Research report

Phencyclidine-induced discriminative stimulus is mediated via phencyclidine binding sites on the N-methyl-D-aspartate receptor-ion channel complex, not via sigma$_1$ receptors

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Abstract

The effects of several N-methyl-D-aspartate (NMDA) receptor- and sigma receptor-related compounds on the discriminative stimulus effects of phencyclidine (PCP) were examined in rats trained to discriminate PCP (1.5 mg/kg, i.p.) from saline under a two-lever fixed ratio 20 schedule of food reinforcement. PCP produced a dose-dependent increase in PCP-appropriate responding. A non-competitive NMDA receptor antagonist, dizocilpine (0.2 mg/kg, i.p.) and a putative sigma$_1$ receptor agonist, (+)-SKF-10047 (10 mg/kg, i.p.) fully substituted for PCP in every rat tested. Neither a competitive NMDA receptor antagonist, CGS-19755 (0.1–3 mg/kg, i.p.), sigma$_1$ receptor agonist, (+)-pentazocine (10–30 mg/kg, i.p.) nor dextromethorphan (10–20 mg/kg, i.p.) produced PCP-like discriminative stimulus effects. The discriminative stimulus effects of PCP (1.5 mg/kg, i.p.), dizocilpine (0.2 mg/kg, i.p.) and (+)-SKF-10047 (10 mg/kg, i.p.) were significantly attenuated by CGS-19755 (1 mg/kg, i.p.), but not by sigma$_1$ receptor antagonist BMY-14802 (10 mg/kg, i.p.) and NE-100 (5 mg/kg, i.p.). These results suggest that the discriminative stimulus effects of PCP are predominantly mediated via PCP binding sites on the NMDA receptor-ion channel complex, not via sigma$_1$ receptors. In addition, the PCP-like discriminative stimulus effects of (+)-SKF-10047 were demonstrated to be mediated via PCP binding sites. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Phencyclidine; Drug discrimination; NMDA receptor; Sigma receptor; Rat

1. Introduction

Phencyclidine (PCP), a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has been demonstrated to produce psychotomimetic effects in humans and to be a widely abused drug [28]. Although a single use of PCP produces aversive effects, long-term use of it causes abuse in humans [16]. In animals, several reinforced studies have shown that PCP produces the discriminative stimulus [13] and self-adminis-

tration [3]. Drug discrimination procedures have proven a valuable means of obtaining information relevant to the subjective effects of drugs [6,14]. The results of drug discrimination studies have suggested that blockade of NMDA neurotransmission by antagonists that act at different modulatory sites on the NMDA receptor-ion channel complex produces different discriminative stimulus effects. For example, non-competitive PCP-like NMDA receptor antagonists (e.g. dizocilpine) fully substitute for PCP [37,39], whereas competitive NMDA receptor antagonists [e.g. (±)-2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid (NPC 12626), 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonate (CPP), *cis*-4-phosphonomethyl-2-piperidine carboxylic acid

(CGS-19755)] substitute partially or not at all for PCP or PCP-like antagonists [9,17,22,37]. Furthermore, the strychnine-insensitive glycine receptor ligands [e.g. 7-chlorokynurenic acid (7-CKA), 3-amino-1-hydrox-ypyrrolid-2-one ((+)-HA-966), 1-amino-1-cyclopro-panecarboxylic acid (ACPC), glycine] and the polyamine antagonist ifenprodil can not substitute for PCP or dizocilpine [42,43]. In addition, competitive NMDA receptor antagonists (e.g. NPC 12626, CPP, CGS-19755) completely block the NMDA-like discriminative stimulus effects, whereas PCP does not [22,40]. These findings suggest that the discriminative stimulus induced through antagonism of the NMDA receptor is highly dependent on the nature of the antagonism. However, the mechanism behind the discriminative stimulus effects of PCP is not well understood.

