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Competitive NMDA and Strychnine-Insensitive Glycine-Site Antagonists Disrupt Prepulse Inhibition

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FURUYA, Y. AND H. OGURA. *Competitive NMDA and strychnine-insensitive glycine-site antagonists disrupt prepulse inhibition.* PHARMACOL BIOCHEM BEHAV **57**(4) 909–913, 1997.—Prepulse inhibition (PPI) is thought to reflect the operation of a sensorimotor gating system in the brain. Sensorimotor gating abnormalities have been identified in schizophrenic patients, and various neural systems are involved in this function. To study the modulation of the sensorimotor gating system by the *N*-methyl-D-aspartate (NMDA) receptor–channel complex, the effects of noncompetitive and competitive NMDA antagonists on PPI were examined in rats. PPI was not disrupted by CGS 19755, a competitive NMDA antagonist, at 30 min after subcutaneous (SC) administration. However, CGS 19755 (40 mg/kg SC) decreased PPI at 120 min after administration with a marked decrease of startle amplitude. Late onset of the effect of CGS 19755 was also observed in the increase of spontaneous locomotor activity (SLA). On the other hand, phencyclidine, a noncompetitive NMDA antagonist, disrupted PPI at 30 min after administration and increased SLA from 20 min after administration. PPI was also disrupted by bilateral intracerebroventricular administration of 5,7-dichlorokynurenate (10 and 20 μg/side × 2), an antagonist at the strychnine-insensitive glycine receptor, which is an allosteric binding site in the NMDA receptor–channel complex. It is concluded that the NMDA receptor–channel complex plays an important role in regulation of PPI. © 1997 Elsevier Science Inc.

Prepulse inhibition CGS 19755 Phencyclidine 5,7-Dichlorokyn urenate NMDA receptor
Strychnine-insensitive glycine receptor Rat Spontaneous locomotor activity

THE amplitude of the acoustic startle response is reduced by a preceding weak stimulation, which by itself does not elicit the startle response. This phenomenon is named prepulse inhibition (PPI) and is thought to reflect the operation of a sensorimotor gating system in the brain (3,8,32). PPI is disrupted in patients suffering from schizophrenia (4,9), Huntington's disease (32,33), obsessive compulsive disorder (31,32), nocturnal enuresis (22), and Tourette's syndrome (6). Pharmacological studies have revealed that various types of receptors modulate the sensorimotor gating system. Activation of dopamine and 5-HT_2 receptors, which produces psychotomimetic effects, disrupts PPI (20,24,29). Recently, multiple serotonin receptor subtypes—not only 5-HT_2, but also 5-HT_{1A} and 5-HT_{1B} receptors—have been proposed to modulate this system (25,29,30).

The *N*-methyl-D-aspartate (NMDA) receptor is also thought to modulate sensorimotor gating. Many studies have shown that the noncompetitive NMDA antagonists MK-801 and phencyclidine disrupt PPI (13,18,19). However, the competitive NMDA antagonists *cis*-4-phosphonomethyl-2-piperidine-carboxylate (CGS 19755) and 2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid (NPC 12626) did not reduce PPI (18). It is not apparent why competitive and noncompetitive antagonists should produce substantially different behavioral effects. However, there may be a difference in the timing of the maximal effect. Some investigators have indicated that the effect of competitive NMDA antagonists shows late onset and persists for a long time (1,2). Hence, we examined the effect of CGS 19755 on PPI at 30 and 120 min after administration. The effect of CGS 19755 on spontaneous locomotor activity (SLA) was also measured to check the time course of its effect.

The aim of this work was to determine whether reduction of NMDA receptor-mediated neurotransmission by various types of antagonists disrupts PPI. The effects of representative competitive and noncompetitive NMDA antagonists,

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CGS 19755 and phencyclidine, on PPI were examined. A strychnine-insensitive glycine receptor is known to modulate allosterically the NMDA receptor–channel complex, and therefore, the effect of 5,7-dichlorokynurenate, an antagonist at this receptor, was also studied.

