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Changes in prepulse inhibition after local administration of NMDA receptor ligands in the core region of the rat nucleus accumbens

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Abstract

The dopamine and glutamate hypotheses are two pharmacological models for schizophrenia. In the present investigations, the prepulse inhibition paradigm was used to evaluate the role of the nucleus accumbens core region in both models. Prepulse inhibition is known to be decreased in schizophrenics, when compared with control patients, and in rats after systemic injection of dopamine receptor agonists and non-competitive antagonists of the NMDA receptor. In the present study injection of dopamine in the rat nucleus accumbens core region also decreased prepulse inhibition. Injections of NMDA decreased, whereas a low dose of the competitive NMDA receptor antagonist (±)-2-amino-5-phosphonopentanoic acid (AP-5) and the non-competitive NMDA receptor antagonist (5*R*,10*S*)-(+)-5-methyl-10,11-dihydroxy-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate (MK-801) increased prepulse inhibition. The results indicate an involvement of the accumbens core in mediating the systemic effects on prepulse inhibition of dopamine receptor agonists but not of non-competitive NMDA receptor antagonists.

Keywords: Dopamine; NMDA (*N*-methyl-D-aspartate); Accumbens; Prepulse inhibition; Schizophrenia; (Rat)

1. Introduction

A large number of hypotheses have been proposed to try to deal with the complex pathophysiology of schizophrenia. Widely discussed and based on pharmacological evidence are the dopamine and the glutamate hypotheses.

The dopamine hypothesis (Snyder, 1976; Sayed and Garrison, 1983; Carlsson, 1988; Davis et al., 1991; Goldstein and Deutch, 1992) is, among others, based on the ability of the dopamine releaser amphetamine to intensify psychotic symptoms in schizophrenics (Janowsky and Davis, 1976; Angrist et al., 1980; Van Kammen et al., 1982).

The glutamate hypothesis (Wachtel and Turski, 1990; Javitt and Zukin, 1991) was formulated after observation of the broad spectrum of psychotomimetic effects in both normals and schizophrenic patients (Luby et al., 1959; Allen and Young, 1978) of phencyclidine, a non-competitive NMDA receptor antagonist (Anis et al., 1983; Johnson and Jones, 1990).

One of the behavioral changes which can be recorded in schizophrenic and schizotypal patients is impaired prepulse inhibition (Braff et al., 1978, 1992; Pearlstein et al., 1989; Cadenhead et al., 1993). Prepulse inhibition is a neural mechanism by which a startle reaction (Davis, 1984) is diminished by a preceding prepulse. This prepulse can be any small visual, acoustic or tactile stimulus (Hoffman and Searle, 1965; Buckland et al., 1969; Pinckney, 1976).

In animal research the prepulse inhibition paradigm has been used to evaluate possible mechanisms by which the dopamine and glutamate neurotransmitter systems play a role in schizophrenia. When amphetamine is injected systemically in rats, they show impaired prepulse inhibition (Mansbach et al., 1988). Systemically injected phencyclidine also decreases prepulse inhibition in rats (Geyer et al., 1989; Mansbach and Geyer, 1989) and the same phenomenon is observed with two other non-competitive NMDA receptor antagonists, MK-801 and ketamine (Geyer et al., 1989; Mansbach and Geyer, 1989, 1991; Mansbach, 1991; unpublished observations).

Swerdlow et al. (1986) showed that rats with 6-hydroxydopamine lesions of the nucleus accumbens had

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less prepulse inhibition when injected with apomorphine, which is a D_2 receptor agonist. Local injections of dopamine in the nucleus accumbens also disrupted prepulse inhibition (Swerdlow et al., 1990, 1992b). These results suggest that the dopamine effect is, at least partly, located in the accumbens (Swerdlow et al., 1992b). In contrast, very little is known about the neural mechanism by which glutamate influences prepulse inhibition. In the accumbens dopamine release is possibly presynaptically regulated by glutamate receptors: in microdialysis studies dopamine release in the accumbens has been reported to increase after local injection of glutamate receptor antagonists (McCullough and Salamone, 1992; Imperato et al., 1990).

