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Disruption of Prepulse Inhibition of Startle Reflex in a Neurodevelopmental Model of Schizophrenia: Reversal by Clozapine, Olanzapine and Risperidone But Not by Haloperidol

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Neonatal ventral hippocampal (NVH) lesions in rats have been shown to induce behavioral abnormalities at adulthood thought to simulate some aspects of positive, negative and cognitive deficits classically observed in schizophrenic patients. Such lesions induced a post-pubertal emergence of prepulse inhibition deficits reminiscent of the sensorimotor gating deficits observed in a large majority of schizophrenic patients. Here we have investigated the capacity of typical and atypical antipsychotics to reverse PPI deficits seen in NVH-lesioned rats.

We show that three atypical antipsychotics (clozapine, olanzapine and risperidone) were able to reverse lesion-induced PPI deficits, in contrast to haloperidol, a classical neuroleptic.

These results show that the NVH lesion model seems to be endowed with a fair predictive validity as, like in schizophrenic patients, PPI deficits in lesioned animals were reversed by atypical antipsychotics but not by the typical neuroleptic haloperidol.

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KEY WORDS: *Schizophrenia; Neonatal lesion; Hippocampus; Prepulse inhibition; Antipsychotics; Animal model*

Schizophrenia has long been associated with abnormalities in information processing and attention mechanisms (Braff 1993; Nuechterlein et al. 1994; Perry and Braff 1994; Swerdlow and Geyer 1998). In an attempt to better understand mechanisms underlying the physiopathology of schizophrenia, sensorimotor information gating processes have received much attention. One well-established method for evaluating sensory filtering is the paradigm of prepulse inhibition (PPI) which refers to the inhibition of a startle reflex by presentation of a weak intensity prepulse immediately before the startle stimulus. Interestingly, PPI is an unlearned phenomenon using virtually identical techniques and parameters across species and it shows similar sensitivity to stimulus parameters in rats and human beings (Swerdlow et al. 1994). Disruption of PPI in schizophrenic patients has been well described in several studies (Braff et al. 1978, 1992; Bolino et al. 1994; Perry and Braff 1994). PPI deficits can also be observed in rats treated with psychotomimetic agents. Indeed, dopamine (DA) agonists such as apomorphine or amphet-

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amine and glutamate (GLU) antagonists induce disruption of PPI. DA agonist-induced PPI deficits are reversed by both typical and atypical antipsychotics whereas those induced by GLU antagonists seem to be reversed only by atypical antipsychotics (Swerdlow and Geyer 1993; Bakshi et al. 1994; Bakshi and Geyer 1995; Varty and Higgins 1995). As a model of schizophrenia, drug-induced PPI deficits in animals exhibit some degree of face, construct, and predictive validity (Ellenbroek and Cools 1990; Swerdlow et al. 1994) and are commonly used to try to identify effective therapies against schizophrenia.

An animal model of an illness is by definition a simplified version of the real condition created to study mechanisms of the disease and to develop effective therapies. The search for new non-pharmacological models which would also exhibit a fair degree of validity to several aspects of schizophrenia is essential. Recently, new such models have appeared, based on the neurodevelopmental hypothesis of schizophrenia which suggests that an abnormal development of the brain connectivity could be one of the mechanisms implicated in the genesis of schizophrenia (Weinberger 1986; Ellenbroek and Cools 1998; Duncan et al. 1999). Among these new models, long-term consequences of neonatal ventral hippocampal (NVH) lesions in the rat have been proposed by Lipska and co-workers as offering a valid simulation of psychotic disorders (Lipska et al. 1993; Lipska and Weinberger 1993, 2000). Indeed, NVH lesions in rats have been shown to induce post-pubertal emergence of behavioral abnormalities thought to simulate some aspects of positive, negative and cognitive symptoms classically observed in schizophrenic patients, such as hyperresponsiveness to stress, novelty, dopamine agonists or glutamate antagonists (Lipska et al. 1993, 1995a; Flores et al. 1996; Black et al. 1998; Brake et al. 1999; Al-Amin et al. 2000, 2001). These post-pubertal anomalies are reminiscent of the classically-described post-pubertal onset of psychotic symptoms in the majority of schizophrenic patients. Indeed, the onset of schizophrenia is frequently precipitated by a stressful event (Duncan et al. 1999), and psychological stress (Duncan et al. 1999) as well as dopamine agonists (Angrist and Van Kammen 1984; Lieberman et al. 1987) and glutamate antagonists (Meador-Woodruff and Healy 2000) are well documented to precipitate or exacerbate psychotic symptoms in humans. NVH-lesioned rats also exhibit deficits in social behavior (Sams-Dodd et al. 1997; Becker et al. 1999), in reward sensitivity (personal observations), in spatial and associative learning and working memory (Chambers et al. 1996; Le Pen et al. 2000) and in social memory (Becker and Grecksch 2000). Finally, NVH lesions induce a reliable post-pubertal emergence of PPI deficits (Lipska et al. 1995b; Le Pen et al. 2000).

