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The effect of zotepine, risperidone, clozapine and olanzapine on MK-801-disrupted sensorimotor gating

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Abstract

Dizocilpine (MK-801; 0.3 mg/kg i.p.)-induced disruption in prepulse inhibition of the acoustic startle response (PPI) can be preferentially restored by "atypical" antipsychotics. In contrast, some findings indicate that not all of the "atypical" antipsychotics, such as clozapine and risperidone, are effective in restoring the NMDA antagonist-induced deficits in PPI.

In our study, we evaluated the effect of four different "atypical" antipsychotic drugs on deficits in PPI induced by MK-801. Zotepine and risperidone have high affinities to D2-like and 5-HT_{2A} receptors, while clozapine and olanzapine have multipharmacological profiles with the highest affinities to serotonin 5-$HT_{1A,2A/2C}$ receptors and muscarinic receptors.

Results have shown that MK-801 disrupted PPI and increased the ASR in rats. Our results showed no effect of zotepine (1 and 2 mg/kg) and risperidone (0.1 and 1 mg/kg) on disrupted PPI by MK-801. Administration of clozapine (5 and 10 mg/kg) and olanzapine (2.5 and 5 mg/kg) restored the deficits in PPI induced by MK-801. Additionally, we found a decrease of approximately 46% in PPI after administration of clozapine (5 mg/kg) and olanzapine (2.5 and 5 mg/kg) without MK-801 treatment.

In summary, the four "atypical" antipsychotics had different efficacies to restore the disrupted PPI by MK-801. Only clozapine and olanzapin restored the MK-801-induced deficits in PPI.

Keywords: Antipsychotics; Prepulse inhibition of the startle response; Rats; MK-801

1. Introduction

The acoustic startle response (ASR) is a fast twitch of facial and body muscles evoked by a sudden and intense acoustic stimulus >80 dB (Koch, 1999). The ASR can be attenuated by a variety of experimental manipulations across species such as prior presentation of a low-intensity prepulse (prepulse inhibition of the startle response: PPI) or repeated presentation of startling stimuli (habituation). Prepulse inhibition of the startle response (PPI) measures sensorimotor gating, which is suggested to regulate environmental inputs and selectively allocate attentional resources to salient stimuli (Braff et al., 2001). Deficits in sensorimotor gating have been observed in patients with several neuropsychiatric disorders including schizophrenia (Swerdlow et al., 1998).

In animals, disruption of PPI is produced by a variety of pharmacological stimuli (Geyer et al., 2001; Swerdlow et al., 2001) such as nonselective dopaminergic agonists (amphetamine; apomorphine) or competitive and non-competitive antagonists of glutamate *N*-methyl-D-aspartate (NMDA) receptors (Mansbach and Geyer, 1989; Wiley and Kennedy, 2002).

Non-competitive antagonists of NMDA receptors (e.g. MK-801, ketamine, phencyclidine) induce psychotomimetic effects in humans (Luby et al., 1959; Snyder, 1980). In rats, the highly selective non-competitive NMDA

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antagonist, MK-801, produces changes in behaviour such as impairments related to PPI, hyperlocomotion, stereotypy and social deficits, which are so-called schizophrenia-like behaviours (Jentsch and Roth, 1999). It was previously described that the MK-801-induced disruption of PPI can be restored preferentially by "atypical" antipsychotics without affecting the startle response in rats (Corbett et al., 1995; Swerdlow et al., 1998; Geyer et al., 2001; Wiley and Kennedy, 2002). The group of antipsychotics includes drugs which ameliorate the negative and positive symptoms of schizophrenia, have a low propensity to produce extrapyramidal side effects and have a low capacity to elevate prolactine levels (Lidow, 2000). Therefore, deficits in PPI produced by MK-801 have been used in adult animals to investigate the efficacy of "typical" and "atypical" antipsychotics, and to predict the efficacy of new putative antipsychotics (Geyer et al., 2001). On the other hand, some findings indicate that not all "atypical" antipsychotics, such as clozapine and risperidone, are effective in restoring the NMDA antagonist-induced deficits in PPI (Compton et al., 2001; Wiley and Kennedy, 2002). Hence, these findings support that the effects on PPI are similar to those observed after administration of "typical" antipsychotics (Wiley and Kennedy, 2002). A majority of the studies compared the effects on sensorimotoric gating by atypical antipsychotics with the "typical" antipsychotic, haloperidol (Bakshi et al., 1998; Swerdlow et al., 1998; Martinez et al., 2002). The current manuscript reports a comparison within a single study of four atypical antipsychotics matched for D2 receptor affinity.