In the present study the role of the NMDA receptor complex is studied. In the first experiment the dopamine effect in the accumbens, found by Swerdlow et al. (1990, 1992b), is replicated. In the other experiments the NMDA receptor in the nucleus accumbens core region is directly modulated by local injections of the agonist NMDA and by the competitive antagonist (±)-2-amino-5-phosphonopentanoic acid (AP-5) (Davies et al., 1981) and the non-competitive antagonist (5*R*,10*S*)-(+)-5-methyl-10,11-dihydroxy-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate (MK-801) (Wong et al., 1986).

2. Materials and methods

2.1. Animals

In all experiments male Sprague-Dawley rats (IFFA CREDO-Broekman BV, Someren, The Netherlands) weighing 225–250 g were used. The animals were housed in pairs and maintained in a temperature-controlled room (21–23°C) under a fixed 12-h light-dark cycle (lights on at 06:00 h). Food pellets and tap water were available ad libitum. Testing occurred between 09:00 and 16:00 h.

Every experiment was evaluated for at least five animals; exact animal numbers are given in the figure legends. Some animals were used in more than one experiment. In these cases experiments were separated by a period of at least 2 weeks.

2.2. Cannulations

The rats were anesthetized with sodium pentobarbital (60 mg/kg intraperitoneally) and placed in a Kopf stereotaxic instrument. Stainless steel cannulae (length: 4.5 mm; outer diameter: 0.6 mm) were implanted bilaterally 3.8 mm above the nucleus accumbens core (anterior/posterior + 3.2 mm from bregma, lateral ±2.0 mm, dorsal/ventral −4.0 mm from skull surface, toothbar 5 mm above the interaural line). Cannulae were held in place by dental cement, anchored with four skull screws, and filled with removable stylet wires.

2.3. Local injections

The rats were given at least 1 week of recovery from the operation before being tested. Before testing sham injections were given. Prior to each test session, the animals received a bilateral intracerebral injection of the drug. Every animal received each dose of the drug in a counter-balanced design with 2–4 days in between. Injections were made by replacing each wire stylet with a needle (outer diameter: 0.3 mm) fashioned to extend 3.8 mm beyond the end of the cannula. The injection volume was 1 μl per side, injected over 90 s using Hamilton microsyringes in a microinjection pump (CMA, Stockholm, Sweden) and connected to the needles via polyethylene tubing. Needles remained in place for 30 s following injection, and then were replaced with stylet wires.

2.4. Drugs

3-Hydroxytyramine hydrochloride (dopamine; Merck, Sharp and Dohme Research Laboratories, West Point, PA, USA) was dissolved in Merlys solution (8.98 g NaCl + 0.25 g KCl + 0.14 g $CaCl_2$ + 0.11 g $MgCl_2$ + 0.07 g Na_2HPO_4 + 0.13 g ureum + 0.60 g glucose/l water) containing 0.1% ascorbic acid. *N*-Methyl-D-aspartic acid (NMDA; Sigma Chemical, St. Louis, MO, USA), (5*R*,10*S*)-(+)-5-Methyl-10,11-dihydroxy-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate (MK-801; Merck, Sharp and Dohme Research Laboratories, West Point, PA, USA) and (±)-2-amino-5-phosphonopentanoic acid (AP-5; Tocris Neuramin, Essex, England) were also dissolved in Merlys solution. Doses of the drugs are as indicated in the figure legends.

2.5. Apparatus

Each startle chamber (SR-LAB system, San Diego Instruments, San Diego, CA, USA) contains a Plexiglas cylinder resting on a piezoelectric accelerometer for detecting total body activity within the cylinder. Bursts of acoustic noise were presented by a loudspeaker mounted 24 cm above the rat. Startle amplitude was defined as the average of 200 1-ms readings collected from the start of the startle stimulus.

2.6. Test session

Each rat was placed into the cylinder 15 min after infusion and 10 min prior to the initial startle stimuli; during this acclimation period only background noise of 79 dB was offered.

Each test session was preceded by 10 startle stimuli (119 dB 25 ms broad-band bursts) to prevent interaction of habituation effects with the test session.