If the ability of this model to mimic some aspects of the schizophrenia symptomatology starts to be well established, relatively few studies have investigated its predictive validity by testing the capacity of antipsychotics to reverse abnormal behaviors induced by NVH lesions. It has only been shown that haloperidol and clozapine are effective in suppressing hyperlocomotion induced by NVH lesions (Lipska and Weinberger 1994), and social memory impairments were partly ameliorated by a subchronic treatment with haloperidol (Becker and Grecksch 2000). Finally, Sams-Dodd et al. have shown that chronic administration of clozapine had no effect on social behavior deficits observed in NVH-lesioned rats (Sams-Dodd et al. 1997) whereas recently Becker and coll. have shown the contrary (Becker et al. 2000).

Thus, this study was undertaken to evaluate the capacity of haloperidol (a typical antipsychotic), clozapine, olanzapine and risperidone (atypical antipsychotics) to reverse deficits of prepulse inhibition of startle reflex observed in NVH-lesioned rats.

MATERIALS AND METHODS

Surgery

Sprague-Dawley rats (BRL, Füllinsdorf, Switzerland) were obtained at 3–4 days of age as whole litters together with their mother. They were kept on a 12-h light/12-h dark cycle (On: 6 A.M., Off: 6 P.M.) and fed ad libitum. All experimental procedures and protocols were approved by the local animal protection authorities. On the seventh day of age and at a body weight of 15 to 20 g, male pups within each litter were randomized to Sham or Lesion status, anaesthetized by isoflurane inhalation (4% for induction and 1.5–3% for maintenance) through a mask, mounted on a stereotaxic Kopf instrument with an adapter for small animals (Harvard Biosciences) and additionally taped on a heating pad placed on the platform. The skin overlying the skull was incised and 0.3 μl of either ibotenic acid (Sigma, St. Louis, MO, USA; 10 μg/μl) or artificial cerebrospinal fluid was bilaterally infused over a 2-min period by a micro-infusion pump (PHD Programmable, Harvard Biosciences) using an injection cannula (0.3 mm Ø) aimed at the ventral hippocampal formation (AP −3.0 mm, ML ±3.5 mm and VD −5.0 mm relative to bregma). Following infusion, the skin overlying the skull was sutured and the animals allowed to recover on a heating pad before being returned to their mother. Eighteen days after surgery (i.e. PND25) rats were weaned and housed four per cage. Behavioral testings occurred between 9 a.m. and 4 p.m., and was initiated after puberty at PND70.

Prepulse Inhibition (PPI) of Startle Reflex

The apparatus consisted of eight startle chambers (SR-LAB, San Diego Instruments, CA, USA), containing a transparent Plexiglas tube (diameter 8.2 cm, length 20 cm) mounted on a Plexiglas frame within a ventilated enclosure. Acoustic noise bursts were presented via a speaker mounted 24 cm above the tube. Throughout the session a background noise level of 68 dB was maintained. A piezoelectric accelerometer mounted below the frame detected and transduced motion within the tube. Startle amplitudes were defined as the average of 100 1 ms stabilimeter readings collected from stimulus onset. Rats were run in squads of eight. Each rat was put into the PPI chamber for a 5-min acclimatization period with a 68 dB background noise. Following this period, 10 startle pulses (120 dB, 40 msec duration) were presented with an average inter-trial interval of 15 s. Then, no stimulus (background noise, 68 dB), prepulses alone (72, 76, 80 or 84 dB, 20 msec duration), startle pulses alone, and prepulses followed 80 msec later by startle pulses were presented six times randomly distributed over the next 20 min. The percentage of PPI induced by each prepulse intensity was calculated as: 100((SP-SPP)/SP) with SP being the average startle amplitude following the startle pulses and SPP being the average startle response following the combination of a certain prepulse and the startle pulse.