PCP and a putative sigma$_1$ receptor agonist (+)-SKF-10047 produce similar stereotyped behavior in rats, characterized by hyperlocomotion and head-weaving [12,27]. PCP- or (+)-SKF-10047-induced stereo-typed behaviors were antagonized by haloperidol having a sigma$_1$ receptor antagonist properties [21,30,44]. Dizocilpine-induced head-weaving was potentiated by (+)-SKF-10047 and this potentiation was completely blocked by sigma$_1$ receptor ligands [20]. Further, PCP fully substitutes in rats trained with (+)-SKF-10047 [7,32,34] and (+)-SKF-10047 fully substitutes in rats trained with PCP [31,38]. These findings suggest a functional interaction between PCP binding sites and sigma$_1$ receptors. However, (+)-SKF-10047 binds to not only sigma$_1$ sites, but also PCP binding sites on the NMDA receptor-ion channel complex.

To examine the possible involvement of NMDA/sigma systems in PCP-induced discriminative stimulus, we investigated the effects of several NMDA receptor- and sigma receptor-related compounds in rats trained to discriminate PCP from saline.

2. Materials and methods

2.1. Animals

Male Fischer rats (Charles River Japan, Atsugi, Japan), weighing 230–250 g at the beginning of the experiments, were used. Each animal was housed individually in a regulated environment (23 ± 1°C, 50 ± 5% humidity) under a 12/12 h light-dark cycle (lights on at 9 h). Animals were food deprived to 85% of free feeding weight. Water was always available ad libitum in the home cage.

All experiments were performed in accordance with the Guidelines for Animal Experiments of the Nagoya University Graduate School of Medicine. The procedures involving animals and their care conformed with the international guidelines 'Principles of Laboratory Animal Care' (NIH publication no. 85-23, revised 1985).

2.2. Apparatus

Experiments were conducted in operant-conditioning chambers (Neuroscience Co., Tokyo, Japan) located in ventilated and sound-attenuated cubicles. The chambers were equipped with two response levers, spaced 16 cm apart, with a food pellet trough mounted midway between the levers. A houselight was located over the trough. Reinforcement consisted of a 45 mg food pellet (Bio Serv. Inc., Frenchtown, NJ, USA). Scheduling of reinforcement contingencies, reinforcement delivery and data recording were controlled by a computer system (Neuroscience Co.).

2.3. Drugs

The following drugs were used: (+)-*N*-allylnormeta-zocine hydrochloride ((+)-SKF-10047, Research Biochemicals, Natick, MA, USA); (+)-pentazocine (Dainippon Pharmaceutical Co. Ltd., Osaka, Japan); dextromethorphan hydrobromide (Sigma Chemical Co., USA); (+)-5-methyl-10,11-dihydro-5H-diben-zo[a,d]cyclohepten-5,10-imine (dizocilpine, Research Biochemicals); *N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenyl-ethoxy)phenyl]-ethylamine monohydrochloride (NE-100, Taisho Pharmaceutical Co., Saitama, Japan); α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazine-butanol hydrochloride (BMY-14802, Bristol-Myers Squibb, Qallinford, CT, USA); cocaine hydrochloride (Takeda Chemical Industries, Osaka, Japan); *cis*-4-phosphonomethyl-2-piperidine carboxylic acid (CGS-19755, Novartis, Basel, Switzerland); phencyclidine hydrochloride (PCP) (synthesized by us according to the method of Maddox et al. [24]).

BMY-14802 and (+)-pentazocine were initially dissolved in a minimum volume of 0.1 N HCl and then diluted with 0.9% NaCl solution and with distilled water, respectively (the pH of the solutions was adjusted to about four with NaHCO$_3$). CGS-19755 and NE-100 were dissolved in distilled water. Other drugs were dissolved in 0.9% NaCl solution. The dose of each drug refers to the drug form listed above. All drugs were injected i.p. in a volume of 1 ml/kg body weight.