The test session consisted of 10 different trial types, each repeated 12 times in random order. The ten trial types were: no stimulus, startle stimulus alone, 4 pre-

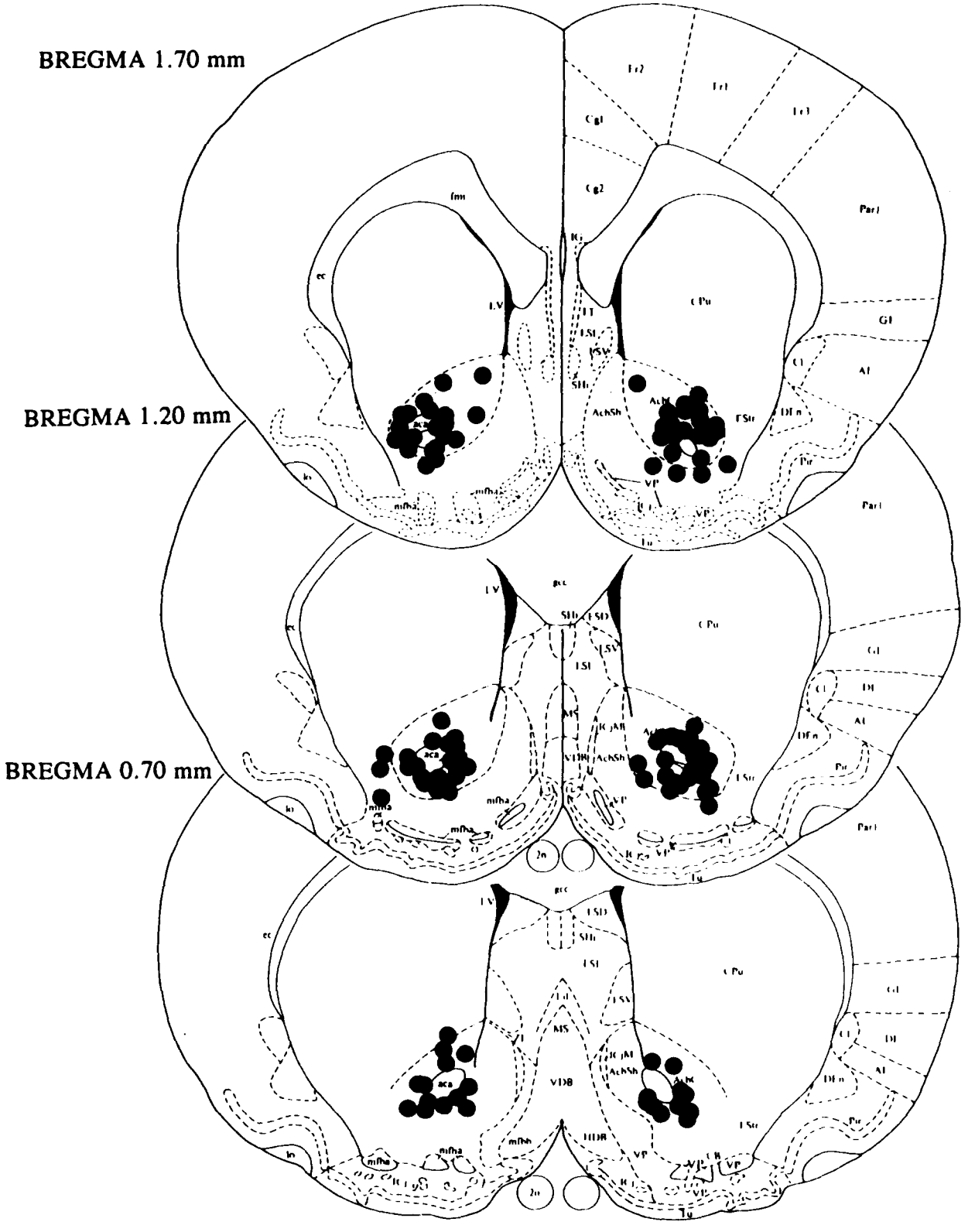

Fig. 1. Distribution of bilateral injection sites in the nucleus accumbens core region for all experiments. Figures taken from Paxinos and Watson (1986).

pulse trials consisting of a 20 ms prepulse with an intensity of 80, 81, 82 or 83 dB, and four prepulse-startle trials consisting of a startle stimulus preceded by one of the four prepulses with an interval of 120 ms between onset of prepulse and onset of startle stimulus. The trials were separated by an average interval of 15 s. During the session the background noise was kept constant at 79 dB.

2.7. Histology

After completion of behavioral testing the rats were killed. Brains were removed and kept in 4% formalin. The injection sites were localized by sectioning the brain into 30-μm slices by means of a freezing microtome (Reichert-Jung). Data from a given animal were excluded from statistical analysis when the injection site fell outside the nucleus accumbens core region. The distribution of injection sites is represented in Fig. 1.