Drugs

Clozapine (Novartis, Switzerland) and olanzapine (synthesized at Roche) were dissolved in 0.1 N HCl in NaCl 0.9% solution and neutralized to pH 6–7 with 0.1 N NaOH. Haloperidol (Janssen-Cilag) was prepared from 5 mg ampoules containing the drug in 1 ml solvent and diluted with NaCl 0.9% solution to obtain the required concentrations. Risperidone (Sigma) was dissolved in Tween 80 (0.3%) in NaCl 0.9%. Solvent injections consisted of NaCl 0.9% injections in haloperidol, clozapine and olanzapine experiments and of Tween 80 (0.3%) in NaCl 0.9% in risperidone experiments. All drugs were administered in a volume of 5 ml/kg intraperitoneally 30 min prior testing. In each experiment, drugs were administered using a pseudo-randomized design over two or three treatment cycles with a minimum period of two weeks between two cycles. For haloperidol, clozapine and olanzapine experiments, rats were tested twice in PPI paradigm, whereas for the risperidone experiment they were tested three times.

Rating of Lesion Size (According to Sams-Dodd et al. 1997)

At the completion of behavioral evaluation, rats were killed by decapitation. Brains were rapidly removed and after fixation in formalin solution (10% in NaCl), 40-μm sections were sliced with a freezing cryostat. The sections through the lesioned area were mounted and stained with cresyl violet. The extent of the lesion on each side of the brain was rated as follows: 0- no discernible cell loss in the hippocampal formation, 1- small, 2- medium, 3- large area of cell loss within the ventral hippocampal formation. Scores for both sides were added to yield a total score ranging from 0 to 6.

Analysis of Data

PPI data were analyzed using a 3-factor ANOVA (lesion status × antipsychotic dose × prepulse intensity) with repeated measurements on factor prepulse intensity, followed when appropriate by separate 2-factor ANOVA or by the Fisher's PLSD post-hoc test. Startle amplitude data were analyzed by a 2-factor ANOVA (lesion status × antipsychotic dose) followed when appropriate by post-hoc comparisons (Fisher's PLSD test).

RESULTS

Histology

Subjects with only unilateral or extrahippocampal damage were discarded from the study (haloperidol experiment: 12 rats, clozapine experiment: 11 rats, olanzapine experiment: 5 rats and risperidone experiment: 2 rats). Neonatally-lesioned rats evaluated in PPI experiments exhibited mean lesion score between 3.51 ± 0.15 and 3.69 ± 0.16 indicating that the cell loss was restricted to the ventral part of the hippocampus (Figure 1). Some animals exhibited cavitation around the site of injection. In control rats that had been injected with artificial cerebrospinal fluid, the hippocampus was morphologically intact (lesion score 0).

PPI

Haloperidol. Neonatal ventral hippocampal lesions induced significant PPI deficits, and these effects were not opposed by haloperidol (Figure 2). A 3-way ANOVA of PPI revealed a significant effect of the lesion ($F_{1,135} = 41.4$, $p < .0001$), no significant overall effect of haloperidol ($F_{3,135} = 0.7$, NS) and a significant interaction lesion × haloperidol ($F_{3,135} = 2.7$, $p < .05$) indicating that haloperidol had different effects in sham and lesioned animals. Post-hoc comparisons revealed that haloperidol 1 mg/kg induced a significant reduction of PPI ($p < .01$) in sham animals but not in NVH lesioned rats. The overall analysis also showed a significant effect of prepulse intensity ($F_{3,405} = 253.9$, $p < .0001$), a significant interaction of lesion × prepulse intensity ($F_{3,402} = 8.2$, $p < .0001$), and no other 2- or 3-way interactions. Separate ANOVAs were performed for each prepulse intensity tested and revealed a lesion-induced