2.4. PCP discrimination procedure

Rats were initially trained to press each of the two levers under a fixed ratio (FR) 1 schedule of food reinforcement. The FR response requirement for food delivery was gradually increased from 1 to 20. After responses under the FR 20 schedule of food reinforcement had stabilized, drug discrimination training was

begun. Training sessions were conducted daily. Rats were injected 10 min before the session with either saline or PCP (1.5 mg/kg, i.p.) according to a previous report [11]. In drug discrimination training sessions, PCP or saline was administered randomly to ensure that no olfactory cues associated with the two levers [8] would bias the discrimination. After administration of PCP, 20 consecutive responses (FR 20) on one lever produced a food pellet, whereas after administration of saline, 20 consecutive responses on the other lever produced a food pellet. Responding on the incorrect lever reset the FR requirement for the correct lever. Each session ended after 20 food pellets were delivered or 20 min had elapsed. The criteria for learning the discrimination were five consecutive sessions with: (1) more than 85% correct-lever responding before the first reinforcement; (2) more than 90% correct-lever responding throughout the session.

2.5. Drug testing procedure

Once the rats reliably discriminated PCP from saline, dose-response, substitution and drug combination tests were initiated. Test sessions were conducted once per week and the rats that fulfilled the criteria in a training session for three consecutive training sessions were used. Test sessions were identical to training sessions except that 20 consecutive responses on either lever resulted in delivery of a food pellet. In the dose-response and substitution tests, lever selection was examined after the administration of various doses of PCP or novel compounds. In the drug combination test, various doses of a test drug were administered before either the training dose of PCP or a dose of compound that engendered >95% PCP-lever responding when given alone.

Test drugs were administered 10 min before the session except CGS-19755, NE-100 and BMY-14802, which were given 30 min before the session.

2.6. Data analysis

The percentage of PCP lever responding (PCP-lever responding/responses on both levers) and response rate (responses on both levers/s to complete session) was calculated for each test session. Lever selection in a test session was not included if the animal did not obtain at least 10 reinforcements, however rate data were included from all test sessions. Drugs were considered to have generalized to the discriminative stimulus properties of PCP if more than 80% of the responses were on the drug-appropriate lever. The paired Student's t-test was used to compare the percentage of PCP lever responding or response rate during the combination test. P's < 0.05 were taken to indicate statistically significant differences.

3. Results

3.1. Acquisition and dose-response tests

The PCP discrimination required an average of 42 training sessions (range 36–48 sessions). Once rats attained the criterion, drug-saline discrimination stabilized and was maintained with a high degree of accuracy (>93%) for the remainder of the investigation (data not shown).

During the dose-response tests, PCP (0.1–3 mg/kg) produced a dose-related increase in PCP-appropriate responding. There was full substitution in all subjects after administration of doses that were equal to or greater than the training dose (Fig. 1, upper panel). The response rate decreased at the highest dose of PCP (Fig. 1, lower panel).

3.2. Substitution test

The effects of NMDA receptor-related compounds and cocaine in rats trained to discriminate PCP from saline are shown in Fig. 1. A non-competitive NMDA receptor antagonist, dizocilpine (0.01–0.2 mg/kg), produced a dose-related increase in PCP-appropriate re-
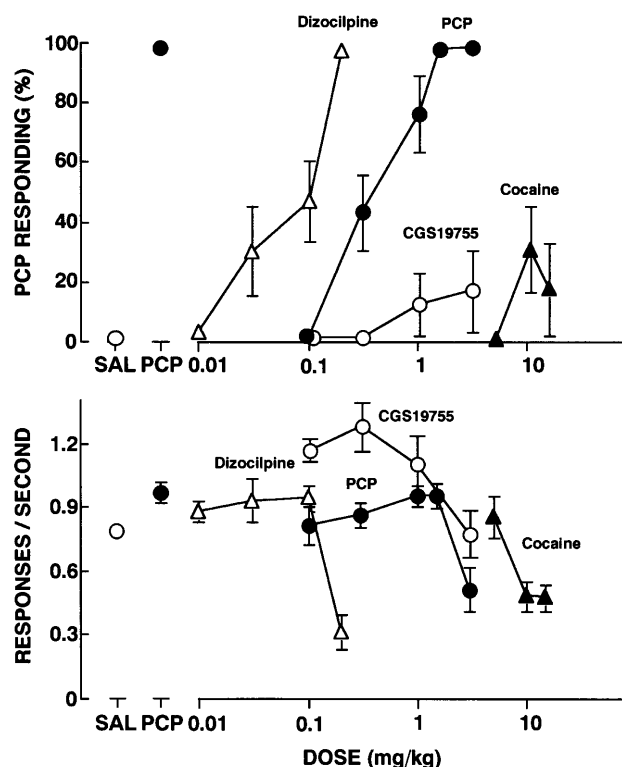