We evaluated the effects of four "atypical" antipsychotic drugs on the deficits in PPI induced by MK-801 and changes in the ASR. We chose commonly used antipsychotics with atypical features (risperidone, zotepine, clozapine, and olanzapine) and grouped them based on their similar pharmacodynamic profiles and dopamine D2 receptor affinity (Arnt and Skarsfeld, 1998; Richelson and Souder, 2000). Zotepine and risperidone have strong affinities to D2-like and 5-HT_{2A} receptors (Richelson and Souder, 2000), while clozapine and olanzapine have rather multipharmacological profiles with the highest affinity to serotonin 5-$HT_{1A,2A/2C}$ (Richelson and Souder, 2000) and muscarinic receptors (Bymaster et al., 2003). In our study, we aimed to establish whether high affinity to dopamine D2 receptors determines the effect of antipsychotics with atypical features on PPI in an animal model of schizophrenia.

2. Materials and methods

2.1. Animals

A total of 339 male Wistar rats (200–250 g, specific pathogen-free animals; Hannover breed Konárovice, Czech Republic) were used in this study. Cages with two male rats were housed in a temperature-controlled room (21–22 °C), having a 12:12 h light/dark regime (lights on at 6:00 a.m.) with free access to food (ST-1 diet) and water. Each rat was experimentally naive and was tested only once. All manipulations with the animals respected the Guidelines of the European Union Council (86/609/EU) and followed the instructions of the National Committee for the Care and Use of Laboratory Animals.

2.2. Procedure

All antipsychotics [zotepine (1 mg/kg and 2 mg/kg); risperidone (0.1 mg/kg and 1 mg/kg), clozapine (5 mg/kg and 10 mg/kg); olanzapine (2.5 mg/kg and 5 mg/kg)] or the vehicle were injected 60 min before the start of the experiment in a volume of 5 ml/kg subcutaneously (s.c.). MK-801 (0.3 mg/kg i.p.; volume 5 ml/kg) or the same volume of saline was administrated 15 min before the PPI experiment. The controls received the vehicle (5 ml/kg) s.c. and a saline injection (5 ml/kg) i.p. The number of animals in each group was 13–15.

2.3. Sources of chemicals

Zotepine was donated from Fujisawa; risperidone and clozapine were purchased from Sigma, Prague, Czech Republic; olanzapine was a gift from the Elli Lilly. All antipsychotics were dissolved in a vehicle (25 μl of acetic acid per one ml of saline). The MK-801 (5*R*,10*S*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-5,10-imine hydrogen-maleate (Sigma, Schnelldorf, Germany) was dissolved in saline.

2.4. Startle and PPI apparatus and experimental schedule

All testing occurred within the startle chamber (SR-LAB, San Diego Instruments, USA), which consisted of a clear Plexiglas cylinder (8.2 cm diameter, 10×20 cm) that rested on a piezoelectric accelerometer inside a ventilated and illuminated chamber. The piezoelectric accelerometer detected and transduced motion within the cylinder. A high frequency loudspeaker inside the chamber (24 cm above the animal) produced both a background noise of 62 dB and the acoustic stimuli. All rats were initially tested by a short session (5 min acclimatization period plus 5 single stimuli; 120 dB strong) 2 days before the experiment.