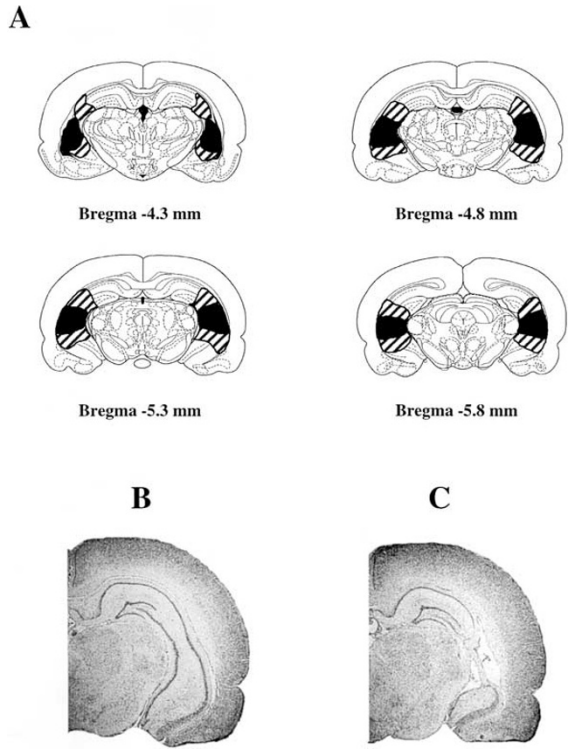

Figure 1. Lesion boundaries in the ventral hippocampus of adult rats infused bilaterally with ibotenic acid at postnatal day 7. (A) A schematic drawing of the ventral hippocampus with boundaries of the largest (stripes) and smallest (black) lesions. Representative photomicrographs of Cresyl violet-stained coronal section through the brains of adult rats that had received sham (B) or neonatal (C) lesions of the ventral hippocampus.

decrease of PPI at each of the four prepulse intensities ($p < .0001$). These ANOVAs also revealed a significant lesion × haloperidol interaction at 80 dB ($p < .05$) and a strong trend toward interaction at 76 and 84 dB ($p = .066$ and $p = .064$ respectively). Post-hoc comparisons revealed that haloperidol 1 mg/kg decreased PPI at 76, 80 and 84 dB in sham animals ($p < .05$, $p < .01$ and $p < .05$ respectively) but not in lesioned rats.

Clozapine. Here also, neonatal ventral hippocampal lesions induced significant PPI deficits, and these effects were opposed by clozapine (Figure 3). A 3-way ANOVA of PPI revealed a significant effect of the lesion ($F_{1,134} = 16.4$, $p < .0001$), a significant effect of clozapine ($F_{3,134} = 4.2$, $p < .01$) and a significant interaction lesion × clozapine ($F_{3,134} = 4.2$, $p < .01$) indicating that clozapine had different effects in sham and lesioned animals. Post-hoc comparisons revealed that PPI was significantly decreased in sham animals pretreated with 5 mg/kg of clozapine ($p < .05$). In contrast, in NVH lesioned rats, PPI was significantly greater in rats pretreated with 12 and 20 mg/kg of clozapine as compared with rats pretreated with solvent (both $p < .01$). The overall analysis also revealed a significant effect of prepulse intensity ($F_{3,402} = 206.9$, $p < .0001$), a significant interaction of lesion × prepulse intensity ($F_{3,402} = 10.3$, $p < .0001$) and no other 2- or 3-way interactions. Separate ANOVAs were performed for each prepulse intensity tested and revealed a lesion-induced decrease of PPI at each of the four prepulse intensities ($p < .0001$, $p < .001$, $p < .05$ and $p < .01$ respectively). At 76, 80 and 84 dB, these ANOVAs also revealed a significant effect of clozapine ($p < .05$, $p < .01$ and $p < .001$ respectively) and a significant lesion × clozapine interaction ($p < .05$, $p < .01$ and $p < .05$ respectively). Post-hoc comparisons showed that clozapine dose-dependently and fully reversed PPI deficits induced by NVH lesions at 76, 80 and 84 dB. Moreover, the post-hoc test revealed that clozapine 5 mg/kg also partially reversed this deficit at 80 dB. In sham operated animals, clozapine 5 mg/kg reduced significantly PPI at 80 and 84 dB ($p < .01$ and $p < .05$ respectively).

Olanzapine. PPI deficits induced by neonatal ventral hippocampal lesions were also opposed by olanzapine treatment (Figure 4). Indeed, a 3-way ANOVA of PPI revealed a significant effect of the lesion ($F_{1,155} = 25$, $p < .0001$), no overall effect of olanzapine ($F_{3,155} = 0.9$, NS) and a significant interaction lesion × olanzapine ($F_{3,155} = 3.8$, $p < .05$) indicating that olanzapine had different effects in sham and lesioned animals. Post-hoc comparisons revealed that olanzapine induced a reduction of PPI at 10 mg/kg in sham animals ($p < .05$). In contrast, in lesioned rats, PPI was significantly greater in rats pretreated with 3 mg/kg of olanzapine than in rats pretreated with solvent ($p < .05$). The overall analysis also showed a significant effect of prepulse intensity ($F_{3,465} = 234.5$, $p < .0001$), a significant interaction of lesion × prepulse intensity ($F_{3,465} = 11.7$, $p < .0001$), a significant lesion × olanzapine interaction ($F_{3,465} = 2.3$, $p < .05$) and no 3-way interaction. Separate ANOVAs were performed for each prepulse intensity tested and revealed a lesion-induced decrease of PPI at each of the four prepulse intensities ($p < .0001$, $p < .0001$, $p < .01$ and $p < .001$ respectively). These ANOVAs also revealed a significant lesion × olanzapine interaction at 76 dB ($p < .01$) and a strong trend toward interaction at 72 and 84 dB ($p = .057$ and $p = .066$ respectively). Post-hoc comparisons revealed that olanzapine 3 mg/kg fully reversed PPI deficits induced by NVH lesions at 72 and 80 dB. Olanzapine 3 and 10 mg/kg also partially reversed this deficit at 76 dB. In sham operated animals, olanzapine 3 and 10 mg/kg reduced significantly PPI at 76 db ($p < .05$).