Fig. 1. Effects of NMDA receptor-related compounds and cocaine in rats trained to discriminate PCP (1.5 mg/kg) from saline. CGS-19755 and others were injected i.p. 30 and 10 min, respectively, before the session. Each point represents the mean ± S.E.M. in 6–10 rats. Points above SAL and PCP show control responses to saline and PCP (1.5 mg/kg), respectively.
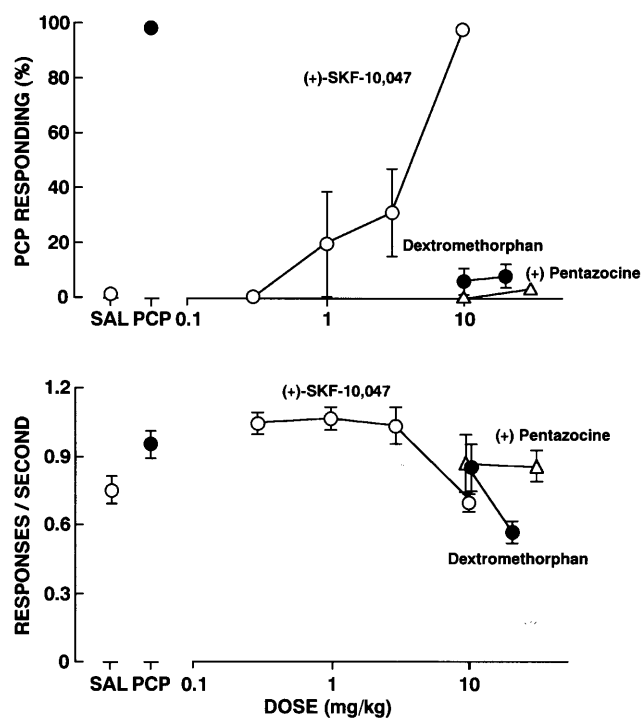
Fig. 2. Effects of sigma receptor-related compounds in rats trained to discriminate PCP (1.5 mg/kg) from saline. Test drugs and saline were injected i.p. 10 min before the session. Each point represents the mean ± S.E.M. in 6–8 rats. Points above SAL and PCP show control responses to saline and PCP (1.5 mg/kg), respectively.

sponding and fully substituted for PCP in all subjects. The response rate decreased at the highest dose of dizocilpine. However, a competitive NMDA receptor antagonist, CGS-19755 (0.1–3 mg/kg), did not engender PCP-appropriate responding and fully substituted for PCP in only one out of seven subjects. The response rate decreased as the dose of CGS-19755 increased.

The monoamine re-uptake inhibitor cocaine (5–15 mg/kg) engendered less than 40% PCP-appropriate responding. Furthermore, the percentage of PCP-appropriate responding produced by cocaine was not dose-related. However, full substitution for PCP was engendered in three out of nine subjects. The response rate decreased at the two highest doses of cocaine (10 or 15 mg/kg).

The effects of sigma receptor-related compounds in rats trained to discriminate PCP from saline are shown in Fig. 2. A sigma$_1$ receptor agonist, (+)-SKF-10047 (0.3–10 mg/kg), produced a dose-related increase in PCP-appropriate responding and fully substituted for PCP in all subjects. In contrast, other sigma$_1$ receptor agonists (+)-pentazocine (10–30 mg/kg) and dextromethorphan (10–20 mg/kg) did not engender PCP-appropriate responding and did not substitute for PCP. Each sigma$_1$ receptor agonist produced dose-related decreases in the response rate.