MATERIALS AND METHODS

Subjects

Adult male Wistar rats (SLC, Shizuoka, Japan), weighing 190–320 g, were housed at 23 ± 1°C in a humidity-controlled (55 ± 10%) animal facility under a 12 L:12 D cycle (lights on at 0700 h) and allowed access to tap water and food ad lib. Six animals were used in each treatment group. Each animal was used only once.

Drugs

cis-4-Phosphonomethyl-2-piperidine-carboxylate hydrochloride (CGS 19755) (synthesized at Eisai) and 1-(1-phenylcyclohexyl)piperidine hydrochloride (phencyclidine) (synthesized at Eisai) were each dissolved in distilled water. They were administered subcutaneously (SC) to animals in a volume of 2 ml/kg. The same volume of distilled water was administered to control animals. 5,7-Dichlorokynurenate (Research Biochemicals International, Natick, MA, USA) was dissolved in PBS (phosphate-buffered saline, pH 7.4) with a small volume of NaOH (aq). Then, the solution was adjusted to pH 8 with HCl, and its final concentration was adjusted to 10 μg/5 μl. By dilution of this solution with PBS, a solution of 5 μg/5 μl was prepared. Each test animal was injected with 5 (5 and 10 μg/side) or 10 (20 μg/side) μl of solution bilaterally into the cerebroventricle. Control animals received PBS (5 μl/side) bilaterally.

Surgery

For intracerebroventricular (ICV) injection of 5,7-dichlorokynurenate, an animal was anesthetized with sodium pentobarbital [50 mg/kg intraperitoneally (IP)] and stainless-steel guide cannulae (external diameter 0.6 mm) were implanted bilaterally 3 or 4 days prior to the experiment. The lower end of the cannula was located at 2.0 mm above the lateral ventricle [AP −0.8 mm, L ± 1.5 mm, V +2.0 mm, according to the atlas of Paxinos and Watson (23)].

Behavioral Test Procedures

Prepulse inhibition. The chamber used consisted of an acrylic cylinder (diameter 8 cm, length 27 cm) mounted on an acrylic board (30 × 30 cm). Acoustic stimuli were generated by a phono stimulator (San-Ei Instrument Co., Ltd., Tokyo, Japan) and an audio amplifier (TA-2650, Sony, Tokyo, Japan). Startle response was defined as the change of weight that was detected by a load cell (LM-1KA, Kyouwa Dengyo Co., Ltd., Tokyo, Japan) attached to the chamber. Data were collected as 512 0.2-ms voltage readings, which were digitized by a digital indicator (AD-4532A, A & D Co., Ltd., Tokyo, Japan) and stored on a data processor (ATAC-450, Nihon Kohden Co, Ltd., Tokyo, Japan).

Rats were placed in the chamber and allowed to acclimate for 10 min, then the experimental session was started. Background noise was set at 65 dB of white noise throughout the acclimination period and the session. In a session, two types of 10 trials (total of 20 trials) were given in pseudorandom order after an initial startle stimulus (20-ms burst of 120-dB white noise). One of the types was a pulse-alone trial (P alone), which involved a 20-ms burst of 120-dB white noise, and the other was a prepulse-and-pulse trial (PP & P), which involved a 20-ms burst of 80-dB white noise followed by the same pulse as in the P alone 100 ms later. The intertrial intervals averaged 40 s (20–60 s) and were pseudorandomized. Startle response data were collected for 102.4 ms from the start of pulse presentation, and the subjects' responses to repetitions of each trial type were averaged across the session. The height of the first, highest peak that appeared about 30 ms after the start of pulse presentation was defined as the startle amplitude. The experimental schedule was controlled by a computer (PC-9801 FA, NEC, Tokyo, Japan).