Risperidone. Here again, neonatal ventral hippocampal lesions induced significant PPI deficits, and these effects were opposed by risperidone (Figure 5). A 3-way ANOVA of PPI revealed a significant effect of the lesion ($F_{1,163} = 32.5$, $p < .0001$), no overall effect of risperidone ($F_{3,163} = 3.8$, NS) and a significant interaction lesion ×

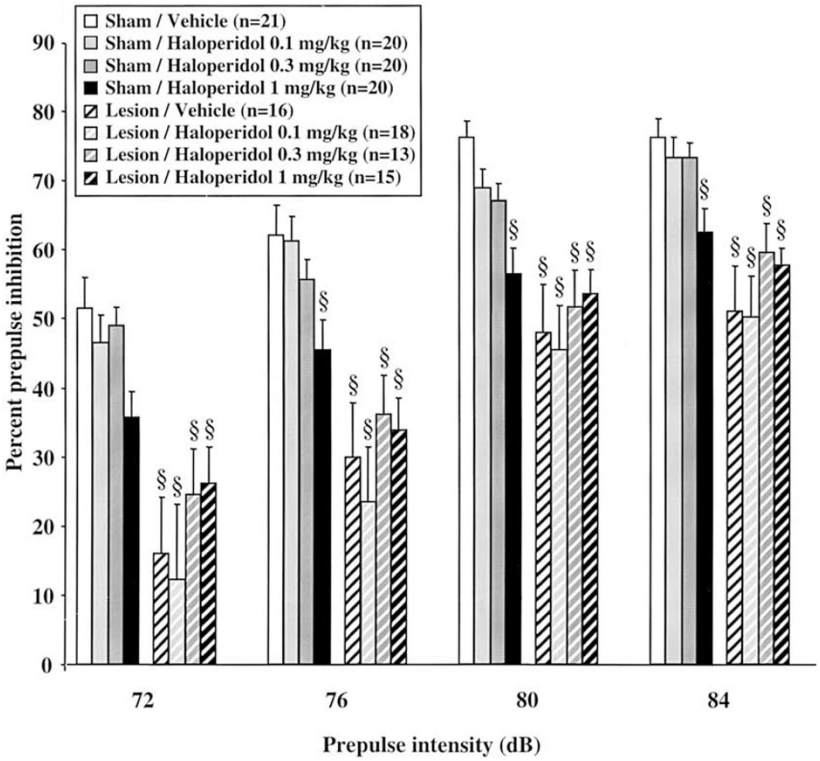

Figure 2. Effects of haloperidol on neonatal ventral hippocampal lesion-induced deficits in prepulse inhibition of startle reflex. A dose response study using vehicle, 0.1, 0.3 or 1 mg/kg of haloperidol injected i.p. 30 min before testing was performed. § $p <$ .05 at least compared with Sham/Vehicle group.

