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In vivo functional interaction between phencyclidine binding sites and σ receptors to produce head-weaving behavior in rats

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Abstract

To investigate the in vivo functional interaction between phencyclidine (1-(1-phenylcyclohexyl)piperidine; PCP) binding sites and σ receptors, we examined the effects of σ receptor ligands on stereotyped head-weaving behavior induced by PCP, a putative PCP/σ receptor ligand, and (+)-5-methyl-10,11-dihydroxy-5*H*-dibenzo(*a*,*d*)cyclo-hepten-5,10-imine ((+)-MK-801; dizocilpine), a selective PCP binding site ligand, in rats. PCP (7.5 mg/kg, i.p.)-induced head-weaving behavior was inhibited by both *N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)-phenyl]-ethylamine (NE-100; 0.03–1.0 mg/kg, p.o.), a selective σ_1 receptor ligand, and α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperidine butanol (BMY-14802; 3 and 10 mg/kg, p.o.), a prototype σ receptor ligand, in a dose-dependent manner, whereas NE-100 (0.1–1.0 mg/kg, p.o.) and BMY-14802 (3 and 10 mg/kg, p.o.) did not inhibit dizocilpine (0.25 mg/kg, s.c.)-induced head-weaving behavior. These results suggest that NE-100 and BMY-14802 act via σ receptors. Dizocilpine-induced head-weaving behavior was potentiated by 1,3-di-*o*-tolyl-guanidine (DTG; 0.03–0.3 μg/kg, i.v.) and (+)-3-(3-hydroxyphenyl)-*N*-(1-propyl)piperidine ((+)-3-PPP; 3 and 6 mg/kg, i.p.), σ_1/σ_2 receptor ligands, as well as by (+)-*N*-allyl-normetazocine ((+)-SKF-10,047; 8 mg/kg, i.p.), a σ_1 receptor ligand, while DTG (0.3 μg/kg, i.v.), (+)-3-PPP (6 mg/kg, i.p.) and (+)-SKF-10,047 (8 mg/kg, i.p.) did not induce this behavior. Potentiation of dizocilpine-induced head-weaving behavior by DTG (0.3 μg/kg, i.v.), (+)-3-PPP (6 mg/kg, i.p.) and (+)-SKF-10,047 (8 mg/kg, i.p.) was completely blocked by NE-100 (0.1 mg/kg, p.o.) and BMY-14802 (10 mg/kg, p.o.). These results suggest that PCP binding sites and σ receptors are involved in PCP-induced head weaving behavior, and that σ_1 receptors play an important role in modulation of the head-weaving behavior.

Keywords: σ Receptor; Phencyclidine (PCP) receptor; Dizocilpine; Head-weaving behavior; (Rat)

1. Introduction

Phencyclidine (1-(1-phenylcyclohexyl)piperidine; PCP), a psychotomimetic drug, is considered useful for investigating neurochemical mechanisms of schizophrenia (see the reviews of Balster, 1987; Javitt and Zukin, 1991). However, the possible role of PCP in the brain is still unclear due to its broad binding affinity to several receptors such as the PCP binding sites associated with the ion channel of *N*-methyl-D-aspartate (NMDA) receptor complexes, sigma (σ) receptors, 5-hydroxytryptamine (5-HT) S_{2A} receptors, and other receptors (Nabeshima et al., 1984; Javitt and Zukin, 1991).

σ Receptors were originally identified as opioid receptors (Martin et al., 1976) in pharmacological studies using benzomorphans. However, they differ from classical μ-, κ- and δ-type opioid receptors (Manallack et al., 1986). Furthermore, σ receptors also differ from PCP binding sites with respect to their anatomical distribution (Largent et al., 1986; Sonders et al., 1988). Recently, σ receptors have been classified into two subtypes, σ_1 and σ_2 receptors (Quirion et al., 1992). Some studies have detected both receptors in rat (Connor and Chavkin, 1992) and guinea-pig brain (Hellewell and Bowen, 1990; Musacchio et al., 1989; Reid et al., 1990). However, since the function, agonists, and antagonists of σ receptor subtypes have not been clarified and there is little documentation of suitable animal models to distinguish between them, the physio-

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logical effects of σ receptor ligands are not yet understood.