The measurement of startle response started 30 or 120 min after SC drug administration or 15 min after ICV administration. 5,7-Dichlorokynurenate was injected into the bilateral cerebroventricles through the injection cannula (external diameter 0.3 mm), which reached 2 mm below the end of the guide cannula. The drug was infused at a rate of 5 μl/min, and the injection cannula was left for 30 s after the injection.

Spontaneous locomotor activity (SLA). A rat was placed in a Plexiglas box (42 × 25 × 18 cm) immediately after SC drug administration. SLA was measured for 240 min with a SCANET SV-10 (Toyo Sangyo Co., Ltd., Toyama, Japan), which detects the movement of an animal in terms of the number of times an infrared beam is broken, and accumulated every 10 min.

Data Analysis

In the prepulse inhibition study, the initial startle stimulus was excluded from statistical analysis. Prepulse inhibition is presented as percent inhibition of P alone startle amplitude according to the formula (1 − SA in PP & P/SA in P alone) × 100, where SA in PP & P and SA in P alone are the averaged startle amplitude in PP & P and P alone, respectively. Data were analyzed by a one-way analysis of variance (ANOVA) with the treatment as a factor. Post hoc individual comparison was carried out by using Dunnett's test.

Data from SLA were analyzed by a two-way ANOVA with the treatment and time bin as factors, followed by Dunnett's post hoc test for individual comparison. A p-value less than 0.05 was considered to represent a significant difference.

RESULTS

Prepulse Inhibition

The effects of drugs on PPI are presented in Fig. 1. CGS 19755 failed to affect % PPI 30 min after treatment [$F(3, 20) = 0.68$, NS]. However, 120 min after treatment CGS 19755 decreased % PPI [$F(3, 20) = 6.94$, $p < 0.01$], having a significant effect at a dosage of 40 mg/kg ($p < 0.01$). Phencyclidine decreased % PPI 30 min after treatment [$F(3, 20) = 4.21$, $p < 0.05$], and the decrement was significant at a dosage of 4 mg/kg ($p < 0.01$). Intracerebroventricularly administered 5,7-dichlorokynurenate also decreased % PPI [$F(3, 20) = 8.71$, $p < 0.01$], and effective dosages were 10 and 20 μg/side × 2 ($p < 0.05$ and $p < 0.01$, respectively).

The effects of the drugs on startle amplitude are presented in Table 1. At 30 min after administration, CGS 19755 decreased the startle amplitude in P alone [$F(3, 20) = 4.53$, $p < 0.05$] but not in PP & P [$F(3, 20) = 2.71$, NS]. At 120 min after administration, CGS 19755 markedly decreased the startle amplitude in both P alone [$F(3, 20) = 29.46$, $p < 0.01$] and PP & P [$F(3, 20) = 8.35$, $p < 0.01$]. Phencyclidine decreased the startle amplitude in P alone [$F(3, 20) = 8.45$, $p < 0.01$] but