risperidone ($F_{3,163} = 3.8$, $p < .05$) indicating that risperidone had different effects in sham and lesioned animals. Post-hoc comparisons revealed no significant effect of risperidone on PPI in sham animals. In contrast, in NVH lesioned rats, a post-hoc test revealed that PPI was significantly greater in rats pretreated with 0.1, 0.3 and 1 mg/kg of risperidone than in rats pretreated with solvent ($p < .05$, $p < .05$ and $p < .001$ respectively). The overall analysis also revealed a significant effect of prepulse intensity ($F_{3,489} = 293.1$, $p <$ .0001), a significant interaction of prepulse intensity × risperidone ($F_{9,489} = 1.9$, $p < .05$) and no other 2- or 3-way interactions. Separate ANOVAs were performed for each prepulse intensity tested and revealed a lesion-induced decrease of PPI at each of the four prepulse intensities ($p < .0001$). These ANOVAs also revealed a significant effect of risperidone 80 and 84 dB ($p < .05$ and $p < .01$ respectively) and a significant lesion × risperidone interaction at the four prepulse intensities tested ($p < .05$, $p < .01$, $p < .05$ and $p < .05$ respectively). Post-hoc comparisons showed that risperidone (0.1 mg/kg) partially reversed PPI deficits induced by NVH lesions at 72 dB. PPI deficits were significantly reversed by risperidone 0.1 and 1 mg/kg at 76 dB (strong tendency at 0.3 mg/kg: $p = .068$). These deficits were dose-dependently and fully reversed by risperidone at 80 and 84 dB (0.3 and 1 mg/kg, strong tendency at 0.1 mg/kg ($p = .068$)). Finally, in sham operated animals, risperidone 0.1 mg/kg significantly reduced PPI at 72 and 76 dB.

Startle Amplitude

Drug effects on startle amplitude (pulse alone) are seen in Figure 6.

In clozapine, olanzapine and risperidone experiments (Figure 6, panels B, C and D respectively), we replicated the previous finding that lesion has no effect on startle amplitude (Lipska et al. 1995b; Le Pen et al. 2000) but surprisingly, a significant overall lesion effect was found in the haloperidol experiment ($F_{1,135} = 7.1$, $p < .01$) (Figure 6, panel A). However, post-hoc comparisons revealed a significant decrease ($p < .05$) of startle amplitude in NVH-lesioned rats only at the 0.1 mg/kg dose of haloperidol.

Moreover, in haloperidol, clozapine, olanzapine and risperidone experiments (Figure 6, panels A, B, C, and D respectively), the amplitude of the startle response decreased significantly with increasing antipsychotic doses ($F_{3,135} = 12$, $p < .0001$; $F_{3,134} = 23.7$, $p < .0001$; $F_{3,157} = 12.3$, $p < .0001$ and $F_{3,157} = 12.3$, $p < .0001$ respectively), but no significant lesion × antipsychotic interaction could be detected. Post-hoc comparisons show that, in both sham and lesioned animals, haloperidol, clozapine and risperidone induced a decrease of startle amplitude at the three doses tested whereas with olanzapine this reduction is only observed at 3 and 10 mg/kg.

DISCUSSION

In good agreement with previous reports (Lipska et al. 1995b; Le Pen et al. 2000), we show in this study that

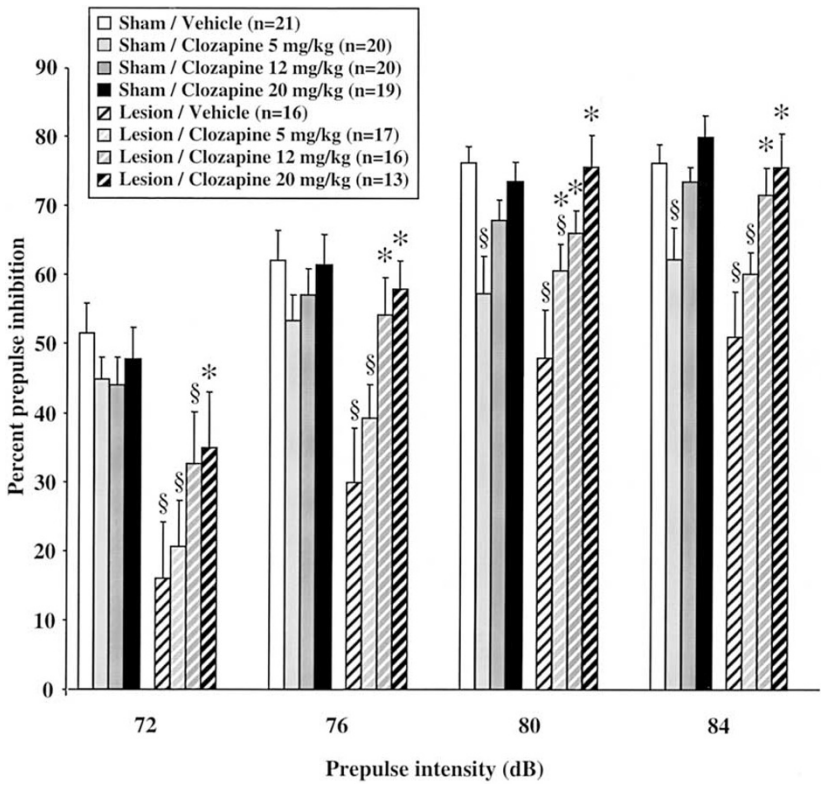

Figure 3. Effects of clozapine on neonatal ventral hippocampal lesion-induced deficits in prepulse inhibition of startle reflex. A dose response study using vehicle, 5, 12 or 20 mg/kg of clozapine injected i.p. 30 min before testing was performed. § $p < .05$ at least compared with Sham/Vehicle group. * $p < .05$ at least compared with Lesion / Vehicle group.