2.8. Statistical analyses

To evaluate drug effects on the startle reaction, data for the startle stimulus alone were analyzed using a one-factor ANOVA, followed by Tukey's protected t-tests.

Prepulse inhibition was defined as (((startle amplitude on startle stimulus alone trials) − (startle amplitude on prepulse-startle trials))/(startle amplitude on startle stimulus alone trials)) × 100%.

Drug effects on prepulse inhibition were analyzed using a two-factor ANOVA with drug dose and prepulse type as factors, followed by Tukey's protected t-tests.

3. Results

3.1. Dopamine

Fig. 2 shows the effects of dopamine (0 and 40 μg/side) on prepulse inhibition. Dopamine decreased prepulse inhibition at all four prepulse intensities. There was an overall dopamine effect ($F(1,40) = 4.19$, $P < 0.05$) and a prepulse intensity effect ($F(3,40) = 3.61$, $P < 0.05$), but no interaction ($F(3,40) = 0.32$, $P = 0.81$) occurred. Post-hoc t-tests showed no significant decreases of prepulse inhibition by dopamine at the individual prepulse-startle combinations. No dopamine effect on the startle reaction alone was found ($F(1,10) = 0.35$, $P = 0.57$; data not shown).

3.2. NMDA

Fig. 3 shows the effects of NMDA (0, 333, 666 and 1000 ng/side) on prepulse inhibition. There was a

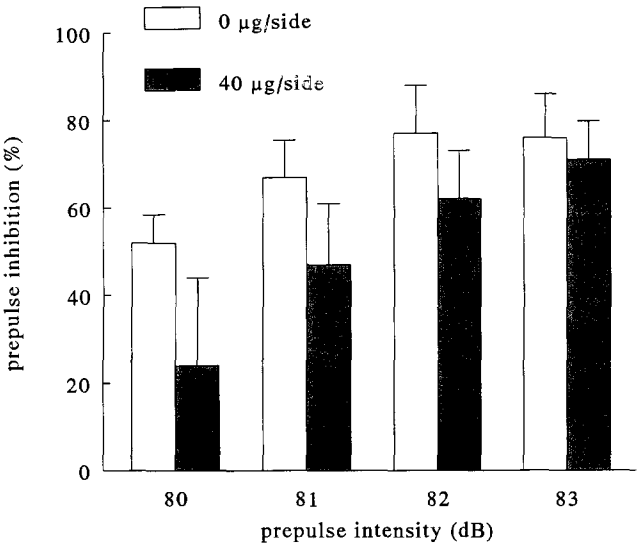

Fig. 2. Effects of dopamine (0 and 40 μg/side; $n = 6$) on prepulse inhibition using four different prepulse intensities.

prepulse intensity effect ($F(3,272) = 49.13$, $P < 0.001$), but no NMDA effect ($F(3,272) = 1.47$, $P = 0.22$) and no interaction ($F(9,272) = 0.96$, $P = 0.47$) occurred. Post-hoc t-tests showed that the highest dose of 1000 ng/side NMDA caused a significant decrease of prepulse inhibition with the 81 dB prepulse, and the lowest dose of 333 ng/side significantly decreased prepulse inhibition with the 80 dB prepulse, while the 666 ng/side NMDA dose had no significant effect with any

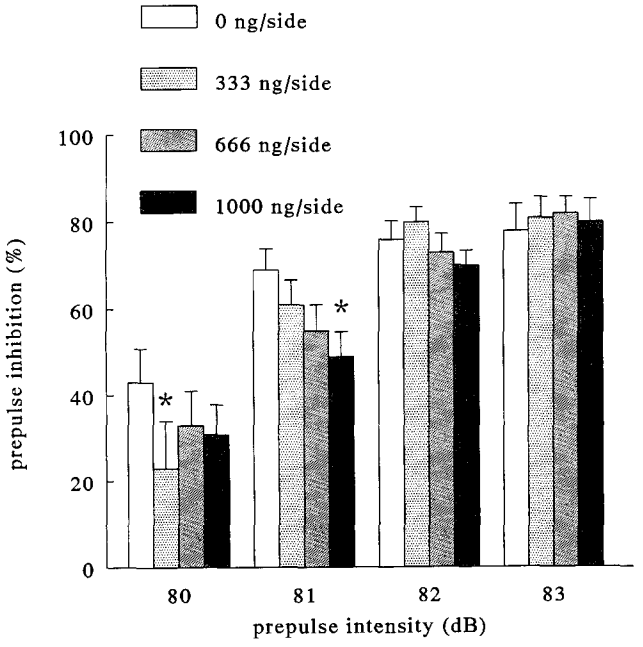

Fig. 3. Effects of NMDA (0, 333, 666 and 1000 ng/side; $n = 18$) on prepulse inhibition using four different prepulse intensities. * Significantly different from vehicle (Merlys solution; Tuckey's protected t-test, $P < 0.05$).