3.3. Drug combination test

CGS-19755 (0.1–3 mg/kg) which resulted in saline-appropriate response when tested alone, was given in combination with a training dose of PCP (Fig. 3A). The discriminative stimulus effects of PCP were significantly attenuated by pretreatment with CGS-19755 (1 mg/kg) without an effect on the response rate. Furthermore, CGS-19755 (0.1–3 mg/kg) was given in combination with either dizocilpine (0.2 mg/kg) or (+)-SKF-10047 (10 mg/kg) which fully substituted for PCP (Fig. 3B and 3C). The PCP-like discriminative stimulus effects of dizocilpine and (+)-SKF-10047 were also significantly attenuated by pretreatment with CGS-19755. Response rates in the combined administration of CGS-19755 with (+)-SKF-10047 significantly increased.

The influence of the sigma$_1$ receptor antagonists NE-100 and BMY-14802 on the discriminative stimulus effects of PCP, dizocilpine and (+)-SKF-10047 were also investigated (Fig. 4). The doses of NE-100 (5 mg/kg) and BMY-14802 (5 and 10 mg/kg) were based on a previous report that they inhibited PCP (7.5 mg/kg)-induced head-weaving behavior [20]. Either NE-100 (5 mg/kg) or BMY-14802 (5 mg/kg) which resulted in a saline-appropriate response when indicate that tested alone (data not shown), was given in combination with each training dose of PCP, dizocilpine (0.2 mg/kg) and (+)-SKF-10047 (10 mg/kg) which fully substituted for PCP. NE-100 affected neither the discriminative stimulus effects of PCP, dizocilpine or (+)-SKF-10047, nor the response rates. BMY-14802 did not affect the discriminative stimulus effects, but significantly decreased the response rates (except in combination with dizocilpine).

