment, we confirmed that basal extracellular GABA levels in the medial prefrontal cortex were partially, but significantly, reduced by perfusion with a Ca^{2+}-free buffer containing high Mg^{2+} (Yonezawa, unpublished data). Therefore, basal extracellular levels of GABA as well as dopamine in the medial prefrontal cortex, as determined by in vivo microdialysis may, in part, represent a neuronal origin. However, previous reports from other laboratories as well as our laboratory have reported that basal extracellular levels of GABA in the striatum were tetrodotoxin- and Ca^{2+}-independent in both anesthetized and unanesthetized rats (Drew et al., 1989; Westerink and De Vries, 1989; Hondo et al., 1995). These discrepancies may be attributable to the differences in the experimental conditions such as the usage of anesthesia, the recovery time from surgery, and the ionic composition including the pH of the perfusion medium. The characteristics of basal extracellular GABA levels may also differ between the brain regions (striatum vs. prefrontal cortex). The majority of GABA neurons in the prefrontal cortex are considered to be interneurons (Fairen et al., 1984; Houser et al., 1984; Rétaux et al., 1993), while the majority of GABA neurons in the striatum seem to be projective neurons, with a small population of GABA interneurons (Cowan et al., 1990; Kita et al., 1990; Smith and Bolam, 1990. Therefore, extracellular GABA levels in the medial prefrontal cortex may reflect the release from both the axon terminals and somatodendrites, whereas extracellular GABA in the striatum may be predominantly derived from the somatodendrites (Bourdelais and Deutch, 1994). Moreover, in this study, PCP decreased basal extracellular GABA levels in the medial prefrontal cortex. In contrast, PCP has been shown to either increase or have no effect on basal extracellular GABA levels in the striatum of anesthetized or unanesthetized rats, respectively (Lillrank et al., 1994; Hondo et al., 1995). The regional difference in the origin of extracellular GABA may also account for this discrepancy.

The present study provided the first in vivo evidence for the regulation of GABA release by the NMDA receptors in the medial prefrontal cortex. The NMDA receptor antagonist PCP and MK-801 decreased basal GABA release, while NMDA alone had no significant effect on basal GABA release in the medial prefrontal cortex. These results suggest that NMDA receptors may regulate the neuronal activity of GABA interneurons in the medial prefrontal cortex under tonic excitatory control. The excitatory amino acid receptors have also been shown to regulate cortical GABA release in vitro since NMDA, L-glutamate, quisqualate and kainate potently stimulate [^{3}H] GABA release from cultured GABA neurons of the mouse cerebral cortex (Drejer et al., 1987; Drejer and Honoré, 1987). Since glutamate neurons in the prefrontal cortex have been demonstrated to project to the ventral tegmental area (Sesack et al., 1989; Kalivas, 1993), some of the glutamate neurons may regulate the neuronal activity of GABA interneurons by recurrent collaterals (Pirot et al., 1992). Taken together, the blockade of NMDA receptors by PCP and MK-801 may inhibit the neuronal activity of GABA interneurons and decrease GABA release in the medial prefrontal cortex. However, this notion remains inconclusive in this study since NMDA itself attenuated the effect of the non-competitive NMDA receptor antagonist PCP and MK-801 on GABA release, as well as dopamine release, as discussed later. If mediated via the non-competitive antagonism of NMDA receptors, the effects of PCP and MK-801 on GABA release would be unaffected by exogenous NMDA receptor agonists. It seems difficult to interpret this finding at present. A possible explanation is that the preceding perfusion with NMDA alone prior to co-perfusion with PCP or MK-801 may influence the in vivo binding of NMDA receptors with these receptor antagonists, while endogenous excitatory amino acids such as glutamate may fully occupy NMDA receptors under the baseline conditions. The mechanism by which NMDA receptors regulate GABA release may be an intricate one rather than a simple hypothesis such as tonic excitatory control by postsynaptic NMDA receptors on GABA interneurons. The dose of NMDA (1 mM) used in this study might be so high as to produce an excitotoxic effect on GABA and dopamine neurons and interfere with the effects of the NMDA receptor antagonists. However, although histological verification was not performed in this study, it seems unlikely since the administration of NMDA alone produced neither convulsive seizure nor behavioral abnormality in rats. The diffusion of NMDA through the probe membrane into the extracellular space may be low (less than 100 μM), according to the in vitro recovery by the probe (less than 10%). Nevertheless, even at such low concentrations, an interaction between NMDA and PCP or MK-801 via other sites of action than NMDA receptors can not be excluded. Further studies are needed to examine the effects of NMDA receptor agonists and antagonists at different doses on prefrontal GABA release.

