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Short communication

Potentiation of phencyclidine-induced dopamine release in the rat striatum by the blockade of dopamine D_2 receptor

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Abstract

Local perfusion with phencyclidine (PCP) increased extracellular dopamine levels in the rat striatum in a dose-dependent manner, as measured by in vivo microdialysis. While pretreatment with SCH 23390, a selective dopamine D_1 receptor antagonist, had no significant effect on PCP-induced increases in extracellular dopamine levels, pretreatment with YM-09151-2 (*cis-N*-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide), a selective dopamine D_2 receptor antagonist, markedly potentiated the effect of PCP. These results suggest that the blockade of dopamine D_2 presynaptic autoreceptors strongly potentiates the PCP-induced dopamine release in the striatum.

Keywords: Phencyclidine; Dopamine D_1 receptor antagonist; Dopamine D_2 receptor antagonist; Striatum, rat; Microdialysis

1. Introduction

Phencyclidine (PCP), which is one of the major commonly abused drugs, has been reported to induce a variety of psychotic reactions that closely resemble the broad symptomatology of schizophrenia (Javitt and Zukin, 1991). Although the exact mechanisms by which PCP elicits psychotomimetic effects are unknown, various behavioral, electrophysiological and neurochemical studies have shown that PCP interacts with central dopaminergic systems. On the other hand, PCP has been known to act as a potent non-competitive antagonist of the *N*-methyl-D-aspartate (NMDA) type, excitatory amino acid receptor. Several studies have suggested that the behavioral effects of PCP may be mediated by non-competitive antagonism of NMDA receptors (Tricklebank et al., 1989). An interaction of PCP with NMDA receptors may explain different characteristics between PCP-induced psychosis and amphetamine-induced psychosis.

Some reports regarding the effects of neuroleptics on PCP-induced abnormal behaviors in experimental animals suggest an interaction between dopamine receptors and actions of PCP (Murray and Horita, 1978; Tsutsumi et al., 1995). However, it still remains equivocal which subtypes of dopamine receptors are involved in the interaction.

To our knowledge, there have been few in vivo neurochemical studies on the effects of neuroleptics on PCP-induced dopamine release. In this study, we investigated the effect of selective dopamine D_1 and D_2 receptor antagonists on PCP-induced increases in extracellular dopamine levels in the striatum of awake, freely moving rats by using in vivo microdialysis technique. It is possible that systemic administered PCP causes the release of dopamine in the striatum through indirect actions mediated by sites other than the dopamine terminal region. To exclude the indirect actions, we examined the effect of local administration of PCP into the striatum via the dialysis probe.

2. Materials and methods

Male Wistar rats weighing 250–350 g were used in all experiments. The rats were anesthetized with chloral hydrate (400 mg/kg i.p.), and concentric dialysis probes (regenerated cellulose membrane, 3 mm in length and 0.22 mm in outer diameter, molecular weight cut-off 50 000) were implanted into the left striatum

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(coordinates: A +1.0 mm, L 2.5 mm from bregma, 5.0 mm below dura surface).

After at least 20 h recovery time following surgery, the implanted probes were 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, 0.3 mM NaH_2PO_4, pH 7.3) at a flow rate of 2.0 μl/min. After a 2 h period of equilibration, dialysis samples were collected every 20 min and dopamine levels in dialysates were assayed by high-performance liquid chromatography with electrochemical detection as previously described (Hondo et al., 1994). After three consecutive samples were collected to determine the basal level of dopamine, the drugs were administered. In vitro recovery of dopamine was approximately 15%. After completion of each experiment, location of the probe was verified by macroscopic examination.

PCP, dissolved in the perfusion medium, was applied into the striatum through the dialysis probe for 20 min. SCH 23390 (Research Biochemicals, Natick, MA, USA) was used as a selective dopamine D_1 receptor antagonist and YM-09151-2 (*cis-N*-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide) (Yamanouchi Pharmaceutical Co., Tokyo, Japan) was used as a selective dopamine D_2 receptor antagonist ($K_i = 0.1$ nM; Terai et al., 1983). SCH 23390 was dissolved in saline and YM-09151-2 was dissolved in 0.1 N formic acid. Both drugs were administered intraperitoneally (SCH 23390, 0.1 mg/kg; YM-09151-2, 0.5 mg/kg) 40 min prior to the perfusion with PCP (50 μM). The doses of dopamine receptor antagonists were chosen on the basis of the previous studies showing them to alter the behavioral effects of PCP and its related compounds (Tsutsumi et al., 1995 for SCH 23390; Kuribara and Uchihashi, 1993 for YM-09151-2).