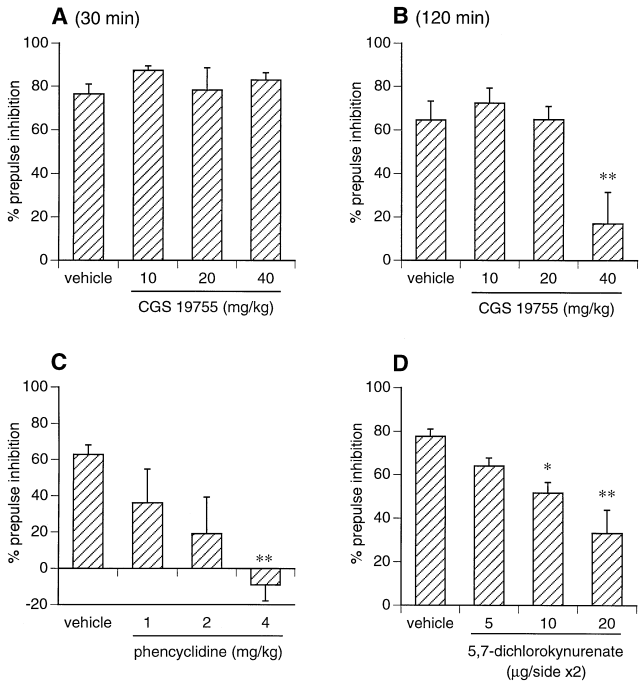

FIG. 1. Effects of CGS 19755 (A and B), phencyclidine (C), and 5,7-dichlorokynurenate (D) on prepulse inhibition in rats. Prepulse inhibition is presented as percent inhibition of P alone startle amplitude according to the formula (1 − SA in PP & P/SA in P alone) × 100, where SA in PP & P and SA in P alone are the averaged startle amplitude in PP & P and P alone, respectively. CGS 19755 and phencyclidine were administered SC 30 min (A) or 120 min (B) and 30 min (C) before the test, respectively. 5,7-Dichlorokynurenate was injected ICV 15 min before the test (D). Data represent mean ± SEM of six animals per group. $*p < 0.05$ and $**p < 0.01$ compared with vehicle control group by Dunnett's post hoc test.

TABLE 1

EFFECTS OF CGS 19755, PHENCYCLIDINE, AND 5,7-DICHLOROKYNURENATE ON ACOUSTIC STARTLE AMPLITUDE IN RATS

Drug	Dose	Startle Amplitude (g)	
		P alone	PP & P
CGS 19755 (30 min)	Vehicle	147.1 ± 20.0	31.7 ± 5.3
	10	149.4 ± 9.8	18.6 ± 2.8
	20	86.4 ± 21.0	17.4 ± 6.3
	40	79.9 ± 17.9*	13.2 ± 4.3
CGS 19755 (120 min)	Vehicle	209.0 ± 28.4	72.2 ± 18.4
	10	50.8 ± 8.4**	12.2 ± 4.8**
	20	42.9 ± 8.7**	15.2 ± 3.2**
	40	28.3 ± 4.9**	21.4 ± 3.0**
Phencyclidine	Vehicle	135.5 ± 17.4	47.0 ± 5.1
	1	111.5 ± 15.7	63.0 ± 14.9
	2	61.6 ± 11.9**	40.1 ± 5.5
	4	54.5 ± 5.8**	57.9 ± 5.6
5,7-dichlorokynurenate	Vehicle	348.9 ± 46.0	74.1 ± 11.1
	5	121.9 ± 26.1**	40.5 ± 6.6
	10	219.6 ± 27.0*	105.0 ± 16.2
	20	140.0 ± 26.1**	102.6 ± 32.5

CGS 19755, phencyclidine, and 5,7-dichlorokynurenate were administered SC 30 min or 120 min, 30 min, and 15 min before the test, respectively. Doses are expressed in mg/kg for CGS 19755 and phencyclidine and in μg/side for 5,7-dichlorokynurenate. P alone means a 120-dB pulse alone. PP & P means a 120-dB pulse 100 ms after an 80-dB prepulse. Data represent mean ± SEM for six animals per group. $*p < 0.05$ and $**p < 0.01$ compared with vehicle control group by Dunnett's post hoc test.

not in PP & P [F(3, 20) = 1.38, NS]. 5,7-Dichlorokynurenate produced an effect similar to that of phencyclidine on the startle amplitude in P alone [$F(3, 23) = 10.14, p < 0.01$] and PP & P [$F(3, 20) = 2.45$, NS].

Spontaneous Locomotor Activity

The effects of CGS 19755 and phencyclidine on SLA are presented in Fig. 2. CGS 19755 increased SLA [$F(3, 20) = 9.75, p < 0.01$]. Post hoc analysis showed that SLA did not increase from 10 to 70 min after administration of CGS 19755. SLA increased 80 min after administration, and the effect persisted for more than 240 min after treatment at 40 mg/kg. Phencyclidine also increased SLA [$F(3, 20) = 22.17, p < 0.01$], causing a significant increment from 20 to 220 min after administration at 4 mg/kg.