4. Discussion

A non-competitive NMDA receptor antagonist PCP (1.5 mg/kg, i.p.) was used as a discriminative stimulus in rats and dose-dependently substituted for PCP (0.1–3 mg/kg) as in previous studies [13,25,38,43]. PCP produced discriminative stimulus effects similar to those produced by a non-competitive NMDA receptor antagonist, dizocilpine, but not by a competitive NMDA receptor antagonist, CGS-19755. These results were consistent with the finding that the competitive and non-competitive NMDA receptor antagonists did not substitute for each other in cross substitution tests [17,23,38,39]. Thus, the competitive and non-competitive NMDA receptor antagonists produced different discriminative stimulus effects. Indeed, several studies indicate that antagonists of different modulatory sites on the NMDA receptor-ion channel complex differ in their discriminative stimulus effects (review introduction) and the order of potency to produce PCP-like
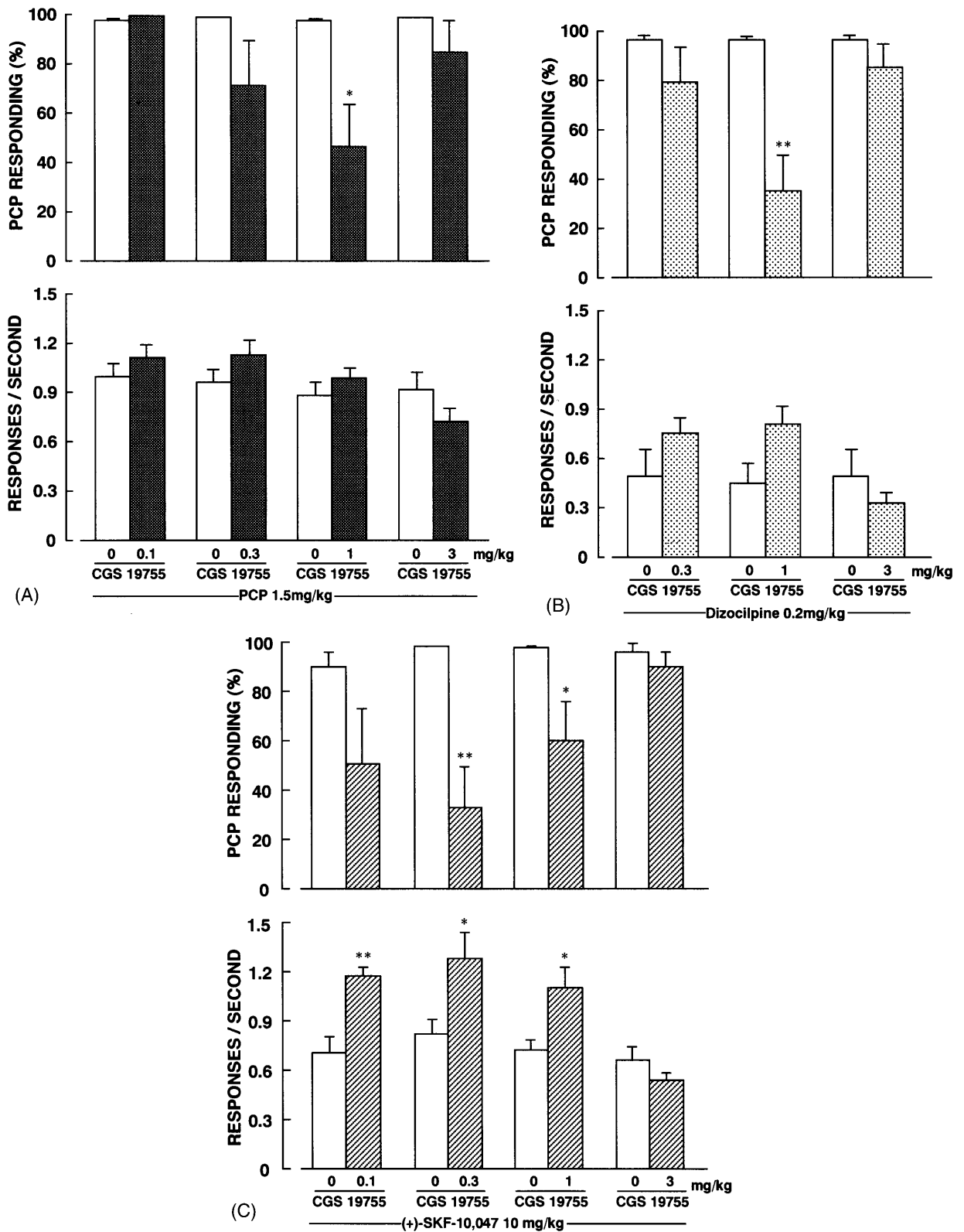
Fig. 3. Effects of CGS-19755 on PCP (A)-, dizocilpine (B)- and (+)-SKF-10047(C)-induced discriminative stimulus in rats trained to discriminate PCP (1.5 mg/kg) from saline. CGS-19755, PCP, dizocilpine and (+)-SKF-10047 were injected i.p. 30, 10, 10 and 10 min, respectively, before the session. Each column represents the mean ± S.E.M. in 6–10 rats. *$P < 0.05$, **$P < 0.01$ vs corresponding PCP (1.5 mg/kg), dizocilpine (0.2 mg/kg) or (+)-SKF-10047 (10 mg/kg) alone (Paired t-test).

discriminative stimulus effects correlates significantly with relative affinity for the PCP binding sites [2,22,38]. In the present study, the order of potency to produce PCP-like discriminative stimulus effects, dizocilpine > PCP, was consistent with relative affinity for the PCP binding sites [29]. Therefore, there is a possibility that the discriminative stimulus effects of PCP are predominantly mediated via PCP binding sites. This hypothesis is supported by the drug combination tests. Namely, the discriminative stimulus effects of PCP or dizocilpine were significantly attenuated by CGS-19755. These results are consistent with the finding that PCP-evoked physiological or behavioral effects were prevented by treatment with competitive NMDA receptor antagonists [10]. Since PCP binds to a site within the channel and thereby blocks NMDA-mediated gating of channel conductance [15], the blockade of L-glutamate-induced channel opening by pretreatment with the competitive NMDA receptor antagonist appears to prevent the binding of PCP by maintaining a closed channel conformation [35]. Consequently, the potency of PCP to block NMDA ion-channel function can be markedly diminished by the competitive NMDA receptor antagonists [10,18]. Based upon the studies described above, it would appear that a negative modulation of the

NMDA channel by the competitive NMDA receptor antagonists is the mechanism, since CGS-19755 attenuated the discriminative stimulus effects of PCP. This notion is also supported by the finding that CGS-19755 markedly reduced [^{3}H] dizocilpine and [^{3}H] 1-[1-(2-thienyl)cyclohexyl]piperidine (TCP) binding to the PCP site [35]. Furthermore, the attenuation of the PCP-like discriminative stimulus effects of dizocilpine by CGS-19755 could as likely be explained by the fact that CGS-19755 negatively modulated NMDA-induced channel opening thereby limiting access of dizocilpine to the PCP binding site and attenuating the PCP-like discriminative stimulus effects of dizocilpine.