The average level of dopamine in the last three samples before treatment was taken as the basal level, and all samples were expressed as percentages of the basal level. The area under the curve (AUC) of extracellular dopamine levels was calculated by the trapezoidal method from the absolute net increase above the basal level during the period from 40 min to 200 min. All data except for the AUC data were analyzed statistically using a two-way repeated measures analysis of variance (ANOVA) followed by Scheffe *F*-test. The AUC data were analyzed using one-way ANOVA followed by Scheffe *F*-test.

3. Results

The basal level of dopamine was 15.4 ± 1.5 pg/40 μl (mean ± S.E.M., not corrected for in vitro recovery, $n = 42$). Local perfusion with PCP (1, 10, 50, 100 and 500 μM) into the striatum increased extracellular dopamine levels in a dose-dependent manner (Fig. 1). The maximal increases were observed 20 min after PCP perfusion for all doses, and returned to the basal level within approximately 40 min after the end of perfusion with PCP. SCH 23390 alone had no significant effects on extracellular dopamine levels, whereas YM-09151-2 alone increased extracellular dopamine levels about two-fold compared to the control group of saline-treated rats for at least 3 h after the injection.

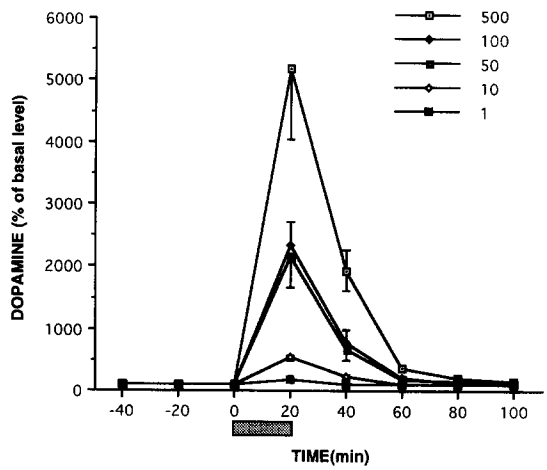

Fig. 1. Time course of extracellular levels of dopamine following intrastriatal perfusion with phencyclidine (PCP; 1, 10, 50, 100 and 500 μM) via the dialysis probe. The dotted bar indicates the period of PCP perfusion for 20 min. Each point represents the mean ± S.E.M. of 4 or 5 rats in each group.

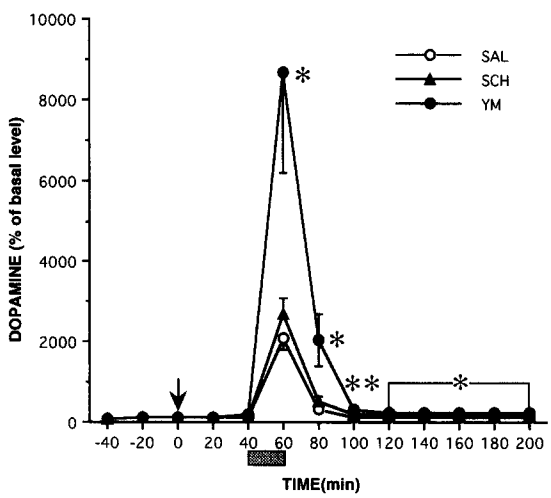

Fig. 2. Effect of SCH 23390 (SCH) and YM-09151-2 (YM) on phencyclidine (PCP)-induced increases in extracellular levels of dopamine in the rat striatum. SCH (0.1 mg/kg) and YM (0.5 mg/kg) were injected intraperitoneally 40 min before the intrastriatal perfusion with 50 μM PCP (denoted by the arrow). The dotted bar indicates the period of PCP perfusion for 20 min. Each point represents the mean ± S.E.M. of 4 rats in each group. ** $P < 0.01$, * $P < 0.05$ vs. control group of saline-pretreated rats. The data were analyzed by two-way repeated measures ANOVA with factors of group and time. To assess further differences among groups, one-way ANOVA followed by Scheffe *F*-test was done at each time point.

Pretreatment with YM-09151-2 markedly potentiated the PCP-induced increases in extracellular dopamine levels (Fig. 2). Maximum increases in extracellular dopamine levels of the YM-09151-2-pretreated group were about 4 times higher than those of saline-pretreated group. Pretreatment with SCH did not cause any significant effect on PCP-induced increases in extracellular dopamine levels compared to the saline-pretreated group (Fig. 2). The AUC (mean ± S.E.M. pg/160 min) for extracellular dopamine levels of the YM-09151-2-pretreated PCP group (742.1 ± 72.2) was significantly higher than both that of the YM-09151-2 alone group (81.2 ± 28.9) and that of the saline-pretreated PCP group (323.4 ± 73.2) ($P < 0.01$).

