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M100907, a selective 5-HT_{2A} receptor antagonist, attenuates phencyclidine-induced Fos expression in discrete regions of rat brain

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Abstract

5-HT and dopamine receptor antagonists have become widely used as atypical antipsychotics. Although 5-HT_{2A} receptor antagonistic activity is thought to contribute to the atypical aspects of these agents, the precise mechanism remains unknown. M100907 (*R*(+)-alpha(2,3-dimethoxyphenyl)-1-[2(4-fluorophenyl)ethyl)]-4-piperidine −methanol), a selective 5-HT_{2A} receptor antagonist, is reported to attenuate phencyclidine (PCP)-induced locomotion in rodents. For the purpose of identifying regions in which M100907 exerts its effect, we investigated the effects of M100907 on PCP-induced Fos expression in rat brain. PCP (5 mg/kg, subcutaneously, s.c.) induced Fos expression in the cingulate cortex area 3, the agranular insular cortex, the piriform cortex, the nucleus accumbens, the anterior paraventricular thalamic nucleus and the ventral lateral septal nucleus. Pretreatment with M100907 (0.5 mg/kg, s.c.) attenuated Fos expression induced by PCP in the nucleus accumbens core, the shell, the agranular insular cortex and the piriform cortex. M100907 did not induce Fos expression in any of the regions investigated including the dorsolateral caudate/putamen when given alone. These results indicate that 5-HT_{2A} receptor antagonism attenuates Fos expression in a regionally specific manner in rat brain in the PCP model of psychosis.

Keywords: Antipsychotic, atypical; Schizophrenia; Nucleus accumbens

1. Introduction

5-HT and dopamine receptor antagonists have been described as effective against negative symptoms, cognitive dysfunction, and have fewer extrapyramidal side-effects than do typical antipsychotics (Baldessarini and Frankenburg, 1991; Lieberman, 1993; Marder, 1996; Meltzer and McGurk, 1999). Because they have higher affinity for 5-HT_{2A} receptors than for dopamine D_2 receptors, recent attention has focused on the role of 5-HT, especially of 5-HT_{2A} receptor antagonism, in mediating atypical aspects of antipsychotics (Meltzer, 1989).

M100907 (*R*(+)-alpha(2,3-dimethoxyphenyl)-1-[2(4-fluorophenyl)ethyl])-4-piperidine-methanol), a selective 5-HT_{2A} receptor antagonist, was developed recently (Kehne et al., 1996; Schmidt et al., 1997; Sorensen et al., 1993). In rodents, it antagonized amphetamine-stimulated locomotion (Moser et al., 1996; O'Neill et al., 1999) and amphetamine-disruption of latent inhibition (Moser et al., 1996). Although blocking of the actions of amphetamine is widely employed for the detection of antipsychotic activity, phencyclidine (PCP)-induced behavioral syndrome in rodents has come to be considered a more suitable model of schizophrenia, because PCP mimics both the positive and negative symptoms of schizophrenia in humans (Allen and Young, 1978; Javitt and Zukin, 1991; Slavney et al., 1977; Steinpreis, 1996). Indeed, atypical antipsychotics block PCP-induced behavior more than amphetamine-induced behavior in animal models, and M100907 is reported to antagonize PCP-stimulated locomotion (Gleason and Shannon, 1997; Maurel-Remy et al., 1995). Therefore, we speculate that investigation of the effects of M100907 on the PCP model may lead to a better understanding of the role of antagonism of the 5-HT_{2A} receptor in the therapeutic efficacy of atypical antipsychotics. PCP shows several neurochemical properties including NMDA receptor antagonism, activation of dopaminergic and serotonergic neurotransmission and affinity for σ receptors. The precise mechanism by which M100907 inhibits the PCP-induced behavioral syndrome, however, remains unknown.

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Quantification of changes in the expression of the immediate early gene c-*fos* has proved to be a very useful method of mapping the distribution of neurons that are activated by physiological or pharmacological stimuli (Dragunow and Faull, 1989; Morgan and Curran, 1991; Sagar et al., 1988).

In this study, for the purpose of identifying regions in which 5-HT_{2A} receptor antagonism exerts its effect on the PCP model of psychosis in rodents, we investigated the regional effects of M100907 on PCP-induced Fos expression in rat brain.

2. Materials and methods

2.1. Animals

All efforts were made to minimize animal suffering and the number of animals used, in accordance with the Guidelines for Animal Experiments of Okayama University Medical School. Male Wistar rats (Clea, Japan; body weight, 250–270 g) were used. They were housed two per cage under a 12-h light–12-h dark cycle (lights on at 7:00 a.m.), and each rat was adapted to handling during the week prior to the beginning of the experiment.