It should also be noted that co-perfusion with NMDA completely blocked the effect of MK-801 on GABA release, while NMDA partially attenuated the effect of PCP on GABA release (Fig. 7). This suggests that the effect of PCP on GABA release may be attributable to not only the NMDA receptor-mediated mechanism but also other mechanism(s). PCP has been known to have considerable affinities for dopamine transporters, sigma receptors and voltage-dependent K^+ channels other than NMDA receptors (Wong et al., 1988; Maurice et al., 1991; Javitt and Zukin, 1991). Since prefrontal dopamine neuron terminals have been known to form synapses with GABA interneurons in the prefrontal cortex (Sesack et al., 1995) while extracellular dopamine in the synaptic clefts has been shown to modulate prefrontal GABA release in vivo (Beauregard and Ferron, 1991; Bernath and Zigmond, 1989; Rétaux et al., 1991; Grobin and Deutch, 1995), the inhibition of dopamine reuptake by PCP might contribute to the decrease in prefrontal GABA release. However, this seems unlikely since, in this study, the dopamine reuptake inhibitor nomifensine increased dopamine release but had no effect on GABA release in the medial prefrontal cortex. Another possibility is that the action of PCP on sigma receptors influences GABA release since haloperidol, which has a high affinity for sigma receptors (McCann and Su, 1990), has been reported to decrease GABA release in the medial prefrontal cortex (Bourdelais and Deutch, 1994). However, this seems unlikely since MK-801, which specifically binds to NMDA receptors but has less affinity for sigma receptors (Wong et al., 1988), decreased GABA release in the medial prefrontal cortex. Thus, the PCP-induced decreases in GABA release in the medial prefrontal cortex may be mainly due to the antagonism of NMDA receptors on GABA interneurons.

The stimulation of NMDA receptors has been demonstrated to cause excitation of the postsynaptic membrane neurons (Collinge and Lester, 1989). However, in this study, NMDA (1 mM) alone did not increase dopamine release in the medial prefrontal cortex while co-perfusion with NMDA attenuated the PCP- and MK-801-induced increases in dopamine release. In addition, local application of NMDA (20 and 100 μM) did not increase dopamine release in the medial prefrontal cortex but did decrease dopamine release at 100 μM (Jedema and Moghaddam, 1996), however, the change was not statistically significant. Feenstra et al. (1995) have also reported that local application of 1 mM NMDA decreased dopamine release in the medial prefrontal cortex and also completely reversed the prefrontal dopamine release induced by D-2-amino-5-phosphonopentanoic acid (AP-5), a competitive NMDA receptor antagonist, while low concentrations of NMDA (0.1, 1 and 10 μM) had no effect on dopamine release in the medial prefrontal cortex. On the other hand, local application of MK-801 did not stimulate the firing rate of the midbrain dopamine neurons (Freeman and Bunney, 1984; Zhang et al., 1992), whereas systemic administration of PCP or MK-801 inhibited the firing rate of the non-dopaminergic neurons, possibly GABA-containing inhibitory interneurons in the midbrain (Zhang et al., 1993). It is therefore unlikely that NMDA receptors directly regulate prefrontal dopamine release. Considering the present results in which both PCP and MK-801 decreased GABA release together with an increase in dopamine release in the medial prefrontal cortex, the PCP- and MK-801-induced inhibition of GABA release via the antagonism of NMDA receptors is considered to possibly facilitate prefrontal dopamine release secondarily. These considerations may be supported by the present results that NMDA attenuated the effects of PCP and MK-801 on the release of not only GABA but also dopamine in the medial prefrontal cortex.