The experimental design was modified by Schulz et al., 2001. The background noise (62 dB) was presented alone for 5 min (acclimatization period) and then continued throughout the session. After the acclimatization period, the test began with five initial startle stimuli followed by four different trial types presented in a pseudorandom order: (1) single pulse: 120 dB broadband burst, 20 ms duration; (2) prepulse: 13 dB, 20 ms duration above the background noise were presented 100 ms before the onset of the pulse alone; (3) prepulse alone: 13 dB, 20 ms duration above the background noise; (4) no

stimulus. A total of five presentations of each trial type were given with an interstimulus interval of about 30 s. The PPI was measured as a difference between the average values of the single pulse and prepulse–pulse trials and was expressed as a percent of the PPI [100−(mean response for prepulse–pulse trials/startle response for single pulse trials) ×100]. In addition, four single pulse trials at the beginning of the test session were not included in the calculation of the PPI values.

Animals which had an average value lower than 10 mV were removed from the calculation of PPI and were marked as non-responders (about 3% from the total amount). The number of animals removed did not significantly differ among all treatment groups.

3. Statistics

Data from both parts of the experiment (ASR and PPI) were collected and statistically evaluated by a two-way analysis of variance (ANOVA) with antipsychotic treatment as one factor and MK-801 treatment as the second factor. When appropriate, comparisons between treatment groups were conducted using a Tukey post hoc test. $P<0.05$ was considered significant.

4. Results

4.1. The effect of antipsychotics on the startle response

Table 1 shows the average values of the startle response [mV] after administration of MK-801 and/or after pre-treatment with antipsychotics. Administration of MK-801 increased the average startle amplitude ($P<0.01$) compared to the controls by about 49%.

Table 1
The effect of antipsychotics alone (drug+saline) or in combination with MK-801 (drug+MK-801)

Drug	Mean amplitude (±S.E.M.)	
Dose (mg/kg)	Drug+saline	Drug+MK-801
Vehicle	108.2±16.19$^{\#\#}$	161.4±15.30
Zotepine		
1	163.9±17.21*	110.1±18.38$^{\#}$
2	80.27±10.25	76.18±10.84$^{\#\#\#}$
Risperidone		
0.1	70.48±8.01	92.55±8.14$^{\#\#\#}$
1	56.44±5.83**	57.03±6.34$^{\#\#\#}$
Clozapine		
5	80.86±16.74	104.3±13.73$^{\#}$
10	35.52±5.4***	65.11±6.44$^{\#\#\#}$
Olanzapine		
2.5	75.25±6.17	82.48±7.7$^{\#\#\#}$
5	41.8±3.79***	66.68±6.82$^{\#\#\#}$

On acoustic startle response (ASR, mV).**$P<0.01$; ***$P<0.001$ when compared to the control animals (vehicle+saline), using a two-way ANOVA with post hoc Tukey test; $^{\#}P<0.05$; $^{\#\#}P<0.01$; $^{\#\#\#}P<0.001$ when compared to the MK-801 group.

4.1.1. The effect of zotepine on the acoustic startle response

There was a statistically significant effect of zotepine on the ASR within control and MK-801 treated rats [$F(2,87)=9.99$; $P<0.001$] and a statistically significant interaction between zotepine and MK-801 [$F(2,87)=6.71$; $P<0.01$]. The lower dose of zotepine (1 mg/kg) increased the spontaneous ASR in animals without MK-801 treatment compared to the control animals ($P<0.05$). However, the higher dose of zotepine (2 mg/kg) had no effect on the spontaneous ASR. In addition, there was no dose-dependent effect of zotepine on the spontaneous ASR. Both doses of zotepine (1 mg/kg and 2 mg/kg) decreased the ASR in the animals treated by MK-801 ($P<0.05$) and 2 mg/kg dose ($P<0.001$ for 1 mg/kg and 2 mg/kg, respectively, Table 1).