2.2. Drugs

PCP was dissolved in saline (5 mg/ml). M100907 was dissolved in 10 μl of 10% acetic acid and was diluted to 1 ml with saline (0.5 mg/ml). PCP and M100907 were provided by Meiji Seika Kaisha and Hoechst Marion Roussel, respectively.

2.3. Experimental protocol

The rats were divided into four groups. Two groups were pretreated with M100907 (0.5 mg/kg subcutaneously, s.c.) and the other two groups were pretreated with vehicle (1 ml/kg; 10 μl of 10% acetic acid diluted to 1 ml with saline). Thirty minutes later, one M100907-pretreated group and one vehicle-pretreated group received PCP (5 mg/kg, s.c.), and the other two groups received saline (1 ml/kg, s.c.). Thus, there were four different treatments: vehicle + saline ($n = 8$), M100907 + saline ($n = 8$), vehicle + PCP ($n = 8$), and M100907 + PCP ($n = 8$). Two hours after the second injection, all animals were anesthetized deeply with pentobarbital (100 mg/kg intraperitoneally, i.p.).

2.4. Immunohistochemistry

The rats were perfused through the ascending aorta with 200 ml saline followed by 250 ml 4% paraformaldehyde in 0.1 M phosphate buffer. Brains were removed immediately after perfusion and soaked in the above fixative. After a 24-h postfixation period, coronal sections (30 μm) were cut from each brain using a Microslicer (DSK, Japan). The sections were washed three times for 20 min in 0.05 M phosphate-buffered saline (PBS; pH 7.4) and then incubated with PBS containing 0.6% hydrogen peroxide for 10 min to remove endogenous peroxidase activity. The sections were washed three times for 20 min in PBS, then incubated with the primary antiserum (1:3000 dilution in PBS containing 0.3% Triton X-100, 0.05% sodium azide and 2% normal goat serum) for 72 h at 4°C. The primary polyclonal antibody (c-Fos(4): cat #sc-52; Santa Cruz Biotechnology, USA) was raised in a rabbit against a peptide corresponding to the amino acid sequence at the amino terminus of human c-Fos p62 (identical to the corresponding mouse sequence). The sections were washed three times in PBS and then incubated with biotinylated goat anti-rabbit secondary antibody (Vector Laboratories, USA; 1:400 dilution in 0.3% Triton X-100 in PBS) for 75 min. The sections were washed three times in PBS and then incubated in PBS containing 0.2% avidin-biotinylated horseradish peroxidase complex (Vector Laboratories) for 75 min. The sections were then washed twice in PBS

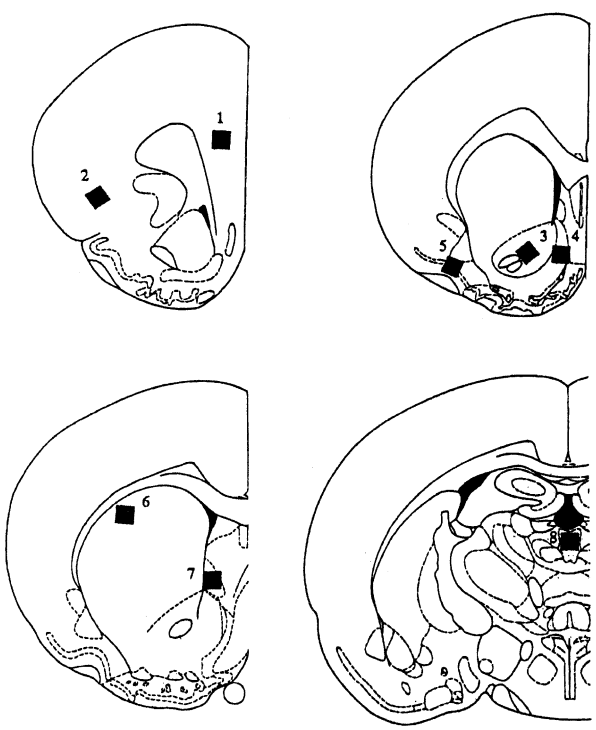

Fig. 1. Drawings of representative sections used for the quantification of Fos-like immunoreactivity-positive neurons in the cingulate cortex area 3 (1), agranular insular cortex (2), nucleus accumbens core (3), and shell (4), piriform cortex (5), dorsolateral caudate/putamen (6), ventral lateral septal nucleus (7), anterior paraventricular thalamic nucleus (8). Drawings are from Paxinos and Watson (1986).

and rinsed twice in 0.1 M acetate buffer (pH 6.0). The sections were visualized using a glucose oxidase-diaminobenzidine-nickel method for 5 min (Shu et al., 1988). The reaction was terminated by washing the sections in acetate buffer, and the sections were mounted on chrome-alum-gelatin-coated slides. The sections were left overnight to dry, counterstained with neutral red and then cover-slipped. As the primary antibody recognizes Fos and some related antigens, we refer to the staining as Fos-like immunoreactivity.