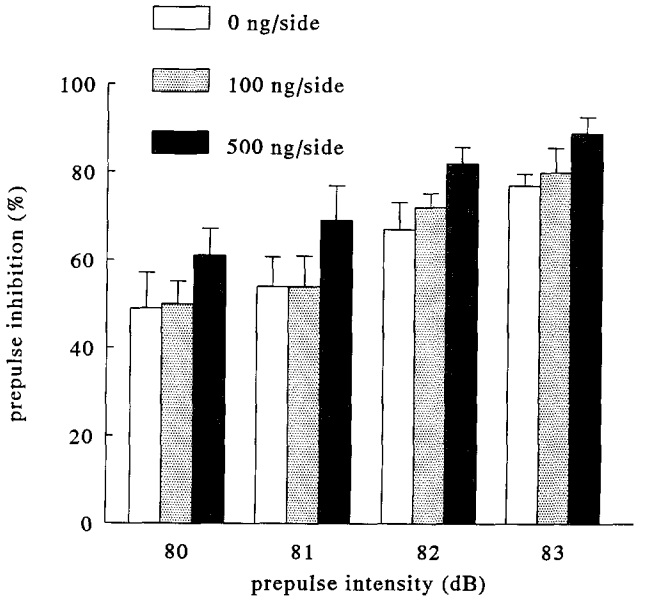

Fig. 4. Effects of MK-801 (0, 100, 500 ng/side; $n = 5$) on prepulse inhibition using four different prepulse intensities.

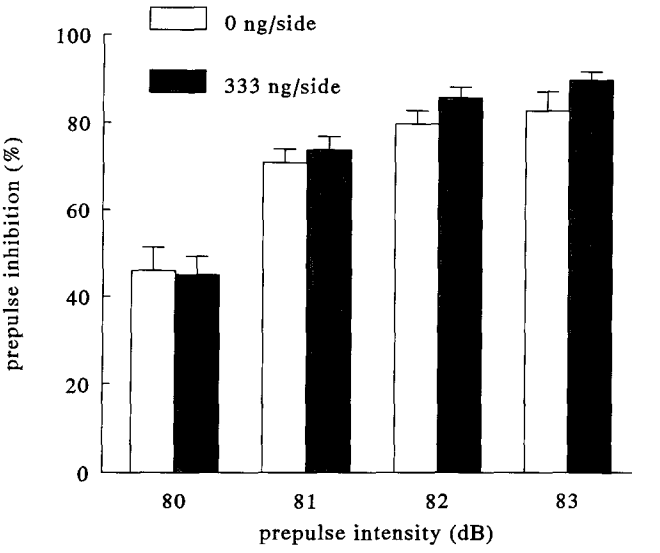

Fig. 5. Effects of AP-5 (0 and 333 ng/side; $n = 27$) on prepulse inhibition using four different prepulse intensities.

prepulse intensity. No overall NMDA effect on the startle reaction alone was found ($F(3,72) = 0.31$, $P = 0.82$; data not shown).

3.3. MK-801

The effects of MK-801 (0, 100 and 500 ng/side) on prepulse inhibition are shown in Fig. 4. An overall MK-801 effect ($F(2,48) = 6.35$, $P < 0.05$) and a prepulse intensity effect was found ($F(3,48) = 15.53$, $P < 0.001$), but no interaction ($F(6,48) = 0.07$, $P = 0.99$) occurred. There was no overall MK-801 effect on the startle reaction alone ($F(2,12) = 0.35$, $P = 0.71$; data not shown).

3.4. AP-5

The effects of AP-5 were evaluated in different experiments, which are shown in Figs. 5–7.