DISCUSSION

Our results provide further evidence that the NMDA receptor–channel complex is involved in modulation of the sensorimotor gating system. We found that a competitive NMDA antagonist, CGS 19755, disrupted PPI as effectively as a noncompetitive NMDA antagonist such as phencyclidine, although the effect of CGS 19755 showed late onset and required a high dosage. The difference between the present results and the previous report that competitive NMDA antagonists had no effect on PPI (18) is therefore due to the differences in timing tested and in dosage administered. As shown in the case of 5,7-dichlorokynurenate in this study, an antagonist at the strychnine-insensitive glycine site of the NMDA receptor–channel complex also diminished PPI. It is highly likely that hypofunction of the NMDA receptor–channel complex is linked to an impairment of the sensorimotor gating system.

A difference in time of onset of the behavioral effects was obvious between competitive and noncompetitive NMDA antagonists. The slow onset of action of CGS 19755 was observed not only in disruption of PPI but also in reduction of startle amplitude. Moreover, CGS 19755 increased SLA from 80 min after administration, whereas the effect of phencyclidine was significant from 20 min after administration. The time course of the effect of CGS 19755 on SLA is similar to that reported by other investigators (2). The late appearance of behavioral effects was also seen in a drug discrimination analysis. Baron and Woods (1) found that the competitive NMDA antagonists tended to produce peak response at more than 60 min after administration in pigeons trained to discriminate either phencyclidine or CGS 19755 from saline, whereas the response of noncompetitive NMDA antagonists peaked much earlier. Competitive NMDA antagonists in general have slow access to the brain when administered systemically, because of their poor lipophilicity (21).

In this study, a relatively high dosage of CGS 19755 was needed for disruption of PPI and increment of SLA compared with doses showing antagonism of NMDA-induced convul-

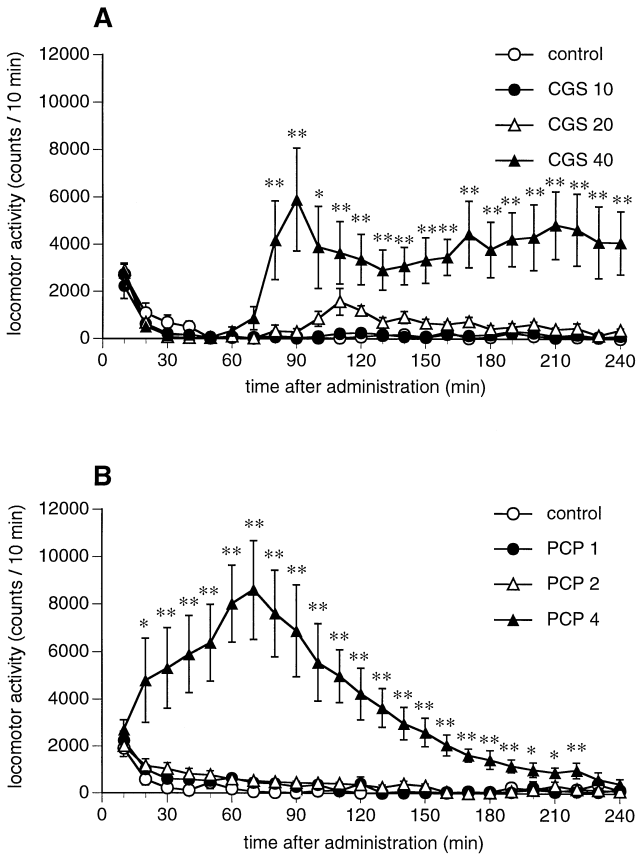

FIG. 2. Effects of CGS 19755 (A) and phencyclidine (B) on spontaneous locomotor activity in rats. CGS 19755 (CGS) and phencyclidine (PCP) were administered SC immediately before the measurement. Data represent mean ± SEM of six animals per group. $*p < 0.05$ and $**p < 0.01$ compared with vehicle control group by Dunnett's post hoc test.