2.5. Quantification

In the pilot study, sections were examined throughout the brain to determine the regions of interest for quantitative analysis. On this basis, six sections were selected for counting the number of Fos-like immunoreactivity-positive nuclei present in eight areas of the brain, according to the coordinates of Paxinos and Watson (1986). The antero posterior (AP) coordinates relative to the bregma and associated structures were as follows. AP + 2.7, cingulate cortex area 3 and agranular insular cortex; AP + 1.6, shell and core of the nucleus accumbens and the piriform cortex ; AP + 0.7, dorsolateral caudate/putamen and the ventral lateral septal nucleus; AP-1.8, anterior paraventricular thalamic nucleus (Fig. 1). Fos-like immunoreactivity was quantified by counting the number of Fos-like immunoreactivity-positive nuclei within a 380×380 μm^2 grid placed over each area at $\times 95$ magnification. Fos-like immunoreactivity-positive nuclei were counted bilaterally on each of six sections through each region from each animal. The counting was performed by a person who was unaware of the animal's treatments. This procedure resulted in a total of 12 determinations of the number of Fos-like immunoreactivity-positive nuclei within a specified region for each animal. An exception was the anterior paraventricular thalamic nucleus, where only six determinations were made. The average of these 12 determinations was used for the subsequent statistical analysis.

2.6. Statistical analysis

A one-way analysis of variance (ANOVA) was performed on the number of Fos-like immunoreactivity-positive neurons within specified regions. Post-hoc individual comparisons were made using *Scheffe's* test.

3. Results

There were significant intergroup differences between the vehicle + saline, M100907 + saline, vehicle + PCP and M100907 + PCP groups in all the brain areas studied: cingulate cortex area 3 ($F(3, 28) = 56.56$, $P < 0.0001$), the agranular insular cortex ($F(3, 28) = 84.01$, $P < 0.0001$), core ($F(3, 28) = 48.13$, $P < 0.0001$), and shell ($F(3, 28) = 43.20$, $P < 0.0001$) of the nucleus accumbens, the piriform cortex ($F(3, 28) = 82.77$, $P < 0.0001$), dorsolateral caudate/putamen ($F(3, 28) = 9.18$, $P = 0.0002$), ventral lateral septal nucleus ($F(3, 28) = 17.74$, $P < 0.0001$), anterior paraventricular thalamic nucleus ($F(3, 28) = 80.61$, $P < 0.0001$). Post-hoc comparison demonstrated that, in the vehicle + PCP group, there was a significant increase in the number of Fos-like immunoreactivity-positive nuclei compared to the vehicle + saline group in seven of the eight areas investigated, the exception being the dorsolateral caudate/putamen. Among these areas, pretreatment with M100907 reduced the number of Fos-like immunoreactivity-positive nuclei induced by PCP in the agranular insular cortex, the nucleus accumbens core and the shell and the piriform cortex (Table 1, Fig. 2).

The M100907 + saline group did not show any significant increase in the number of Fos-like immunoreactivity-

Table 1
Effect of pretreatment with M100907 on the number of phencyclidine-induced Fos-like immunoreactivity-positive neurons
Values are the mean ± S.E.M. of the number of Fos-like immunoreactivity-positive neurons in each of four groups of animals. Significant differences between groups as determined by ANOVA followed by Scheffe's test.

Brain regions	Vehicle + saline	M100907 + saline	Vehicle + PCP	M100907 + PCP
cingulate cortex area 3	1.7 ± 0.6	2.3 ± 0.8	39.1 ± 3.3[a]	31.0 ± 3.9
agranular insular cortex	0.1 ± 0.0	0.1 ± 0.0	27.7 ± 2.6[a]	17.8 ± 1.4[b]
nucleus accumbens				
core	0.2 ± 0.1	0.3 ± 0.1	9.3 ± 1.1[a]	3.8 ± 0.6[b]
shell	0.4 ± 0.3	0.5 ± 0.3	14.3 ± 1.6[a]	8.3 ± 1.3[b]
piriform cortex	0.4 ± 0.2	0.4 ± 0.2	12.8 ± 0.9[a]	5.3 ± 0.9[b]
dorsolateral caudate/putamen	0.0 ± 0.0	0.0 ± 0.0	1.3 ± 0.4	2.1 ± 0.6
ventral lateral septal nucleus	0.3 ± 0.3	0.4 ± 0.2	11.5 ± 1.8[a]	6.8 ± 1.8
anterior paraventricular thalamic nucleus	7.1 ± 0.9	7.9 ± 2.0	49.5 ± 3.2[a]	48.5 ± 3.6

[a] $P < 0.01$, the vehicle + saline group vs. vehicle + PCP (5 mg/kg) group.
[b] $P < 0.01$, the vehicle + PCP group vs. M100907 (0.5 mg/kg) + PCP group.