NVH lesions induced deficits in sensorimotor gating using PPI of startle paradigm. These experiments are also the first to investigate the capacity of antipsychotics to reverse the PPI deficits observed in the NVH-lesioned rats.

We show that NVH lesions-induced PPI deficits are fully or partially reversed by atypical antipsychotics such as clozapine, olanzapine and risperidone but not by haloperidol, a typical antipsychotic. These results partly replicate previous data obtained in other neurodevelopmental animal models of schizophrenia. Indeed, it has been shown that clozapine, risperidone, quetiapine or olanzapine were able to reverse PPI deficits induced by isolation rearing (Geyer et al. 1993; Varty and Higgins 1995; Bakshi et al. 1998; Bakshi and Geyer 1999) and quetiapine reversed those induced by maternal deprivation (Ellenbroek et al. 1998). In contrast to our results, in these studies, PPI deficits were also antagonized by haloperidol.

However, our results are also in good agreement with clinical data obtained in schizophrenic patients. Indeed, disruptions of sensorimotor gating processes are commonly shown in schizophrenic patients using PPI of the startle reflex (Perry and Braff 1994; Kumari et al. 2000; Parwani et al. 2000). These PPI deficits seem to be best treated by atypical antipsychotics, as clozapine normalized information processing functions in clinically-stable psychotic patients (Kumari et al. 1999) whereas this was not the case in such patients treated with typical neuroleptics (Braff et al. 1978; Braff and Geyer 1990; Braff et al. 1992; Bolino et al. 1992; Grillon et al. 1992).

Another parallel between our results and data obtained in humans lies in the fact that, in normal volunteers, haloperidol on its own reduced prepulse inhibition of the startle reflex (Abduljawad et al. 1998; Kumari et al. 1998). Indeed, in our studies, in sham-operated animals, reduction of PPI has been observed after a high dose of haloperidol (1 mg/kg) at three of the prepulse intensities tested. This reduction was also observed after olanzapine (3 and 10 mg/kg), clozapine (5 mg/kg) and risperidone (0.1 mg/kg). These PPI reductions could be explained in part by antipsychotic-induced reductions in startle amplitudes and associated floor effects. However, this is unlikely to be the case since no reductions of PPI have been noticed with high doses of clozapine or risperidone which drastically affected startle.

In good agreement with the literature (Davis and Aghajanian 1976; Swerdlow and Geyer 1993; Varty and Higgins 1995; Schwarzkopf et al. 1996; Bakshi et al. 1998), we also showed that haloperidol, clozapine, olanzapine and risperidone dose-dependently reduced the startle in sham-operated animals, but also in NVH-lesioned rats. Thus, it is worth noting that the inability of haloperidol to reverse PPI deficits observed in NVH-lesioned rats is unlikely to be simply a consequence of its reduction of startle, as: (1) such a reversal is obtained with doses of clozapine, olanzapine or risperidone which by themselves inhibit startle;