4.1.2. The effect of risperidone on the acoustic startle response

A two-way ANOVA showed a statistically significant effect of risperidone [$F(2,89)=26.19$; $P<0.001$] and MK-801 [$F(2,89)=7.8$; $P<0.01$] on the ASR without a significant interaction between risperidone and MK-801 [$F(2,89)=2.78$; $P>0.05$]. The higher dose of risperidone (1 mg/kg) decreased the spontaneous ASR ($P<0.01$) in control animals and both doses of risperidone decreased the ASR in animals treated by MK-801 ($P<0.001$; $P<0.001$, for 0.1 mg/kg and 1 mg/kg, respectively, Table 1).

4.1.3. The effect of clozapine on the acoustic startle response

A two-way ANOVA showed a statistically significant effect of clozapine [$F(2,82)=23.443$; $P<0.001$] and MK-801 [$F(2,82)=15.1$; $P<0.01$) on the ASR without a significant interaction between clozapine and MK-801. A decrease of spontaneous startle response was observed at the higher dose of clozapine (10 mg/kg; $P<0.001$] and after MK-801 treatment. A decrease of startle response was observed after both doses of clozapine ($P<0.05$ and $P<0.001$ for 5 and 10 mg/kg, respectively, Table 1).

4.1.4. The effect of olanzapine on the acoustic startle response

A two-way ANOVA showed a statistically significant effect of olanzapine [$F(2,87)=31.305$; $P<0.001$] and MK-801 [$F(2,87)=13.7$; $P<0.001$) on the ASR without a significant interaction between olanzapine and MK-801. A decrease of spontaneous startle response was observed after the higher dose of olanzapine (5 mg/kg; $P<0.001$] and after MK-801 treatment the decrease of startle response was observed after both doses of olanzapine ($P<0.001$ and $P<0.001$ for 2.5 and 5 mg/kg, respectively, Table 1).

4.2. The effect of antipsychotics on PPI

MK-801 produced a deficit in sensorimotor gating with decreases of about 84.6% compared to the controls (Figs. 1 (Parts A and B) and 2 (Parts A and B)).

