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Role of the NMDA receptor subunit in the expression of the discriminative stimulus effect induced by ketamine

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Abstract

Ketamine, which is a non-competitive NMDA receptor antagonist, has been used as a dissociative anesthetic agent. However, chronic use of ketamine produces psychotomimetic effects, such as nightmares, hallucination and delusion. Therefore, the present study was designed to ascertain the role of the NMDA receptor and σ receptor in the discriminative stimulus effect induced by ketamine. Fischer 344 rats were trained to discriminate between ketamine (5 mg/kg, i.p.) and saline under a fixed-ratio 10 food-reinforced procedure. Non-competitive antagonists for both NR2A- and NR2B-containing NMDA receptors, such as phencyclidine (0.1–1 mg/kg, i.p.) and dizocilpine (3–30 μg/kg, i.p.), and the NR2A-containing NMDA receptor-preferred antagonist dextromethorphan (3–56 mg/kg, i.p.) fully substituted for the ketamine cue in a dose-dependent manner. By contrast, the NR2B-containing NMDA receptor antagonist ifenprodil (5–20 mg/kg, i.p.) exhibited no generalization. Additionally, the competitive NMDA antagonist 3-[(±)-2-carboxypiperazine-4-yl] propyl-1-phosphonic acid ((±)-CPP; 0.3–5.6 mg/kg, i.p.) and a σ receptor ligand DTG (0.3–3 mg/kg, s.c.) displayed no generalization to the ketamine cue. These results suggest that NR1/NR2A subunit containing NMDA antagonism may be critical for the production of the ketamine cue.

Keywords: Ketamine; Drug discrimination; NMDA receptor; Ifenprodil

1. Introduction

The NMDA receptor is the most clearly defined and the best characterized excitatory amino acid receptor subtype in the mammalian central nervous system (Monaghan et al., 1989). This receptor is a ligand-gated, ion channel-associated receptor complex with several pharmacologically distinct sites at which activity can produce alterations in NMDA neurotransmission (Foster and Fagg, 1987; Monaghan et al., 1989).

The behavioral, cognitive, and electrophysiological effects of antagonists to the NMDA receptor subtype in healthy subjects resemble some of the signs and symptoms of schizophrenia and dissociative disorders (Luby et al., 1959; Domino et al., 1965; Øye et al., 1993; Krystal et al., 1994; Malhotra et al., 1996). Ketamine, which is a non-competitive NMDA receptor antagonist, has been widely used as an intravenous or intramuscular anesthetic (Miyasaka and Domino, 1968). Furthermore, pain experienced by cancer patients that could not be relieved by morphine alone was effectively controlled by the co-infusion of ketamine with morphine (Yang et al., 1996). However, the chronic use of ketamine has been somewhat limited by its tendency to produce psychotomimetic effects such as nightmares, hallucination and delusion. Ketamine has also been shown to produce either positive symptoms of psychosis, such as illusions, disturbances in thought organization and delusions, or negative symptoms similar to those associated with schizophrenia including blunted emotional responses, emotional detachment and psychomotor retardation (Krystal et al., 1994). Thus, the very properties that restrict its clinical use have made ketamine an increasingly popular drug of abuse (Hancock and Stamford, 1999).

A major explanatory hypothesis for the pathophysiology of schizophrenia is the dopamine hypothesis, which maintains that dysfunction of the dopamine neurotransmitter system underlies the behavioral abnormalities associated with schizophrenia. An alternative explanation for the etiology of schizophrenia is dependent on dysfunction of the glutaminergic system. This hypothesis originates from the observation that intoxication induced by the non-competitive NMDA antagonist phencyclidine (PCP) closely

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mimics schizophrenia (Luby et al., 1959). Like PCP, ketamine and dizocilpine, another NMDA receptor antagonist, also produce schizophrenic symptoms (Ellison, 1995; Abi-Saab et al., 1998) and exacerbate symptoms in patients with schizophrenia (Javitt and Zukin, 1991). These findings suggest that PCP- and dizocilpine-treated animals may be useful as models for schizophrenia (Carlsson and Carlsson, 1990; Corbett et al., 1993, 1995).

It has been reported that PCP possesses an affinity for sigma (σ) receptors as well as NMDA receptors (Gundlach et al., 1985). The potential involvement of σ receptors in schizophrenia has been considered ever since their discovery (Debonnel and de Montigny, 1996). Furthermore, a major role for σ receptors is thought to regulate the glutamatergic system via NMDA receptors (Debonnel and de Montigny, 1996).

Therefore, the present study was designed to ascertain the role of the NMDA receptor and σ receptor in the discriminative stimulus effect induced by ketamine.