The precise mechanism of such a GABA-dopamine interaction in the prefrontal cortex has yet to be elucidated. GABA interneurons seem to regulate the prefrontal dopamine release at least in part, via $GABA_A$ receptors since co-perfusion with the $GABA_A$ receptor agonist muscimol reduced the PCP- and MK-801-induced dopamine release in the medial prefrontal cortex but had no effect on the nomifensine-induced dopamine release in this region. In addition, the $GABA_A$/benzodiazepine receptor agonist diazepam has also been shown to attenuate the increases in dopamine metabolism in the prefrontal cortex following systemic administration of PCP and MK-801 (Bowers and Hoffman, 1989; Bowers and Morton, 1992). Muscimol alone had no effect on prefrontal dopamine release while the $GABA_A$ receptor antagonist picrotoxin has been reported to increase dopamine release in the prefrontal cortex (Santiago et al., 1993b). Therefore, $GABA_A$ receptors may tonically inhibit dopamine release in the medial prefrontal cortex. Such a GABA-dopamine interaction in the medial prefrontal cortex via $GABA_A$ receptors may play a critical role in the mechanism of PCP- and MK-801-induced prefrontal dopamine release. However, it should be noted that, although the doses of MK-801 used in this study would be equivalent to or more potent than those of PCP for the antagonism of NMDA receptors, PCP increased prefrontal dopamine release to a greater extent than MK-801 (Fig. 2), as previously reported (Hondo et al., 1994). In addition, muscimol partially attenuated the PCP-induced prefrontal dopamine release (Fig. 4a), while the effects of nomifensine, a dopamine reuptake inhibitor, on dopamine release were the same in the presence or absence of muscimol (Fig. 5). These results suggest that PCP-induced prefrontal dopamine release may be due to not only the NMDA and GABA receptor-mediated mechanism but also other mechanism(s) such as interactions with dopamine transporters, sigma receptors and voltage-dependent K^+ channels (Wong et al., 1988; Maurice et al., 1991; Javitt and Zukin, 1991). Further studies await to elucidate the contribution of all these effects to PCP-induced prefrontal dopamine release. Despite considerable limitations, however, the glutamate–GABA–dopamine in-

teraction in the medial prefrontal cortex, as suggested by the present results, seems most likely to account for the preferential increase by PCP in prefrontal dopamine release.

Recently, mesocortical dopamine neurons have been demonstrated to inhibit the activity of glutamate neurons in the prefrontal cortex both directly (via synaptic contact with pyramidal cells) and indirectly (via GABA interneurons) (Penit-Soria et al., 1987; Rétaux et al., 1991; Pirot et al., 1992). It is likely that such dopamine neurons inhibit glutamate neurons in the medial prefrontal cortex, and vice versa. If a decrease in GABA neurotransmission in the prefrontal cortex activates these cortical glutamate neurons, the glutamatergic projection to the ventral tegmental area could facilitate the neuronal activity of mesocortical dopamine neurons (Pirot et al., 1992; Kalivas, 1993). Such a cortico–meso–cortical circuit might also partially account for the present results.

It should be noted that both GABA and glutamate neurons have been demonstrated to modulate the stress-induced activation of prefrontal dopamine neurons (Kaneyuki et al., 1991; Morrow et al., 1993). The interactions between these neurons may therefore play an important role in the emotional and cognitive functions. An excessive dopaminergic activity in the prefrontal cortex has been suggested to impair the cognitive functions (Murphy et al., 1996). The preferential activation of prefrontal dopaminergic activity by PCP, as a consequence of the inhibition of glutamate and GABA neurotransmission, may be the basis for certain aspects of the symptomatology of PCP-induced psychosis; e.g. alterations in perception (Krystal et al., 1994).

In conclusion, local perfusion via the dialysis probe into the medial prefrontal cortex with PCP and MK-801, a selective non-competitive NMDA receptor antagonist, increased extracellular dopamine levels, and these increases were attenuated by co-perfusion with either NMDA or the $GABA_A$ receptor agonist muscimol. On the other hand, local perfusion with PCP and MK-801 decreased extracellular GABA levels in the medial prefrontal cortex. Coperfusion with NMDA reduced the PCP- and MK-801-induced decreases in extracellular GABA levels. These results indicate that the PCP-induced dopamine release in the medial prefrontal cortex is accompanied by the inhibition of GABA release via the antagonism of NMDA receptors.

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