Recently, several compounds which selectively bind to σ receptors have been developed, and several investigators have suggested an interaction between PCP binding sites and σ receptors. Hiramatsu et al. (1987) found that a putative PCP/σ receptor ligand, (±)-*N*-allyl-normetazocine ((±)-SKF-10,047), produces certain types of PCP-induced behavior in rats. Okuyama et al. (1993) demonstrated that a selective σ receptor ligand, *N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)-phenyl]-ethylamine (NE-100), as well as several putative σ receptor ligands, such as α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperidine butanol (BMY-14802), 1-(cyclopropylmethyl)-4-(2′(4″-fluorophenyl)-2′-oxoethyl)-piperidine (Dup 734) and 4-[2′-(4′-cyanophenyl)-2′-oxoethyl]-1-(cyclopropylmethyl)piperidine (XJ448), inhibit PCP-induced head-weaving behavior. It is worth noting that NE-100, the most selective σ receptor ligand among them, did not inhibit any forms of PCP-induced behavior other than head-weaving. Such findings suggest that σ receptors are involved in certain forms of PCP-induced stereotyped behavior, especially head-weaving behavior. However, it is still not clear whether PCP produces its behavioral effect via PCP binding sites or σ receptors (or both), since the selective PCP binding site ligand, (+)-5-methyl-10,11-dihydroxy-5*H*-dibenzo(*a*,*d*)cyclo-hepten-5,10-imine ((+)-MK-801; dizocilpine), also induces head-weaving behavior (Hiramatsu et al., 1989).

To address these issues, we investigated the in vivo interaction between PCP binding sites and σ receptors using head-weaving behavior in rats. Initially, we investigated whether NE-100, a selective σ_1 receptor ligand, and BMY-14802, a prototype σ_1/σ_2 receptor ligand, block PCP- and/or dizocilpine-induced head-weaving behavior. Secondly, to elucidate the roles of the σ receptor subtypes in PCP-induced head-weaving behavior, we examined whether 1,3-di-*o*-tolyl-guanidine (DTG) and (+)-3-(3-hydroxyphenyl)-*N*-(1-propyl)piperidine ((+)-3-PPP), σ_1/σ_2 receptor ligands, as well as (+)-SKF-10,047, a σ_1 receptor ligand, modulate dizocilpine-induced head-weaving behavior. Finally, we investigated whether NE-100 and BMY-14802 inhibit the modulating effects of DTG, (+)-3-PPP and (+)-SKF-10,047 on dizocilpine-induced head-weaving behavior.

2. Materials and methods

2.1. Animals

Male Wistar rats (Oriental Bio Service, Kyoto, Japan), weighing 200–300 g, were used. The animals were kept in a room in which temperature, humidity, and light were regulated (22–24°C, 55 ± 5%, and 12 h of light and dark, respectively) with food and water available ad libitum, for at least 3 days before the experiment. The procedures involving animals and their care were conducted in line with the international guidelines listed in the 'Principles of Laboratory Animal Care' (NIH publication No. 85-23, revised 1985).

2.2. Drugs

Phencyclidine HCl (1-(1-phenylcyclohexyl)piperidine; PCP) was synthesized in our laboratory. (+)-5-Methyl-10,11-dihydroxy-5*H*-dibenzo(*a*,*d*)cyclo-hepten-5,10-imine hydrogen maleate ((+)-MK-801; dizocilpine), 1,3-di-*o*-tolyl-guanidine (DTG), *R*(+)-3-(3-hydroxyphenyl)-*N*-(1-propyl)piperidine HCl ((+)-3-PPP), and (+)-*N*-allyl-normetazocine HCl ((+)-SKF-10,047) were purchased from Research Biochemicals International (Natick, MA, USA). *N*,*N*-Dipropyl-2-[4-methoxy-3-(2-phenylethoxy)-phenyl]-ethylamine (NE-100) and α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperidine butanol (BMY-14802) were kindly provided by Taisho Pharmaceutical Co. (Ohmiya, Saitama, Japan) and from Bristol Myers-Squibb Co. (Wallingford, CT, USA), respectively. PCP, dizocilpine, (+)-3-PPP, and (+)-SKF-10,047 were dissolved in saline, and NE-100 and BMY-14802 in distilled water. DTG was suspended in saline containing 0.25% (w/v) carboxymethyl cellulose.