2. Materials and methods

The present study was conducted in accordance with the Guiding Principles for the Care and Use of Laboratory Animals, Hoshi University, as adopted by the Committee on Animal Research of Hoshi University, which is accredited by the Ministry of Education, Science, Sports and Culture of Japan.

2.1. Animals

Eight male Fischer 344 rats (Charles River Japan, Atsugi, Japan.) weighing between 210 and 230 g (80% free-feeding weight) were used in this study. Water was freely available for all of the rats in their individual home cages. The rats were housed at a room temperature of 22 ± 1 °C with a 12-h light/dark cycle (lights on 8:00–20:00).

2.2. Apparatus

Experiments were conducted in operant chambers (model GT8810; O'Hara, Tokyo, Japan) equipped with two levers, with a food cup mounted midway between the levers. White lamps were installed above each of the levers. White noise was used to mask extraneous sound. Reinforcement consisted of 20-mg food pellets (O'Hara).

2.3. Training procedure

Discrimination training was performed according to the method described by Suzuki et al. (1997). Briefly, before they were trained to discriminate between ketamine and saline, all rats were trained to press a lever. Training began under a reinforcement schedule of fixed ratio 1 (FR 1), in which the rat was presented with a food pellet each time it pressed a lever. When reinforcement was provided, the light above the lever was illuminated. The FR requirement for food reinforcement was gradually increased to a value of 10. After the response rates had stabilized under FR 10, rats were trained to discriminate between 5 mg/kg of ketamine and saline under an FR 10 schedule. In the discrimination training, ketamine (D) or saline (S) was administered i.p. 10 min before each session in a daily sequence of DDSS, according to a double alternation schedule, and the assignment of left and right levers to drug and saline states was counter-balanced. Rats were required to respond on the stimulus-appropriate lever to obtain reinforcement; there were no programmed consequences for responding on the incorrect lever. Generalization sessions were only performed after the discrimination criterion described below had been satisfied for at least five consecutive daily discrimination-training sessions (accuracy of at least 83% and fewer than 12 responses to obtain the first food pellet).

2.4. Generalization testing

Following the successful acquisition of discrimination between ketamine and saline, test sessions were usually conducted once or twice per week with training sessions on intervening days. During the test session, rats were placed in the operant box until they had made 10 responses on either lever or 5 min had elapsed. The pretreatment times and doses of drugs used were: 10 min for ketamine (1.25–5 mg/kg, i.p.); 30 min for PCP (0.1–1 mg/kg, i.p.), dizocilpine (3–30 μg/kg, i.p.), dextromethorphan (3–56 mg/kg, i.p.), ifenprodil (5–20 mg/kg, i.p.) and DTG (0.3–3 mg/kg, s.c.); 60 min for (±)-CPP (0.3–5.6 mg/kg, i.p.). Control tests with ketamine and saline indicate that the animals used in this study were under good stimulus control throughout the duration of all generalization testing.

2.5. Drugs

Ketamine hydrochloride (Sigma, St. Louis, MO, USA), phencyclidine hydrochloride (PCP; Taisho Pharmaceutical, Tokyo, Japan), (+)-5-methyl-10, 11-dihydro-5-*H*-dibenzo (a,d) cyclohepten-5, 10-imine maleate (dizocilpine; Merck/Banyu Pharmaceutical, Tokyo, Japan) and 3-[(±)-2-carboxypiperazine-4-yl] propyl-1-phosphonic acid ((±)-CPP; Sigma) were dissolved in saline. D-3-Methoxy-*N*-methylmorphinan (dextromethorphan; Sigma), ifenprodil tartrate (Grelan Pharmaceutical, Tokyo, Japan) and 1,3-di-*o*-tolyguanidine (DTG; Aldrich Chemical, Milwaukee, WI, USA) were dissolved in 5% DMSO (dimethyl sulfoxide; Wako, Tokyo, Japan) with 9% Tween 80/saline. All drugs were administered in a volume of 1.0 ml/kg, except for dextromethorphan (2.0 ml/kg for the 56 mg/kg dose).