As described in introduction, PCP binding sites on the NMDA receptor-ion channel complex has been demonstrated to functionally interact with sigma$_1$ receptors [20]. Therefore, the discriminative stimulus effects of PCP might be linked to a sigma$_1$ receptor system. In the present study, (+)-SKF-10047 fully substituted for PCP, whereas neither other sigma$_1$ receptor agonist, (+)-pentazocine or dextromethorphan, produced PCP-like discriminative stimulus effects. (+)-SKF-10047 binds to both the PCP binding sites and the sigma$_1$ site in brain with some selectivity. In rats trained with (+)-SKF-10047, sigma receptor ligands such as
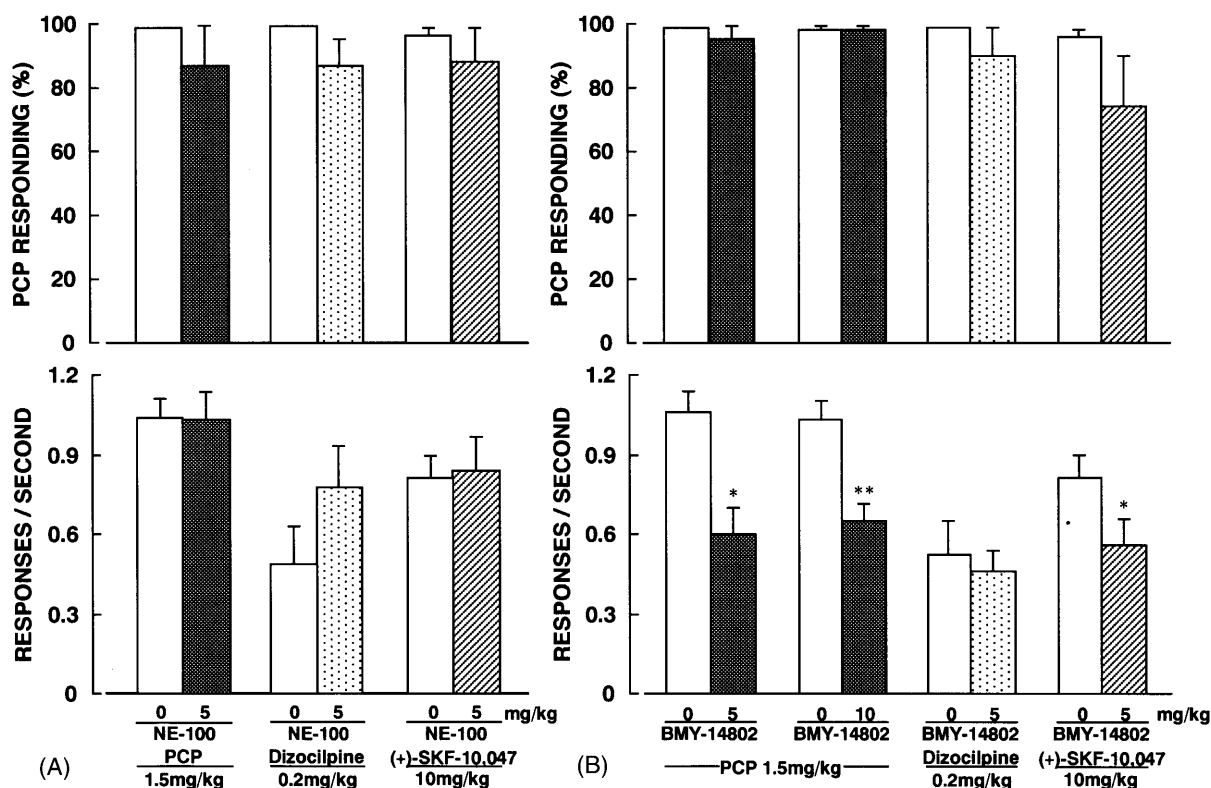