2.3. Behavioral studies

Behavioral experiments were conducted between 11:00 and 19:00 h, at a room temperature of 22–24°C. After at least 2 h for familiarization with the test room and food deprivation, and 30 min before the experiments were due to commence, the rats were placed individually into test cages (30 × 35 × 17 cm high). The animals were assigned randomly to different drug treatment groups.

Rats were treated with PCP (7.5 mg/kg, i.p.) and dizocilpine (0.25 mg/kg, s.c.), and the resulting stereotyped head-weaving behavior measured (by the number of times the animal made slow, side-to-side head movements) for 45 min and 60 min, respectively, according to the method described by Nabeshima et al. (1987a,b). The observation period for each drug was determined once the head-weaving behavior induced by PCP and dizocilpine had completely ceased (Hiramatsu et al., 1989).

2.4. Drug administration

PCP (7.5 mg/kg, i.p.) and dizocilpine (0.25 mg/kg, s.c.) were administered immediately before the behavioral observation study. Maximum doses of PCP and dizocilpine that would produce head-weaving behavior without producing severe ataxia (Hiramatsu et al., 1989) were selected so as identify the effects of σ receptor ligands. NE-100 (0.03–1.0 mg/kg, p.o.) and BMY-14802 (3–10 mg/kg,

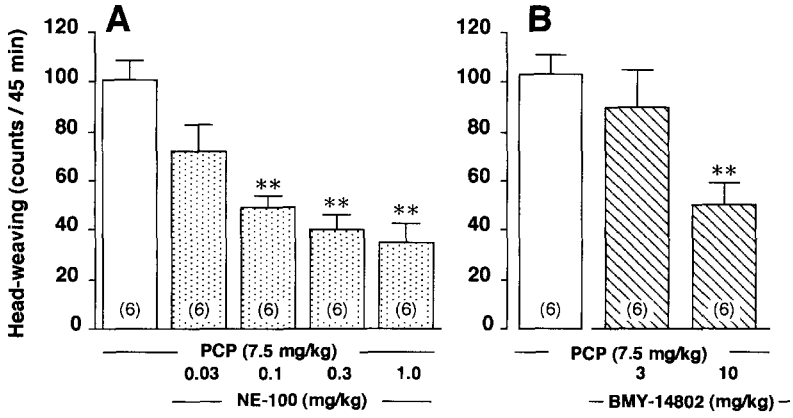

Fig. 1. Effects of NE-100 (A) and BMY-14802 (B) on PCP-induced head-weaving behavior in rats. Rats were injected with PCP (7.5 mg/kg, i.p.) 10 and 30 min after the administration of NE-100 (0.03–1.0 mg/kg, p.o.) and BMY-14802 (3–10 mg/kg, p.o.), respectively, and the resulting stereotyped head-weaving behavior was observed for 45 min. Each column represents the mean ± S.E.M. Numbers in parentheses show the number of animals used. ** $P < 0.01$ vs. (PCP alone)-treated group (Scheffe test, followed by one-way ANOVA).