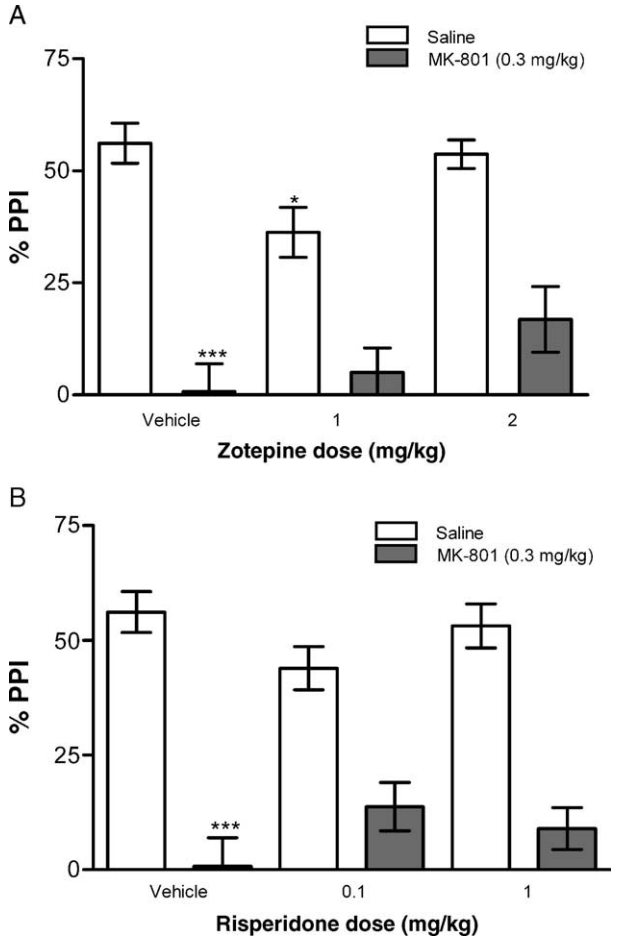

Fig. 1. Effect of zotepine (1 and 2 mg/kg s.c., Part A) and risperidone (0.1 and 1 mg/kg s.c., Part B) alone and in combination with MK-801 (0.3 mg/kg i.p.) on the %PPI of the acoustic startle response (mean±S.E.M.). *P<0.05; ***P<0.001 when compared to the control animals (vehicle+saline), using a two-way ANOVA with post hoc Tukey test. The number of animals in each group was 15.

4.2.1. The effect of zotepine on PPI

A two-way ANOVA showed a statistically significant effect of zotepine [F(2,87)=3.566; P=0.033) and MK-801 [F(2,87)=85.792; P<0.001) on PPI without a significant interaction between zotepine and MK-801. The post hoc analysis showed a statistically significant decrease of PPI after administration of the lower dose of zotepine (1 mg/kg) without MK-801 treatment (P<0.05, Fig. 1, Part A).

4.2.2. The effect of risperidone on PPI

A two-way ANOVA showed a statistically significant interaction between risperidone and MK-801 [F(2,89)= 3.157; P=0.048], and a significant effect of MK-801 [F(2,89)=110.585; P<0.001] on PPI. There were no statistically significant differences in post hoc analysis (Fig. 1, Part B).

4.2.3. The effect of clozapine on PPI

A two-way ANOVA showed a statistically significant interaction between clozapine and MK-801 [F(2,82)=8.946; P<0.001] and a significant effect of MK-801 [F(2,82)= 49.910; P<0.001) on PPI. We found a statistically significant decrease in spontaneous PPI (without MK-801 treatment) after administration of 5 mg/kg of clozapine (P<0.01). Furthermore, we found a restorative effect on the PPI deficit induced by MK-801 after administration of the lower dose of 5 mg/kg (P<0.05) as well as after administration of 10 mg/kg of clozapine (P<0.05) (Fig. 2, Part A).

4.2.4. The effect of olanzapine on PPI

A similar effect on PPI was described after administration of olanzapine in the doses 2.5 mg/kg and 5 mg/kg. A two-way ANOVA showed a significant interaction between olanzapine and MK-801 [F(2,87)=12.319; P<0.001] and a significant effect of MK-801 [F(2,87)=62.483; P<0.001]. The spontaneous level of PPI was decreased after administration of both applied doses of 2.5 mg/kg (P<0.01) and 5 mg/kg (P<0.05), respectively, compared to the controls. The deficit in PPI induced by MK-801 was restored by