Fig. 4. Effects of NE-100 (A) and BMY-14802 (B) on PCP-, dizocilpine-, and (+)-SKF-10047-induced discriminative stimulus in rats trained to discriminate PCP (1.5 mg/kg) from saline. NE-100, BMY-14802 and others were injected i.p. 30, 30, and 10 min, respectively, before the session. Each column represents the mean ± S.E.M. in 6–10 rats. *$P < 0.05$, **$P < 0.01$ vs. corresponding PCP (1.5 mg/kg) and (+)-SKF-10047 (10 mg/kg) alone, respectively (Paired t-test).

haloperidol, 1,3-di-(2-tolyl)guanidine (DTG) and BMY-14802 did not substitute for (+)-SKF-10047 [33]. However, haloperidol antagonized the discriminative stimulus effects of (+)-SKF-10047 [1]. Thus, it is equivocal whether sigma receptor systems are involved in the discriminative stimulus effects of (+)-SKF-10047. BMY-14802 and NE-100, having high affinity and selectivity for the sigma$_1$ receptors, were examined for the ability to block the PCP-like discriminative stimulus effects. There are no reports on the use of BMY-14802 and NE-100 in this particular experimental context. BMY-14802 and NE-100 had a negligible effect on the discriminative stimulus effects of PCP or dizocilpine. Moreover, the PCP-like discriminative stimulus effects of (+)-SKF-10047 were also significantly attenuated by CGS-19755, but not BMY-14802 and NE-100. These results suggest that the interoceptive stimulus induced by PCP is not mediated by the sigma$_1$ receptor system and that the PCP-like discriminative stimulus effects of (+)-SKF-10047 are mediated via PCP binding sites, not sigma$_1$ receptors.

In the drug combination tests, the dose response curves of CGS-19755 showed a U shape, where higher doses did not significantly attenuate the discriminative stimulus effects of PCP, dizocilpine and (+)-SKF-10047. Since higher doses of CGS-19755 produced PCP-like responding in the substitution test, the loss of effectiveness of CGS-19755 at higher doses may be due to the partial PCP-like discriminative stimulus effects. Furthermore, CGS-19755 failed to completely antagonize the PCP-like discriminative stimulus effects, whereas it completely blocked the excitatory effects of PCP in the electrophysiological study [10]. Therefore, there is a possibility that PCP binding sites are not a pure component in mediating the PCP-like discriminative stimulus effects, although PCP-like discriminative stimulus effects are predominantly mediated via PCP binding sites. However, this point must be considered with caution, as the neuropharmacology of PCP and association with discriminative stimulus remain to be clarified.

The mesolimbic–mesocortical dopaminergic pathways have been implicated as important substrates both in schizophrenia and in the rewarding qualities of drugs of abuse [5,41]. The fact that PCP produces psychotomimetic effects and is widely abused in humans seems to suggest an involvement with mesolimbic–mesocortical dopaminergic pathways. In the present study, a monoamine re-uptake inhibitor, cocaine produced partial substitution in rats trained with PCP, whereas PCP fully substituted in rats trained with cocaine [19]. Since several studies reported that dopaminergic system plays a more important role than serotonergic or noradrenergic system in mediating the discriminative stimulus effects of cocaine [4,26,36], a partial cross substitution between PCP and cocaine suggests that the discrimina-

tive stimulus effects of PCP are mediated, at least in part, via dopaminergic system. However, the present result do not entirely rule out the possible involvement of serotonergic and noradrenergic systems. Therefore, further studies need to clarify the involvement of dopaminergic system in PCP-like discriminative stimulus effects.

In conclusion, this study provides evidence that the discriminative stimulus effects of PCP are predominantly mediated via PCP binding sites on the NMDA receptor-ion channel complex, and not via sigma$_1$ receptors. Further, the PCP-like discriminative stimulus effects of (+)-SKF-10047 were shown to be mediated via PCP binding sites.

Acknowledgements

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