p.o.) were administered 10 and 30 min, respectively, before the administration of PCP or dizocilpine. The doses of NE-100 and BMY-14802 were selected so as to inhibit PCP-induced head-weaving behavior (Okuyama et al., 1993). DTG (0.03–0.3 mg/kg, i.v.), (+)-3-PPP (3–6 mg/kg, s.c.) and (+)-SKF-10,047 (8 mg/kg, i.p.) were administered 10, 0 and 0 min, respectively, before the administration of dizocilpine. The doses of DTG were selected so as to modulate the activation of NMDA-induced firing of the CA_3 dorsal hippocampal neurons, similar to other σ receptor ligands (Monnet et al., 1992), while the doses of (+)-3-PPP and (+)-SKF-10,047 were selected so as not to produce any typical stereotyped behavior or hyperambulation (data not shown), based on previous findings that hyperambulation and stereotyped behavior were produced by (+)-3-PPP (> 12 mg/kg) (Ujike et al., 1992), (+)-SKF-10,047 (> 10 mg/kg) (Brent, 1991) and (±)-SKF-10,047 (> 10 mg/kg) (Hiramatsu et al., 1987).

2.5. Statistics

All data were expressed as means ± S.E.M. The data were analyzed by one-way analysis of variance (ANOVA), followed by a Scheffe test when F ratios were significant ($P < 0.05$).

3. Results

3.1. Effects of NE-100 and BMY-14802 on PCP-induced head-weaving behavior

As shown in Fig. 1A and B, both NE-100 (0.03–1.0 mg/kg) and BMY-14802 (3–10 mg/kg) inhibited PCP

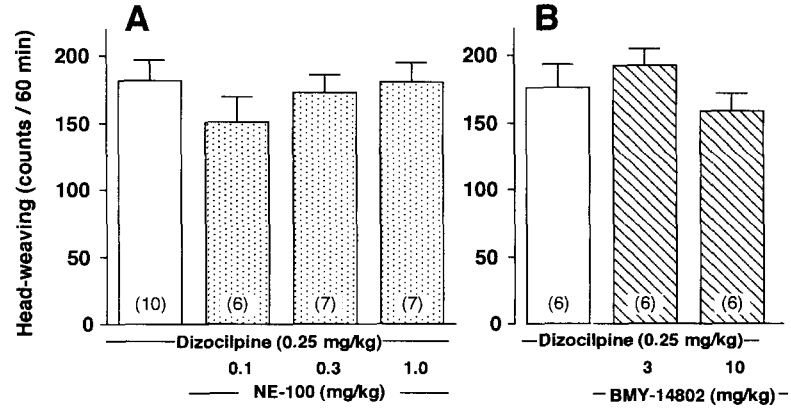

Fig. 2. Effects of NE-100 (A) and BMY-14802 (B) on dizocilpine-induced head-weaving behavior in rats. Rats were injected with dizocilpine (0.25 mg/kg, s.c.) 10 and 30 min after the administration of NE-100 (0.1–1.0 mg/kg, p.o.) and BMY-14802 (3–10 mg/kg, p.o.), respectively, and the resulting stereotyped head-weaving behavior was observed for 60 min. Each column represents the mean ± S.E.M. Numbers in parentheses show the number of animals used. ** $P < 0.01$ vs. (dizocilpine alone)-treated group (Scheffe test, followed by one-way ANOVA).

(7.5 mg/kg)-induced head-weaving behavior in a dose-dependent manner (NE-100: $F(4,25) = 13.072$, $P < 0.0001$; BMY-14802: $F(2,15) = 17.527$, $P < 0.0001$). NE-100 (0.1, 0.3 and 1.0 mg/kg) and BMY-14802 (10 and 30 mg/kg) had significant effects ($P < 0.01$ vs. the corresponding (PCP alone)-treated group).

3.2. Effects of NE-100 and BMY-14802 on dizocilpine-induced head-weaving behavior

NE-100 (0.1–1.0 mg/kg) and BMY-14802 (10 mg/kg) at doses which inhibited PCP-induced head-weaving behavior, did not inhibit dizocilpine (0.25 mg/kg)-induced head-weaving behavior (Fig. 2A and B).