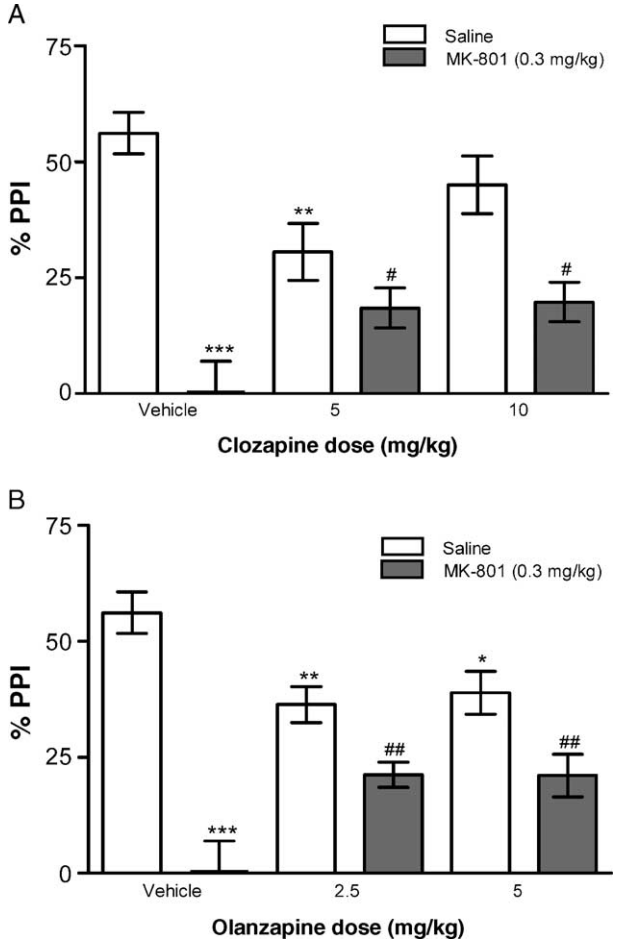

Fig. 2. Effect of clozapine (5 and 10 mg/kg s.c., Part A) and olanzapine (2.5 and 5 mg/kg s.c., Part B) alone and in combination with MK-801 (0.3 mg/kg i.p.) on the %PPI of the acoustic startle response (mean± S.E.M.). * P<0.05; **P<0.01; ***P<0.001 when compared to the control animals (vehicle+saline) and $^{\#}P$<0.05; $^{\#\#}P$<0.01 when compared to the MK-801 group (vehicle+MK-801), using a two-way ANOVA with post hoc Tukey test. The number of animals in each group was 13–15.

administration of both the 2.5 mg ($P<0.01$) and 5 mg/kg ($P<0.01$) doses (see Fig. 2, Part B).

5. Discussion

In our experimental schedule, administration of MK-801 (0.3 mg/kg) in male Wistar rats decreased PPI by about 85% and increased the ASR by about 49% compared to the control animals. These results are in accordance with previous studies (Bakshi et al., 1994; Bast et al., 2000; see review Geyer et al., 2001; Schulz et al., 2001). It was established that doses of MK-801 higher than 0.05 mg/kg s.c. can disrupt PPI of the acoustic startle response (Bast et al., 2000). Thus, we chose the dose of 0.3 mg/kg of MK-801 based on our previous observations and published findings that this dose produces so-called schizophrenia-like behaviour on a large scale (Martin et al., 1997; Stuchlik et al., 2004).

In our experiment, we compared the effect of two groups of antipsychotics on the deficits in PPI induced by MK-801. The first group of chosen antipsychotics included zotepine and risperidone and is characterized by a high affinity of the drugs at dopamine D2 and serotonin 5-HT_{2A} receptors (Arnt and Skarsfeld, 1998; Richelson and Souder, 2000). Our results showed no effect of zotepine (1 mg/kg; 2 mg/kg) and risperidone (0.1 mg/kg; 1 mg/kg) on the disrupted PPI by MK-801. We found a decrease of the ASR when zotepine or risperidone were pre-treated by MK-801. These results could be explained by a high affinity at dopamine D2 receptors, similarly expressed by haloperidol (Arnt and Skarsfeld, 1998; Richelson and Souder, 2000). Our finding that risperidone did not restore the deficit in PPI induced by MK-801 is in accordance with the results published by Swerdlow et al., 1996; Varty et al., 1999.

The second group of chosen antipsychotics, which are characterized by multipharmacological profiles (Arnt and Skarsfeld, 1998; Richelson and Souder, 2000), had a different effect on PPI than the first group. Administration of both drugs restored the deficits in PPI induced by MK-801; however, the PPI did not reach the values measured in the controls (Fig. 2). The higher doses of clozapine and olanzapine decreased the spontaneous level of ASR and the level induced by MK-801. The pharmacological profiles of these drugs are also different and are characterized by a lower affinity at dopamine D2 receptors. The highest affinity is detected at serotonin 5-$HT_{2A/2C}$ receptors, muscarinergic and adrenergic α1 receptors for clozapine (Arnt and Skarsfeld, 1998; Richelson and Souder, 2000). For olanzapine, high affinity was also established (K_i approximately 3 nM) at serotonin 5-HT_{1A} human cloned receptors (Schotte et al., 1996).