Figs. 5 and 6 show experiments with low doses of AP-5. At 333 ng/side (Fig. 5) AP-5 did not change prepulse inhibition ($F(1,208) = 2.21$, $P = 0.14$); there was a prepulse intensity effect ($F(3,208) = 53.33$, $P < 0.001$) but no interaction occurred ($F(3,208) = 0.53$, $P = 0.66$). No effect on the startle reaction alone was found ($F(1,52) = 0.33$, $P = 0.57$; data not shown).

Fig. 6 shows the effects of 0, 100 and 666 ng/side AP-5 on prepulse inhibition. A nearly significant overall AP-5 effect ($F(2,216) = 2.44$, $P = 0.09$) and a significant prepulse intensity effect ($F(3,216) = 52.02$, $P < 0.001$) were found but no interaction ($F(6,216) = 0.62$, $P = 0.72$) occurred. Because the two doses of AP-5 induced different effects, the 100 ng/side dose alone was compared with the effect of vehicle (Merlys solution). There was an almost significant AP-5 effect ($F(1,144) = 3.49$, $P = 0.06$) and prepulse intensity effect ($F(3,144) = 42.98$, $P < 0.001$) with no interaction ($F(3,144) = 0.60$, $P = 0.62$). No effect of 100 ng/side AP-5 on the startle reaction alone was found ($F(1,36) = 0.04$, $P = 0.84$; data not shown).

The effects of high doses of AP-5 (0, 1, 2 and 3.5 μg/side) on prepulse inhibition are shown in Fig. 7. There was an overall AP-5 effect ($F(3,144) = 7.71$, $P < 0.001$) and prepulse intensity effect ($F(3,144) =$

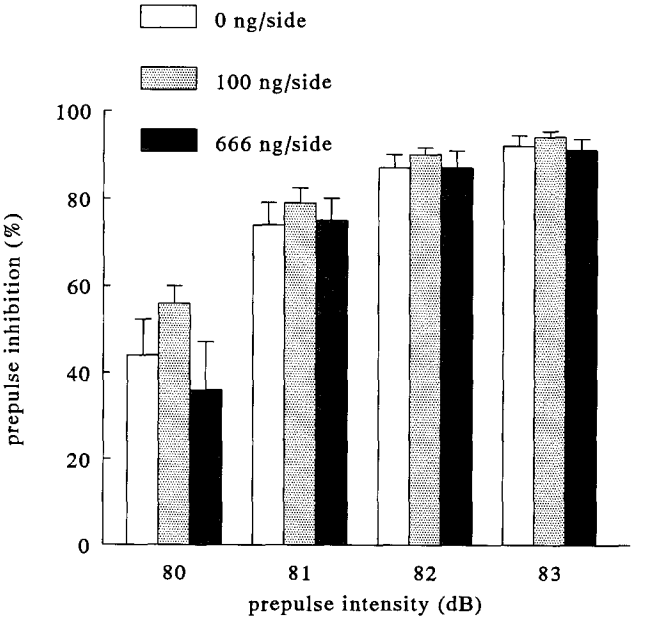

Fig. 6. Effects of AP-5 (0, 100 and 666 ng/side; $n = 19$) on prepulse inhibition using four different prepulse intensities.

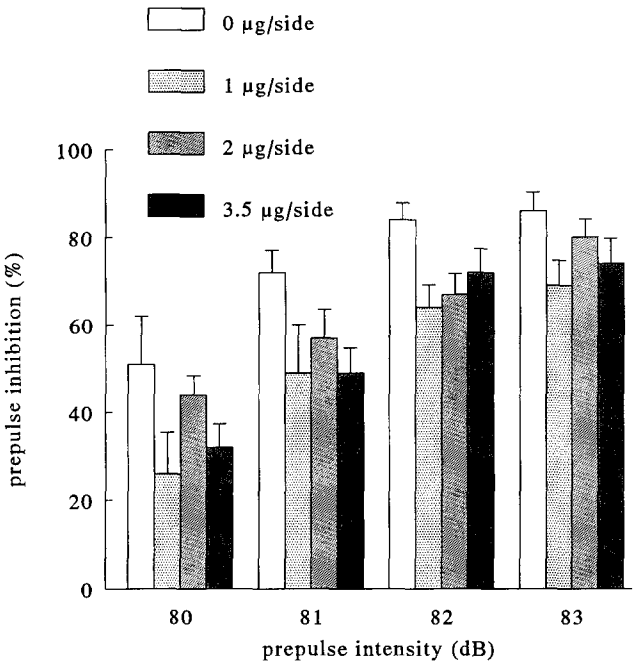

Fig. 7. Effects of AP-5 (0, 1, 2, 3.5 µg/side; $n = 10$) on prepulse inhibition using four different prepulse intensities.