3.3. Effects of DTG, (+)-3-PPP and (+)-SKF-10,047 on dizocilpine-induced head-weaving behavior

DTG (0.03–0.3 μg/kg), (+)-3-PPP (3–6 mg/kg) and (+)-SKF-10,047 (8 mg/kg) augmented the head-weaving behavior produced by dizocilpine (DTG: $F(3,31) = 4.879$, $P < 0.01$; (+)-3-PPP: $F(2,21) = 6.042$, $P < 0.01$; (+)-SKF-10,047: $F(1,10) = 34.784$, $P < 0.0005$) (Fig. 3A, B and C). Scheffe analyses indicated that DTG (0.3 μg/kg), (+)-3-PPP (6 mg/kg) and (+)-SKF-10.047 (8 mg/kg) had significant effects (DTG (0.3 μg/kg): $P < 0.05$; (+)-3-PPP (6 mg/kg): $P < 0.05$; (+)-SKF-10,047 (8 mg/kg): $P < 0.01$, respectively, vs. the corresponding (dizocilpine alone)-treated group) (Fig. 3A, B and C). Treatments with DTG (0.3 μg/kg), (+)-3-PPP (6 mg/kg) and (+)-SKF-10,047 (8 mg/kg) alone did not induce head-weaving behavior (data not shown).

3.4. Effects of NE-100 and BMY-14802 on the potentiation of dizocilpine-induced head-weaving behavior by DTG, (+)-3-PPP and (+)-SKF-10,047

In this study, we used NE-100 (0.1 mg/kg) and BMY-14802 (10 mg/kg) at the minimum doses so as to inhibit PCP-induced head-weaving behavior without affecting dizocilpine-induced head-weaving behavior. The significant potentiation of dizocilpine-induced head-weaving behavior by DTG (0.3 μg/kg) was completely inhibited by NE-100 (0.1 mg/kg) and BMY-14802 (10 mg/kg) (NE-100 (0.1 mg/kg): $P < 0.01$; BMY-14802 (10 mg/kg): $P < 0.01$ vs. the corresponding (dizocilpine + DTG (0.3 μg/kg))-treated group) (Fig. 4A). NE-100 (0.1 mg/kg) also inhibited the significant potentiation of dizocilpine-induced head-weaving behavior by (+)-3-PPP (6 mg/kg) and (+)-SKF-10.047 (8 mg/kg) ($P < 0.01$ vs. (dizocilpine + (+)-3-PPP (6 mg/kg))- and (dizocilpine + (+)-SKF-10.047 (8 mg/kg))-treated group) (Fig. 4B and C).

4. Discussion

Results of some studies have suggested behavioral interactions between PCP binding sites and σ receptors in rats. (±)-SKF-10,047, a σ receptor ligand, induces some PCP-like behavior in rats (Hiramatsu et al., 1987), while (+)-SKF-10,047 induces similar behavioral effects to dizocilpine, a selective PCP receptor ligand, in guinea pigs (Brent, 1991). However, the details of the behavioral interaction between PCP binding sites and σ receptors