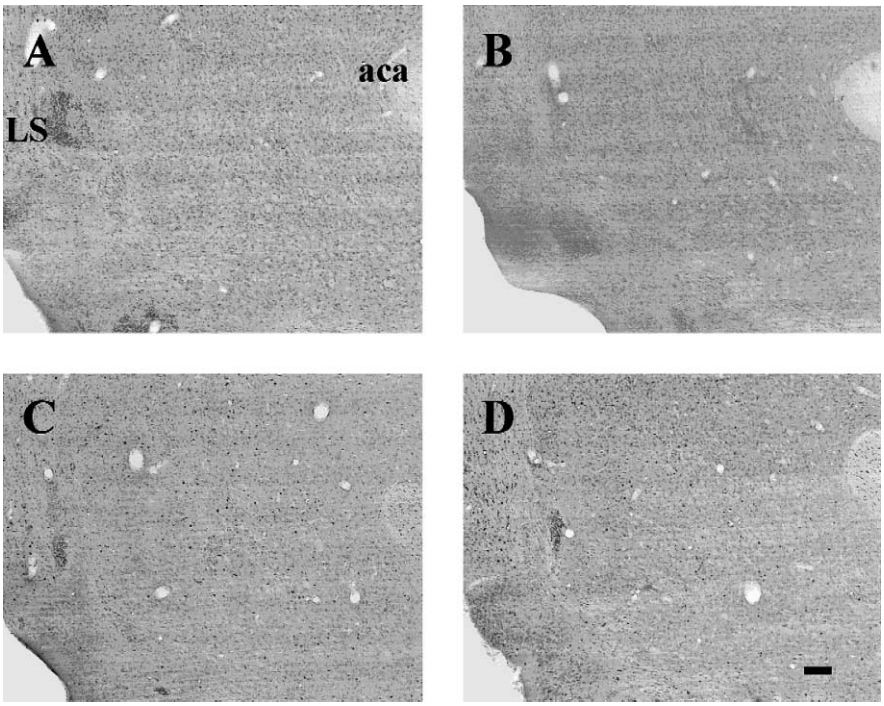

Fig. 2. Photomicrographs of Fos-like immunoreactivity in the nucleus accumbens: vehicle + saline (A), M100907 (0.5 mg/kg) + saline (B), vehicle + PCP (5 mg/kg) (C), and M100907 + PCP (D). Magnification is ×50. LS, lateral septum; aca, anterior commissure. Bar = 100 μm.

positive nuclei in any of the brain areas studied compared to the vehicle + saline group.

4. Discussion

In the present study, PCP induced Fos expression in the cingulate cortex area 3, the agranular insular cortex, the piriform cortex, the nucleus accumbens, the anterior paraventricular thalamic nucleus and the ventral lateral septal nucleus. The distribution of Fos expression induced by PCP was consistent with the findings from previous studies (Nakki et al., 1996; Sato et al., 1997; Sharp, 1997). In these areas, M100907, a selective 5-HT_{2A} receptor antagonist, attenuated Fos expression induced by PCP in the nucleus accumbens core (by 58.8%), shell (by 41.8%), the agranular insular cortex (by 35.6%) and the piriform cortex (by 58.4%). These regions are rich in 5-HT_{2A} receptors (Cornea-Hebert et al., 1999; Mijnster et al., 1997; Pompeiano et al., 1994). In contrast, in the ventral lateral septal nucleus and anterior paraventricular thalamic nucleus, which have few 5-HT_{2A} receptor, M100907 did not attenuate Fos expression induced by PCP. These findings support the view that the suppressive effect of M100907 on Fos expression induced by PCP was mediated by the block of 5-HT_{2A} receptors.