29.11, $P < 0.001$), but no interaction ($F(9,144) = 0.34$, $P = 0.96$) occurred. There was no overall AP-5 effect on the startle reaction alone ($F(3,36) = 1.46$, $P = 0.24$; data not shown).

4. Discussion

In the first experiment 40 µg/side dopamine diminished prepulse inhibition. This effect was similar to that earlier described by Swerdlow et al. (1990, 1992b).

The results of the other experiments indicate that NMDA receptors in the nucleus accumbens core region can also affect prepulse inhibition: the agonist NMDA decreased prepulse inhibition, while both the non-competitive antagonist MK-801 and the competitive antagonist AP-5, in a low dose, induced an increase.

AP-5 given at higher doses decreased prepulse inhibition. Apparently different neural mechanisms are involved, which is consistent with earlier reports for other behavioral paradigms. AP-5 in the accumbens has been reported to both stimulate and decrease locomotor activity (Kelley and Throne, 1992; Svensson and Carlsson, 1992; Svensson et al., 1992). CPPene ((*E*)-4-(3-phosphonoprop-2-enyl)piperazine-2-carboxylic acid), another competitive NMDA receptor antagonist, can also induce hypermotility when perfused in the accumbens (Imperato et al., 1990). Possibly the effect of the low dose of AP-5 is due to its binding to NMDA receptors in the accumbens core, while the effect of the high dose is caused by diffusion to neighbouring structures.

The local effect of MK-801, which gave an improvement of prepulse inhibition, was the opposite of the systemic effect of MK-801 and other non-competitive NMDA receptor antagonists like phencyclidine, which gave a disruption of prepulse inhibition (see Introduction). It can be concluded that the systemic effects of non-competitive NMDA receptor antagonists on prepulse inhibition are not due to a blockade of NMDA receptors in the accumbens core region.

A lot of research has focussed on finding the mechanism by which systemically administered phencyclidine induces its psychotomimetic effects, and there are indications that part of its effects might be mediated by dopamine systems in the brain. Phencyclidine and MK-801 can activate A10 neurons, which include dopaminergic projections to the accumbens, increasing dopamine turnover in this structure (Brush and French, 1984; Freeman and Bunney, 1984; Zhang et al., 1992). However, it seems that the effects of non-competitive antagonists on prepulse inhibition are independent of accumbal dopamine activation, because the effects of phencyclidine and MK-801 cannot be antagonized by the dopamine receptor antagonist haloperidol (Geyer et al., 1989). This does not interfere with our hypothesis that the effect of MK-801 in the accumbens, which is not the same as the systemic effect, could be mediated by dopamine. This will be investigated in future experiments.

Although the present results are not consistent with the systemic effects of NMDA ligands, they might be in line with the results of studies investigating neuroanatomical and chemical dysfunctioning of the hippocampus (Jeste and Lohr, 1989; Altshuler et al., 1990; Benes et al., 1991; Breier et al., 1992; Nestor et al., 1993; Scheibel and Conrad, 1993) in schizophrenics.

Impaired functioning of the hippocampus has been proposed to underlie the deficit in sensorimotor gating and consequently the impaired prepulse inhibition. Prepulse inhibition is disrupted by local infusion of the acetylcholine receptor agonist carbachol in regions of the hippocampus (Caine et al., 1991, 1992) and it has been suggested that this effect could be mediated by glutaminergic projections from the hippocampus to the accumbens (Swerdlow et al., 1992a; Caine et al., 1992). Indeed prepulse inhibition is disrupted by local infusion of glutamate in the accumbens (Swerdlow et al., 1991) and the present results indicate that NMDA receptors are involved.

In conclusion, the results of the present study indicate that NMDA receptors in the accumbens core region are not involved in mediating the systemic effects of non-competitive NMDA receptor antagonists like phencyclidine and MK-801 on prepulse inhibition.

The results are in line with reports of hypofunctioning of the hippocampus in schizophrenics, and NMDA receptors in the accumbens core could link this hypofunctioning with an increase in dopaminergic transmission in the accumbens.

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