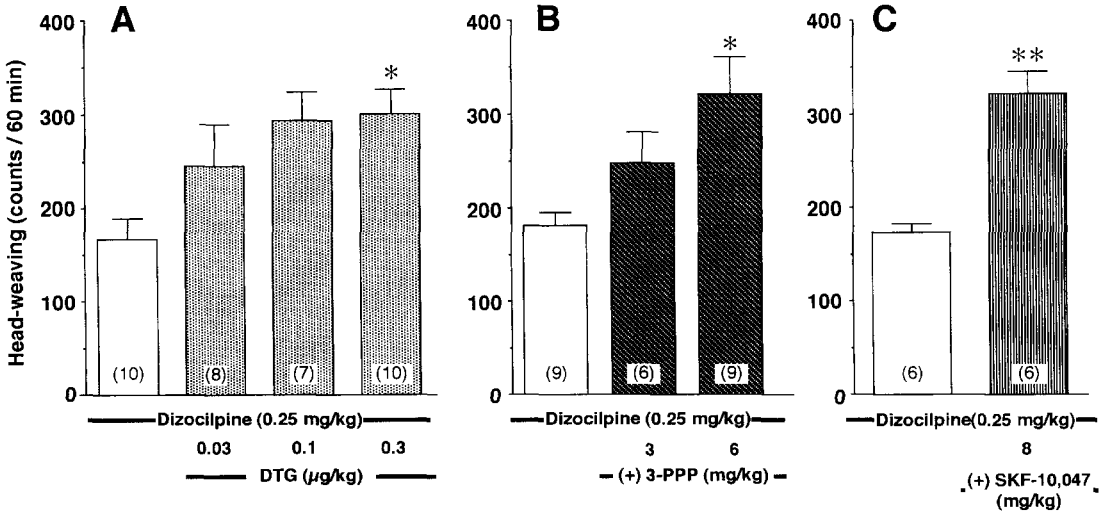

Fig. 3. Effects of DTG (A), (+)-3-PPP (B) and (+)-SKF-10,047 (C) on dizocilpine-induced head-weaving behavior in rats. Rats were injected with dizocilpine (0.25 mg/kg, s.c.) 10, 0 and 0 min after the administration of DTG (0.03–0.3 mg/kg, i.v.), (+)-3-PPP (3 and 6 mg/kg, i.p.) and (+)-SKF-10,047 (8 mg/kg, i.p.), respectively, and the resulting stereotyped head-weaving behavior was observed for 60 min. Each column represents the mean ± S.E.M. Numbers in parentheses show the number of animals used. * $P < 0.05$ and ** $P < 0.01$ vs. (dizocilpine alone)-treated group (Scheffe test, followed by one-way ANOVA).