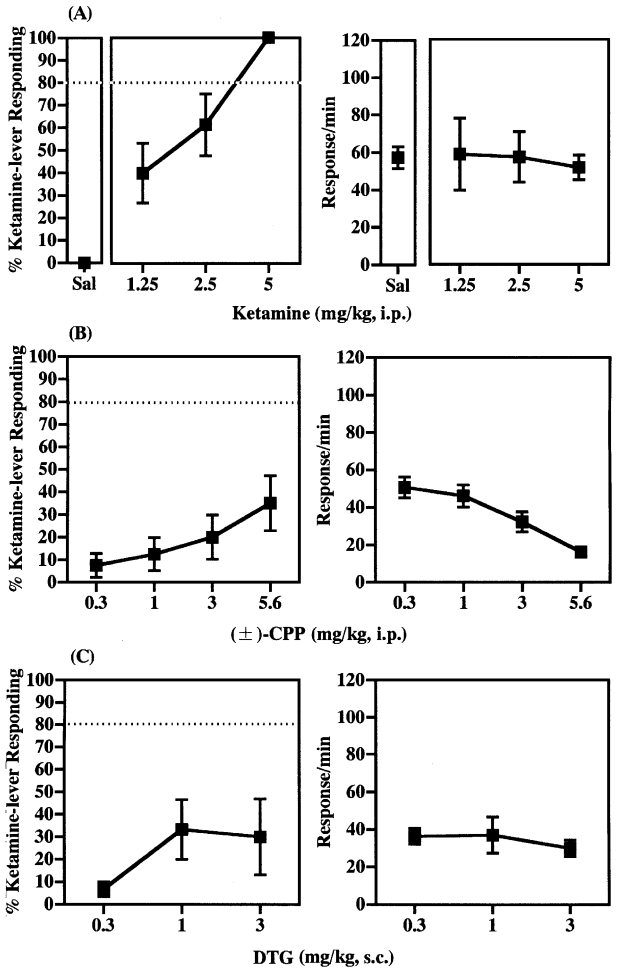

Fig. 1. (A) Dose–response curve for % ketamine-lever responding (left panel) and response rates (right panel) in rats trained to discriminate between 5 mg/kg ketamine and saline. Each point represents the mean percentage of ketamine- or saline-appropriate responding with S.E.M. of eight animals. (B) Lack of generalization to (±)-CPP to the discriminative stimulus properties of ketamine in rats trained to discriminate between 5 mg/kg ketamine and saline. Each point represents the mean percentage of ketamine-appropriate responding (left panel) and the mean response rates (right panel) with S.E.M. of eight animals. (C) Lack of generalization to DTG to the discriminative stimulus properties of ketamine in rats trained to discriminate between 5 mg/kg ketamine and saline. Each point represents the mean percentage of ketamine-appropriate responding (left panel) and the mean response rates (right panel) with S.E.M. of four animals.

2.6. Data analysis

During the training sessions, accuracy was defined as the number of correct responses as a percentage of the total responses before the first food pellet. During the test sessions, performance was expressed as the number of drug–lever responses as a percentage of the total responses upon completion of FR 10. Drugs were considered to have substituted for the discriminative stimulus effect of ketamine if more than 80% of the responses were on the drug-appropriate lever. Further, in rats that made fewer than 10 responses before 5 min had elapsed, responding was considered to be disrupted and the data obtained were not included in the calculations. ED_{50} values and their 95% confidence limits (95% CL) were determined by the method of Litchfield and Wilcoxon (1949).

3. Results

3.1. Acquisition and dose–response test

All rats acquired ketamine–saline discrimination, as determined by successful completion of five consecutive tests with ketamine and saline, within 45 training sessions (data not shown). Once rats attained the criterion, drug–saline discrimination stabilized and was maintained with a high degree of accuracy. Ketamine (1.25–5 mg/kg) was dose-dependently generalized to the training dose without a reduction in the response rate (Fig. 1A).

3.2. Generalization testing with competitive NMDA receptor antagonist

The results of a generalization test with the competitive NMDA recepor antagonist (±)-CPP are shown in Fig. 1B.