sions (2–5 mg/kg IP in mice) (2), whereas phencyclidine exhibited these pharmacological effects at a similar dosage (17). It is not clear why CGS 19755 showed such a discrepancy of effective dosages among the tests, but other investigators have also reported that a higher dosage of competitive NMDA antagonist is needed to induce increment of SLA and motor impairment than to produce the anticonvulsive effect (2,7,26).

The disrupting effect of CGS 19755 on PPI was accompanied by a marked decrease of startle response when the test was started 120 min after administration. The decrease may be a consequence of muscle relaxation (2). The possibility that the reduction of startle amplitude affects PPI cannot be entirely excluded. However, it seems unlikely, because haloperidol and 1-(*m*)-chlorophenylpiperazine (mCPP), a 5-HT_{2C} agonist, which decrease startle response, had no effect on PPI (20,29). Furthermore, drug-induced changes in PPI have been reported to occur independently of changes in startle amplitude (13). In our study, the relation between PPI and startle amplitude in P alone was examined in each CGS 19755 group (120 min after administration) and no significant correlation was found. In addition, the effects of reduced startle response on PPI and of CGS 19755 on baseline amplitude were investigated to see whether disruption of PPI by CGS 19755 was based on a floor effect of startle amplitude in PP & P. When the pulse intensity was decreased from 120 dB to 105 dB and the startle amplitude in P alone was as small (27.5 ± 5.0) as at the high dosage of CGS 19755, PPI was not reduced (93.7 ± 1.7%). CGS 19755 at 10, 20, or 40 mg/kg did not affect the baseline amplitude without pulse presentation (about two in each group). These results suggest that there is no direct relation between disruption of PPI and decrement of startle amplitude, and that CGS 19755-induced disruption of PPI is not based on a floor effect of startle amplitude in PP & P.

As another approach to ascertaining the influence of the NMDA receptor–channel complex on the sensorimotor gating system, we tested the effect on PPI of 5,7-dichlorokynurenate, an antagonist at the strychnine-insensitive glycine receptor. The strychnine-insensitive glycine receptor is an allosteric site of the NMDA receptor–channel complex. Glycine and/or D-serine are thought to be endogenous ligands at the site and to play a co-agonist role at the complex (10,34). Intracerebroventricularly administered 5,7-dichlorokynurenate inhibited PPI in a dose-dependent manner and slightly inhibited startle amplitude. It appears that the NMDA receptor–channel complex in the brain is important for regulation of PPI.

A hypothesis of glutamatergic deficiency in schizophrenia has been proposed (5,15), for the following reasons. First, PCP mimics both positive and negative symptoms in schizophrenic patients (12,14). Second, the glutamatergic system is hypofunctional in the brain of schizophrenic patients. The release of glutamate is reduced in synaptosomes from the frontal cortex of schizophrenics (27,28). Furthermore, increments of [^{3}H]MK-801 and [^{3}H]glycine binding, which may result from compensation of the reduction of glutamate release, have been observed in some brain regions of schizophrenic patients (11,16). Therefore, abnormal behavior in animals induced by NMDA antagonists is thought to be a model of schizophrenia. The results of this study, together with the clinical evidence that PPI is disrupted in the schizophrenic patient (4,9), support this hypothesis.

In conclusion, we have found that PPI is inhibited by a competitive NMDA antagonist and a strychnine-insensitive glycine-site antagonist, as well as by a noncompetitive NMDA antagonist. These results provide further evidence that the NMDA receptor–channel complex in the brain plays a significant role in regulation of PPI and may be related to some symptoms in various neuropsychiatric disorders, especially schizophrenia.

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