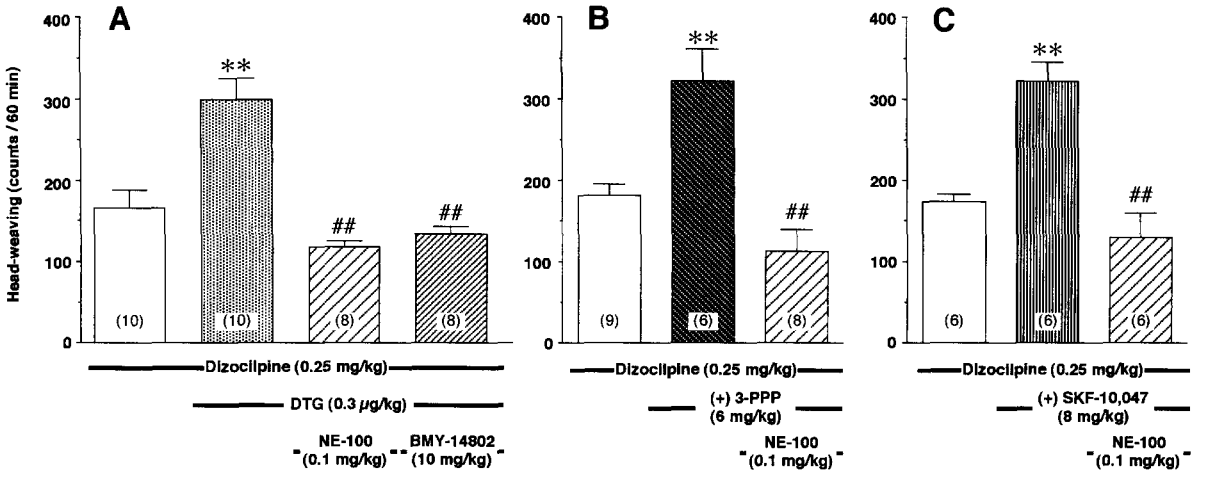

Fig. 4. Effects of NE-100 and BMY-14802 on the potentiation of dizocilpine-induced head-weaving by DTG (A), and the effects of NE-100 on the potentiation of dizocilpine-induced head-weaving by (+)-3-PPP (B) and (+)-SKF-10,047 (C). Rats were injected with dizocilpine (0.25 mg/kg, s.c.) 10, 0 and 0 min after the administration of DTG (0.3 μg/kg, i.v.), (+)-3-PPP (6 mg/kg, i.p.) and (+)-SKF-10,047 (8 mg/kg, i.p.), respectively, and the resulting stereotyped head-weaving behavior was observed for 60 min. NE-100 (0.1 mg/kg, p.o.) and BMY-14802 (10 mg/kg, p.o.) were administered 10 or 30 min before the injection of dizocilpine. Each column represents the mean ± S.E.M. Numbers in parentheses show the number of animals used. ** $P < 0.01$ vs. (dizocilpine alone)-treated group (Scheffe test, followed by one-way ANOVA). ## $P < 0.01$ vs. (dizocilpine + (DTG (0.3 μg/kg), (+)-3-PPP (6 mg/kg) or (+)-SKF-10,047 (8 mg/kg))-treated group (Scheffe test, followed by one-way ANOVA).

remain unclear. To address this, we designed a study using head-weaving behavior in rats.

The present study showed that NE-100 and BMY-14802 inhibit PCP-induced head-weaving behavior in a dose-dependent manner. The doses and route of administration (p.o.) of NE-100 and BMY-14802 used in this study, as well as the results, are consistent with those in a previous report (Okuyama et al., 1993). We used an oral route for the administration of NE-100 and BMY-14802 instead of an i.p., s.c., or i.v. route, to avoid the drug-drug interaction at local sites observed in recent studies. The detailed mechanisms of action of both drugs and their binding profiles are still not clear. Thus, it is possible that the metabolites of drugs ingested inhibited PCP-induced head-weaving behavior via other receptors than σ receptors. For example, BMY-14802 is metabolized to BMY-14786 which possesses a lower affinity for dopamine receptors (Taylor et al., 1992). However, the effects of BMY-14786 seem negligible since a previous report by Okuyama et al. (1993) showed that p.o. administration of other putative σ receptor ligands, such as Dup 734 and XJ 448, also inhibited PCP-induced head-weaving behavior. Thus, these findings, together with the receptor binding profile of NE-100 (IC_{50}: σ receptors (4.2 nM) ≪ PCP binding sites and other receptors (> 10000 nM)) and BMY-14802 (IC_{50}: σ receptors (158 nM) < 5-HT S_{1A} and other receptors (> 1000 nM)), suggest that σ receptors are involved in PCP-induced head-weaving behavior.

In contrast to the inhibitory effects of NE-100 and BMY-14802 on PCP-induced head-weaving behavior, neither drug inhibited dizocilpine-induced head-weaving behavior. The finding that the total dizocilpine-induced head-weaving count was approximately twice that of the total PCP-induced head-weaving count, suggests that the lack of effect of NE-100 and BMY-14802 was due to the extremely strong effect of dizocilpine. However, the differences in PCP- and dizocilpine-induced head-weaving behavior did not seem to result from differences in dose potency, but rather from differences in the time course of the effect of the two drugs. That is, PCP-induced head-weaving behavior became maximum 15 min after administration, rapidly decreased then terminated 30–40 min after administration, whereas dizocilpine-induced head-weaving behavior became maximum 15–20 min after administration, and gradually decreased before stopping 50–60 min after administration (unpublished observation). The head-weaving counts at the appropriate time point (for PCP: 15 min after injection; for dizocilpine: 15–20 min after injection) were not significantly different between PCP and dizocilpine (unpublished observation), which is consistent with results of a previous study (Hiramatsu et al., 1989). Dizocilpine-induced head-weaving behavior at the maximum dose was readily enhanced by several σ receptor ligands (DTG, (+)-3-PPP and (+)-SKF-10,047) without producing severe ataxia. These results suggest that σ receptors are not involved in dizocilpine-induced head-weaving behavior. This, together with the effects of NE-100 and BMY-14802 on PCP-induced head-weaving behavior, led us to hypothesize that PCP produces its behavioral effect via both PCP binding sites and σ receptors.