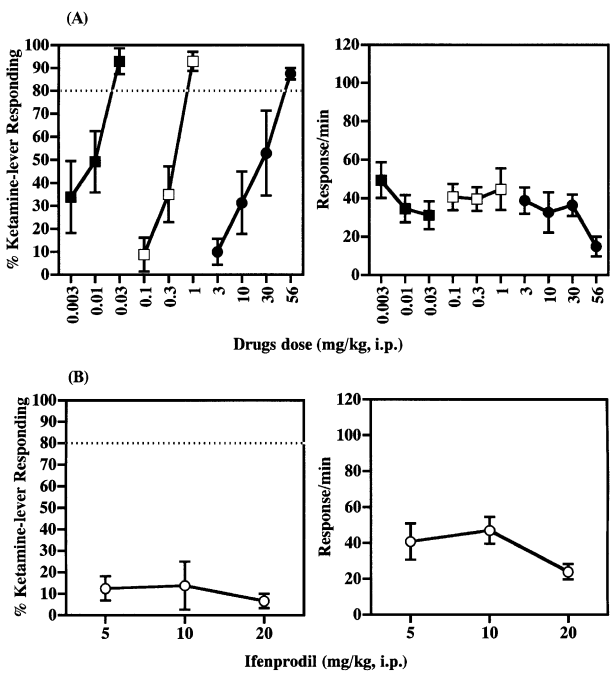

Fig. 2. (A) Generalization to phencyclidine (closed square), dizocilpine (open square) and dextromethorphan (closed circle) to the discriminative stimulus properties of ketamine in rats trained to discriminate between 5 mg/kg ketamine and saline. Each point represents the mean percentage of ketamine-appropriate responding (left panel) and the mean response rates (right panel) with S.E.M. of four to eight animals. (B) Lack of generalization to ifenprodil to the discriminative stimulus properties of ketamine in rats trained to discriminate between 5 mg/kg ketamine and saline. Each point represents the mean percentage of ketamine-appropriate responding (left panel) and the mean response rates (right panel) with S.E.M. of eight animals.

(±)-CPP displayed no generalization to a ketamine cue. (±)-CPP produced a maximum mean ketamine-lever selection of only 35% at a dose (5.6 mg/kg) that caused about a 72% reduction in the response rate compared to the control training session.

3.3. Generalization testing with non-competitive NMDA receptor antagonists

The results of generalization tests with the non-competitive NMDA receptor antagonists are shown in Fig. 2. The vehicle alone had no effect on the generalization to ketamine (data not shown). In contrast to the competitive NMDA receptor antagonist, PCP and dizocilpine fully substituted for a ketamine cue in a dose-dependent manner. Both PCP and dizocilpine produced dose-related generalization to ketamine, up to 92%. Furthermore, dextromethorphan dose-dependently substituted for ketamine with ketamine-lever responding of greater than 87.5%, with a reduction in the response rate to about 74% compared to the control training session. By contrast, the NR2B-containing NMDA receptor antagonist ifenprodil failed to substitute for a ketamine cue. Ifenprodil produced a maximum mean ketamine-lever selection of only 14% at 10 mg/kg, which did not affect the response rate. A higher dose of ifenprodil (20 mg/kg) was associated with a reduction in the response rate to about 58% compared to the control training session. The ED_{50} values and their 95% CL for all compound tested in the present study are presented in Table 1.

Table 1
ED_{50} values (expressed as mg/kg of each compound with 95% CL) for percentage of ketamine-appropriate responding when different NMDA receptor antagonists were substituted for the 5 mg/kg training dose of ketamine

Compound	ED_{50} values (95% CL) mg/kg	n/N
Competitive antagonist (±)-CPP	None	1/8
Non-competitive antagonist Ketamine (NR1/NR2A≒NR1 /NR2B)	1.71 (1.01–2.91)	8/8
Phencyclidine (NR1/NR2A≒NR1 /NR2B)	0.35 (0.19–0.65)	7/8
Dizocilpine (NR1/NR2A≒R1/NR2B)	0.0071 (0.003–0.016)	6/7
Dextromethorphan (NR1/NR2A > NR1/NR2B)	17.74 (7.33–42.93)	4/4
Ifenprodil (NR1/NR2A ≪ NR1/NR2B)	None	0/8
σ Receptor ligand DTG	None	1/4

n/N: the number of subjects that generalized to the discriminative stimulus effects of ketamine (n)/the number of animals that shown at least 10 responses on either the ketamine or saline lever (N).

3.4. Generalization testing with σ receptor ligand

The results of a generalization test with the σ receptor ligand DTG are shown in Fig. 1C. The vehicle alone had no effect on the generalization to ketamine. DTG displayed no generalization to a ketamine cue. DTG produced a maximum mean ketamine-lever selection of only 33% at 1 mg/kg, which did not affect the response rate.

4. Discussion

Drug-discrimination studies that provide information relevant to the subjective effects of drugs in humans are a sensitive and pharmacologically specific measure of behavior (Balster, 1990; Bobelis and Balster, 1993). The present study demonstrated that the non-competitive NMDA receptor antagonist ketamine produced a discriminative stimulus effect in rats. After discrimination acquisition, rats maintained ketamine-saline discrimination with a high degree of accuracy. Under these conditions, the competitive NMDA receptor antagonist (±)-CPP failed to substitute for a ketamine cue. Similar findings have been previously observed regarding the lack of generalization between non-competitive and competitive NMDA receptor antagonists in rats (Willetts et al., 1989; Bobelis and Balster, 1993; Grant et al., 1996). Since the non-competitive NMDA receptor antagonist blocks NMDA receptor-mediated responses by binding to the cation channel of the NMDA receptor complex (Collingridge and Lester, 1989), the present data clearly suggest that the discriminative stimulus effects of ketamine may be related to its ability to block the NMDA receptor-associated channel.