Most studies with Wistar rats did not find any effect of clozapine on the deficits in PPI induced by non-competitive antagonists of NMDA receptors (Bast et al., 2000). We found a marked effect of clozapine and olanzapine in restoring the deficits in PPI induced by a dose of MK-801 three times higher than was used in some studies (Varty and Higgins, 1995; Bast et al., 2000). It has been suggested that the effect of antipsychotics on the deficits in PPI induced by a non-competitive antagonist of the NMDA receptor could be due to their antagonistic activity with adrenergic α1 receptors (Bakshi and Geyer, 1997). Zotepine, risperidone and clozapine have high affinity at adrenergic α1 receptors of approximately 3 nM in the rat cortex (Schotte et al., 1996; Richelson and Souder, 2000), while olanzapine shows a 10 times lower affinity at the same receptors. However, both clozapine and olanzapine restored the deficits in PPI induced by MK-801 in our study. Our results indicate that the effect of antipsychotics on the deficits in PPI induced by MK-801 is not different based on their affinity to adrenergic α1 receptors.

Surprisingly, the low dose of clozapine (5 mg/kg) and both doses of olanzapine produced statistically significant decreases in spontaneous PPI (without MK-801 treatment) by about 46%. These results are in conflict with the study by Depoortere et al. (1997) where no effect was found using a 5 mg/kg dose of clozapine on spontaneous PPI. This discrepancy in the effect of clozapine on spontaneous PPI could be explained by differences between strains of rats or the study designs. The effect of olanzapine was not tested in the study. In general, we supposed that the effect of clozapine and olanzapine on spontaneous PPI could be explained by their antimuscarinic activity in the central and peripheral systems (Bymaster et al., 2003). It was published that full antagonists of muscarinic receptors, such as scopolamine and benztropine, decrease PPI of the acoustic startle response (Jones and Shannon, 2000).

The effect of different antipsychotics on deficits in PPI induced by non-competitive antagonists of NMDA receptors has been investigated for a long time (Varty and Higgins, 1995; Feifel and Priebe, 1999; see review Geyer et al., 2001; Mansbach et al., 2001). It was suggested that preferentially "atypical" antipsychotics restore the deficits in PPI induced by non-competitive antagonists of NMDA receptors (Swerdlow et al., 1998). However, in some studies the effects have not been confirmed (Varty and Higgins, 1995; Swerdlow et al., 1996; Bast et al., 2000; Wiley and Kennedy, 2002). Discrepancies between these studies could be explained by different sensitivities of rat strains to non-competitive antagonists of NMDA receptors (Bast et al., 2000) and different types of procedures followed for PPI testing (Swerdlow et al., 1998; Wiley and Kennedy, 2002). In addition, most studies used phencyclidine or ketamine as the non-competitive antagonists of NMDA receptors. We chose MK-801, because it is the most selective non-competitive antagonist of NMDA receptors in vivo (Bressink et al., 1995) and for its lower affinity at other receptors in the brain compared to phencyclidine and ketamine (Hustveit et al., 1995; Ault and Werling, 1999).

6. Conclusions

Systemic administration of MK-801 produced marked deficits in sensorimotor gating and increased the response to acoustic stimuli. Administration of antipsychotics with multipharmacological profiles and low affinity to dopamine D2 receptors (clozapine, olanzapine) restored the deficits in PPI induced by MK-801. Antipsychotics with high affinities at dopamine D2 receptors had no effect on the disrupted PPI induced by MK-801. We observed a decrease of spontaneous PPI after administration of clozapine and olanzapine, which could be related to their anti-muscarinic properties.

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