In the cingulate cortex area 3, which is rich in 5-HT_{2A} receptors, M100907 did not alter the Fos expression induced by PCP. Thus, PCP-induced Fos expression in this area was not mediated via 5-HT_{2A} receptors. Results of previous studies provided two possible mechanisms of induction of Fos expression by PCP in the cingulate cortex area 3. The σ_2 receptor antagonist inhibited PCP-induced Fos expression in the cingulate cortex, but not in the piriform cortex and the paraventricular thalamic nucleus (Sharp, 1997), so one possibility is that Fos expression is mediated by the σ receptor agonistic action of PCP. On the other hand, PCP has been reported to increase the release of dopamine in the medial prefrontal cortex (Carboni et al., 1989; Hondo et al., 1994; Steinpreis and Salamone, 1993; Tanii et al., 1990), and a dopamine agonist induced Fos expression in the medial prefrontal cortex (Deutch and Duman, 1996; Scheideler et al., 1997). Together, these findings suggest another possibility, that Fos expression induced by PCP in the cingulate cortex area 3 is mediated by activation of dopamine release in this area. Because M100907 did not attenuate the release of dopamine in the medial prefrontal cortex induced by MK-801 ((5*R*,10*S*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine), a selective NMDA receptor antagonist (Schmidt and Fadayel, 1996), it is conceivable that M100907 did not attenuate PCP-induced Fos expression in the cingulate cortex area 3.

In rodents, locomotion is measured as an index for quantitative analysis in the PCP model of psychosis, and M100907 is reported to antagonize PCP-induced locomotion (Gleason and Shannon, 1997; Maurel-Remy et al., 1995). In addition, the nucleus accumbens is considered to play a major role in PCP-induced locomotion (Millan et

al., 1999). Consistent with these findings, the present study clearly demonstrated that M100907 attenuated PCP-induced Fos expression in the nucleus accumbens core and shell. Maurel-Remy et al. (1995) reported that M100907 antagonized PCP-induced hyperlocomotion at doses approximately 10-fold lower than those that antagonized amphetamine-induced hyperlocomotion, and that the potencies of a series of neuroleptics in blocking PCP-induced hyperlocomotion were correlated with their affinity for 5-HT_{2A} receptors. In dialysis studies, PCP increased the release of serotonin in the nucleus accumbens (Hernandez et al., 1988), and lesions of the serotoninergic terminals in the nucleus accumbens abolished PCP-induced locomotion. Therefore, PCP may increase the release of serotonin, and consequently activate the 5-HT_{2A} receptors in the nucleus accumbens, resulting in the induction of locomotion. Thus, it is conceivable that M100907 attenuates PCP-induced Fos expression by antagonizing 5-HT_{2A} receptors in the nucleus accumbens. On the other hand, PCP has also been reported to increase dopamine release in the nucleus accumbens (Adams and Moghaddam, 1998; Carboni et al., 1989; Hernandez et al., 1988). 6-Hydroxydopamine lesions in the nucleus accumbens abolished PCP-induced locomotion (French and Vantini, 1984; French et al., 1985; Steinpreis and Salamone, 1993). Moreover, dopamine D_1 and D_2 receptor antagonists attenuated PCP-induced locomotion (Freed et al., 1984; Tsutsumi et al., 1995). These findings suggest that the dopaminergic system is also involved in PCP-induced locomotion. M100907 antagonized the MK-801-induced increase of dopamine release in the nucleus accumbens (Schmidt and Fadayel, 1996). Therefore, it is possible that M100907 may attenuate the increase in dopamine release that is induced by PCP in the nucleus accumbens. To support this speculation, Schmidt et al. (1992) proposed a "permissive" role of 5-HT_{2A} receptors in the activation of the dopamine system which occurs during states of high serotonergic activity and in PCP psychosis. This indicates that activation of the 5-HT_{2A} receptor may be necessary for maintaining an increase of dopamine release. If this is the case, the major mechanism of inhibition of PCP-induced Fos expression by M100907 is via blockade of 5-HT_{2A} receptors, and the indirect inhibition of dopamine release plays an additional role in the nucleus accumbens.

M100907 did not induce Fos expression when given alone in any of the regions investigated, including the dorsolateral caudate/putamen. This is consistent with a previous report that ritanserin, a 5-$HT_{2A/2C}$ receptor antagonist, also did not induce Fos expression in any regions examined (Wan et al., 1995). Because neuroleptic-induced Fos expression in the dorsolateral caudate/putamen has been shown to predict extrapyramidal side-effects, M100907 may have few side-effects including extrapyramidal symptoms. These findings suggest that M100907 may be valuable to treat a PCP-related psychosis in patients.

In conclusion, the present study has demonstrated that M100907 attenuates Fos expression induced by PCP region specifically in the nucleus accumbens core and the shell, the agranular insular cortex and the piriform cortex. We postulate that, among these areas, M100907 exerts its suppressive effect mainly in the nucleus accumbens in the PCP model of psychosis.

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