Most NMDA receptors in the brain are thought to be pentameric or tetrameric complexes of the NR1 subunit and one or more of four NR2 subunits (NR2A-2D) (Kutsuwada et al., 1992; Monyer et al., 1992). Thus, the differential expression of NR2 subunits in various regions of the brain may account for the diversity of NMDA receptor subtypes in the central nervous system (Watanabe et al., 1993; Standaert et al., 1994; Mori and Mishina, 1995). The distribution of NMDA receptor channel subunit mRNAs in the adult rodent brain has been examined by in situ hybridization analyses (Kutsuwada et al., 1992). NR1 subunit mRNA is distributed ubiquitously in the brain. In contrast, the four NR2 subunit mRNAs show characteristic distributions in the brain. The molecular diversity of the NR2 subunit family probably underlies the pharmacological and electrophysiological heterogeneity of the NMDA receptor channel. Generally, the NMDA receptor is composed of a common NR1 subunit and one of four NR2 subunits (NR2A-2D) (Kutsuwada et al., 1992; Monyer et al., 1992).

The non-competitive NMDA receptor antagonist PCP, which shows the antagonistic action on both NR1/NR2A- and NR1/NR2B-subunit containing receptors (Avenet et

al., 1997), causes an associated apathetic state and a type of formal thought disorder that is a distinctive feature of schizophrenia in humans (Javitt and Zukin, 1991; Krystal et al., 1994; Malhotra et al., 1996). It has been shown that like PCP, the prototypical NMDA receptor antagonist dizocilpine possesses a similar affinity for NR1/NR2A- and NR1/NR2B-subunit containing receptors (Avenet et al., 1997). It is of interest to note that dextromethorphan, which is one of the most widely used non-narcotic antitussive drugs, is thought to be NR1/NR2A-containing NMDA receptor-preferred antagonist (Avenet et al., 1997). In the present study, we demonstrated that PCP, dizocilpine and dextromethorphan substituted for a ketamine cue. These findings indicate that the blockade of NR1/NR2A subunit of NMDA receptors is, at least in part, implicated in the discriminative stimulus effects of ketamine.

It should be the noted that a competitive NMDA receptor antagonist (±)-CPP posesses its affinity for both NR1/NR2A- and NR1/NR2B-subunit containing NMDA receptors. Considering the present evidence for the lack of generalization of (±)-CPP to the ketamine cue, these findings suggest that the blockade of both NMDA binding site and its associated channel may be dissociated from the ketamine cue.

The dextromethorphan-induced discriminative stimulus effect was elicited only when high doses of dextromethorphan were used. Thus, it is unlikely that the doses of dextromethorphan used clinically to produce adequate antitussive effects may produce ketamine-like side effects.

Several lines of evidence have suggested that ifenprodil shows a high specificity for recombinant heteromeric NR1/NR2B-subunit containing NMDA receptors (Avenet et al., 1997; Williams, 1993). We found here that ifenprodil failed to substitute for a ketamine cue. These data suggest the possibility that the NR1/NR2B-subunit containing NMDA receptor may not be responsible for the expression of ketamine-like discriminative stimulus effects. This phenomenon may lead to the idea that the antagonist that can selectively block the NR1/NR2B-subunit containing NMDA receptor does not produce the ketamine-like side effects, such as psychotomimetic effects.

In the present study, DTG, a highly selective and high-affinity ligand of the σ site in vitro (Weber et al., 1986), failed to substitute for a ketamine cue. However, it was reported that DTG at doses used in the present study displayed generalization to a PCP cue in a dose-dependent manner (Holtzman, 1989). It is well characterized that PCP has the affinity not only for NMDA receptor but also σ receptor (Gundlach et al., 1985). It is therefore likely that the different mechanisms may be involved in the expression of the discriminative stimulus effects induced by PCP and ketamine. Furthermore, the present data provide evidence for the lack of direct involvement of σ receptor in the production of the ketamine-induced discriminative stimulus effect.

In conclusion, the non-competitive NR1/NR2A-subunit containing NMDA receptor antagonist may be critical for the expression of the discriminative stimulus effect induced by ketamine. Furthermore, the non-competitive NMDA receptor antagonist without these mechanisms is unlikely to produce ketamine-like side effects.

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