4. Discussion

The most striking finding in this study is that YM-09151-2, a selective dopamine D_2 receptor antagonist, but not SCH 23390, a selective dopamine D_1 receptor antagonist, markedly potentiated PCP-induced increases in extracellular dopamine levels in the striatum in vivo. Even though YM-09151-2 itself increased extracellular dopamine levels in the striatum most likely by the blockade of presynaptic dopamine D_2 receptors, the AUC of the YM-09151-2-pretreated PCP group was still much higher than the additive amount of the AUC of the YM-09151-2 alone group and the saline-pretreated PCP group. Therefore, the effect of YM-09151-2 on PCP-induced increases in extracellular dopamine levels seems to be not only additive but also synergistic. These results suggest that the blockade of dopamine D_2 presynaptic autoreceptors strongly potentiates the PCP-induced dopamine release in the striatum.

The blockade of dopamine D_2 receptors has been also shown to potentiate amphetamine-induced dopamine release (Sharp et al., 1986). Since dopamine D_2 autoreceptors have been known to regulate dopamine synthesis, it has been suggested that the blockade of dopamine D_2 autoreceptors increases the intraneuronal pool of newly synthesized dopamine which is preferentially released by amphetamine, and then more dopamine can be available for amphetamine to release (Sharp et al., 1986). The similar mechanism may also account for the present findings.

However, it is unlikely that PCP shares the mechanism for dopamine release with amphetamine. Although PCP may have various sites of action in the central nervous systems, the mechanism of PCP-induced dopamine release appears to be closely related to that of drugs which interact with dopamine transporters, at least in the striatum (Doherty et al., 1980). We previously showed that PCP-induced dopamine release was tetrodotoxin-sensitive (Hondo et al., 1994). Dopamine reuptake blockers (Hurd and Ungerstedt, 1989; Westerink et al., 1987), as well as cocaine (Pani et al., 1990a), have been also shown to increase the extracellular dopamine levels in a tetrodotoxin-sensitive and calcium-dependent manner. By contrast, amphetamine-induced dopamine release has been known to be tetrodotoxin-insensitive (Westerink et al., 1987) and calcium-independent (Hurd and Ungerstedt, 1989). In regard to the effect of dopamine D_2 receptor antagonism, pretreatment with dopamine D_2 receptor antagonists (e.g. (−)-sulpiride, haloperidol) has been shown to potentiate both cocaine- and dopamine reuptake blocker-induced increases in extracellular dopamine levels in the striatum (Pani et al., 1990b; Westerink et al., 1987). Considering these findings, it seems that PCP enhances striatal dopamine release through a similar mechanism to that of dopamine reuptake blockers rather than that of amphetamine. A recent molecular pharmacological study has shown that the potency of PCP for the inhibiton of dopamine uptake is higher than that of amphetamine and is approximately equal to that of cocaine (Giros et al., 1992). These findings suggest that the site of action of PCP, within the doses which we used, might be mainly dopamine transporters, at least in the striatum.

Recently, by using in vivo electrochemistry technique, Cass and Gerhardt (1994) demonstrated that raclopride, a selective dopamine D_2 receptor antagonist, but not SCH 23390 inhibited the clearance of dopamine in the rat striatum, and suggested that dopamine D_2 receptors could modulate dopamine uptake. The strong synergistic potentiation of PCP-induced dopamine release by the blockade of dopamine D_2 receptors shown in this study could be explained by an interaction between dopamine D_2 receptors and dopamine transporters. However, since PCP has been known to have other pharmacological properties such as non-competitive antagonism of NMDA receptors and antagonism of sigma receptors as well as inhibition of dopamine reuptake, further studies are needed to elucidate the contribution of all these effects of PCP.

In summary, pretreatment with YM-09151-2, a selective dopamine D_2 receptor antagonist, but not SCH 23390, a selective dopamine D_1 receptor antagonist, markedly potentiated PCP-induced dopamine release in the rat striatum. These results suggest that the blockade of dopamine D_2 presynaptic autoreceptors strongly potentiates the PCP-induced dopamine release in the striatum. An interaction between dopamine D_2 receptors and dopamine transporters could account for this synergistic effect.

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