To confirm our hypothesis, we examined the effects of σ receptor ligands such as DTG, (+)-3-PPP and (+)-SKF-10,047 on dizocilpine-induced head-weaving behavior. We used DTG, which has a high affinity for both σ_1 and σ_2 receptors, (+)-3-PPP, which has a high affinity for σ_1 receptors and a moderate to high affinity for σ_2 recep-

tors, and (+)-SKF-10,047, which has a high affinity for σ_1 receptors but only a low affinity for σ_2 receptors (Quirion et al., 1992). Dizocilpine-induced head-weaving behavior was potentiated by DTG, (+)-3-PPP and (+)-SKF-10,047 at doses which, if administered alone, failed to induce head-weaving behavior. These studies strongly support our hypothesis. This evidence, in combination with the binding properties of DTG, (+)-3-PPP and (+)-SKF-10,047 to σ_1 receptors and σ_2 receptors, suggests that σ_1 receptors mainly regulate dizocilpine-induced head-weaving behavior. Alternatively, the finding that NE-100 completely blocked the effects of DTG, (+)-3-PPP, and (+)-SKF-10,047 on dizocilpine-induced head-weaving behavior also suggests the involvement of σ_1 receptors, since NE-100 binds preferentially to σ_1 receptors (IC_{50} = 1.54 nM) rather than σ_2 receptors (IC_{50} = 84.6 nM) (Chaki et al., 1994).

The underlying mechanism associated with σ receptor-induced modulation of PCP- and dizocilpine-induced head-weaving behavior is still unknown. However, two possibilities exist: (1) direct modulation of PCP binding sites by σ receptor ligands, and (2) indirect modulation of PCP binding site-mediated head-weaving behavior by σ receptor ligands. The former possibility may not be negligible due to the previous findings (Yamamoto et al., 1995a,b) that DTG, (+)-3-PPP, and (+)-SKF-10,047, as well as NE-100, inhibited the binding of [^{3}H]*N*-[1-(2-thienyl) cyclohexyl] piperidine, a selective PCP binding site ligand in cultured neuronal cells. Concerning the latter possibility, it has already been reported that several neuronal systems may be involved in producing the behavioral effects of PCP, dizocilpine (Javitt and Zukin, 1991), and σ receptor ligands (see the reviews of Sonders et al., 1988; Nabeshima and Okuyama, 1994). Previous studies using selective receptor antagonists (Yamaguchi et al., 1986; Löscher and Hönack, 1992; Kitaichi et al., 1994) and selective neurotoxins (Nabeshima et al., 1983, 1987b), have suggested the importance of both dopaminergic and 5-HTergic neuronal systems in PCP- and dizocilpine-induced head-weaving behavior. The involvement of the 5-HTergic neuronal system in the modulating effects of σ receptor ligands may be less than that of the dopaminergic neuronal system, because no interaction between the 5-HTergic neuronal system and σ receptors has been reported so far. Taking these findings, together with those that σ receptors are abundant in the substantia nigra pars compacta (Largent et al., 1984; Tam and Cook, 1984; Graybiel et al., 1989) and that dopaminergic neuronal denervation by the microinjection of 6-hydroxydopamine reduces the number of σ receptors (Gundlach et al., 1986), we speculate that σ receptors located on the nigrostriatal dopaminergic neurons regulate PCP- and dizocilpine-induced head-weaving behavior. However, our present studies still do not rule out the possible involvement of PCP binding sites and/or other neurons. Further studies need to be carried out regarding both possibilities.

In summary, we demonstrated both that the interaction between PCP binding sites and σ receptors is involved in rat behaviors and the possible importance of σ_1 receptors in the regulation of head-weaving behavior. Moreover, the finding that the effects on dizocilpine-induced head-weaving behavior differed between some σ receptor ligands (DTG, (+)-3-PPP, and (+)-SKF-10,047) and others (NE-100 and BMY-14802) suggests that the study of this behavior could become a useful tool for clarifying the roles of σ receptor agonists and antagonists. Further studies using selective σ receptor subtype ligands and related probes may elucidate the functional interaction of these receptors.

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