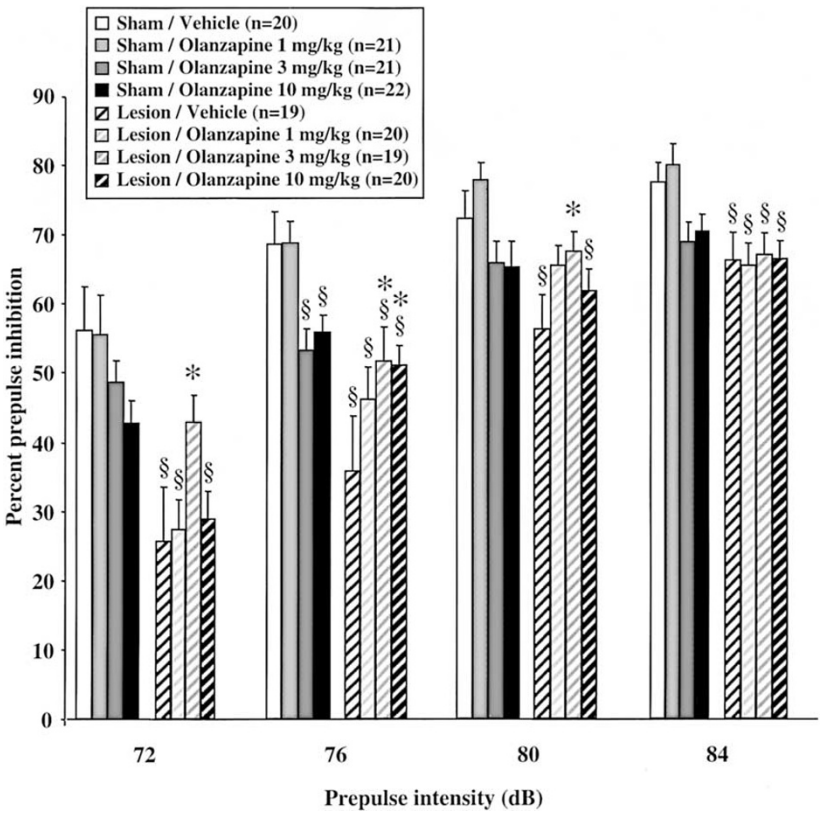

Figure 4. Effects of olanzapine on neonatal ventral hippocampal lesions-induced deficits in prepulse inhibition of startle reflex. A dose response study using vehicle, 1, 3 or 10 mg/kg of olanzapine injected i.p. 30 min before testing was performed. § $p <$ .05 at least compared with Sham/Vehicle group. * $p <$ .05 at least compared with Lesion/Vehicle group.

and (2) antipsychotics appeared to reduce startle similarly in both sham and lesioned rats while only altering PPI in the lesioned rats. Thus, as previously stated, there is no consistent relationship between the startle amplitude value and the effectiveness of a given antipsychotic to restore PPI deficits (Schwarzkopf et al. 1992; Varty and Higgins 1995; Swerdlow et al. 1996).

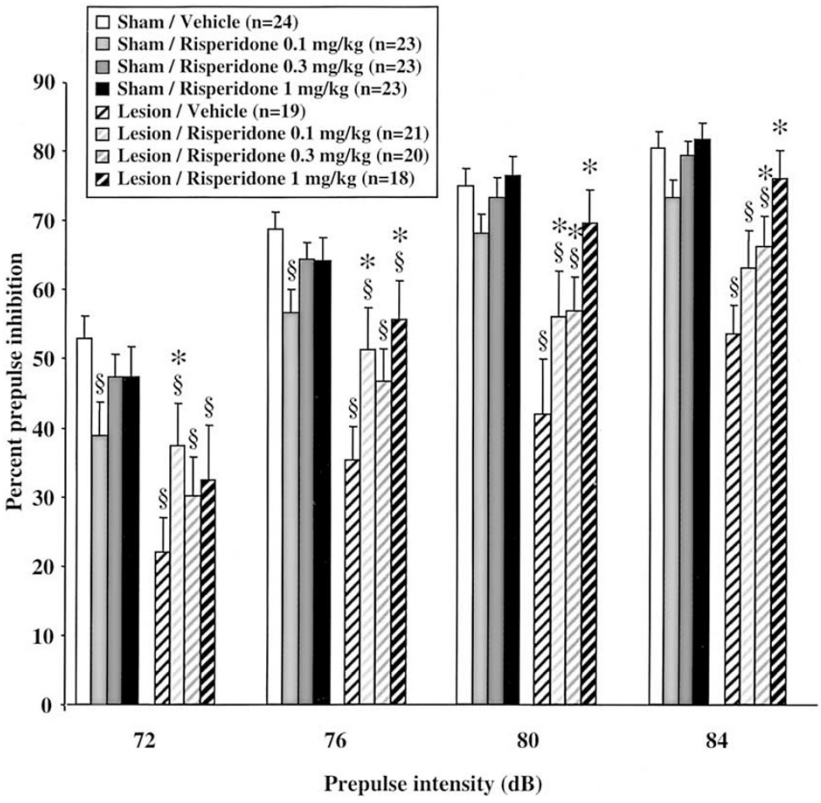

Figure 5. Effects of risperidone on neonatal ventral hippocampal lesion-induced deficits in prepulse inhibition of startle reflex. A dose response study using vehicle, 0.1, 0.3 or 1 mg/kg of risperidone injected i.p. 30 min before testing was performed. § $p <$ .05 at least compared with Sham/Vehicle group. * $p <$ .05 at least compared with Lesion/Vehicle group.

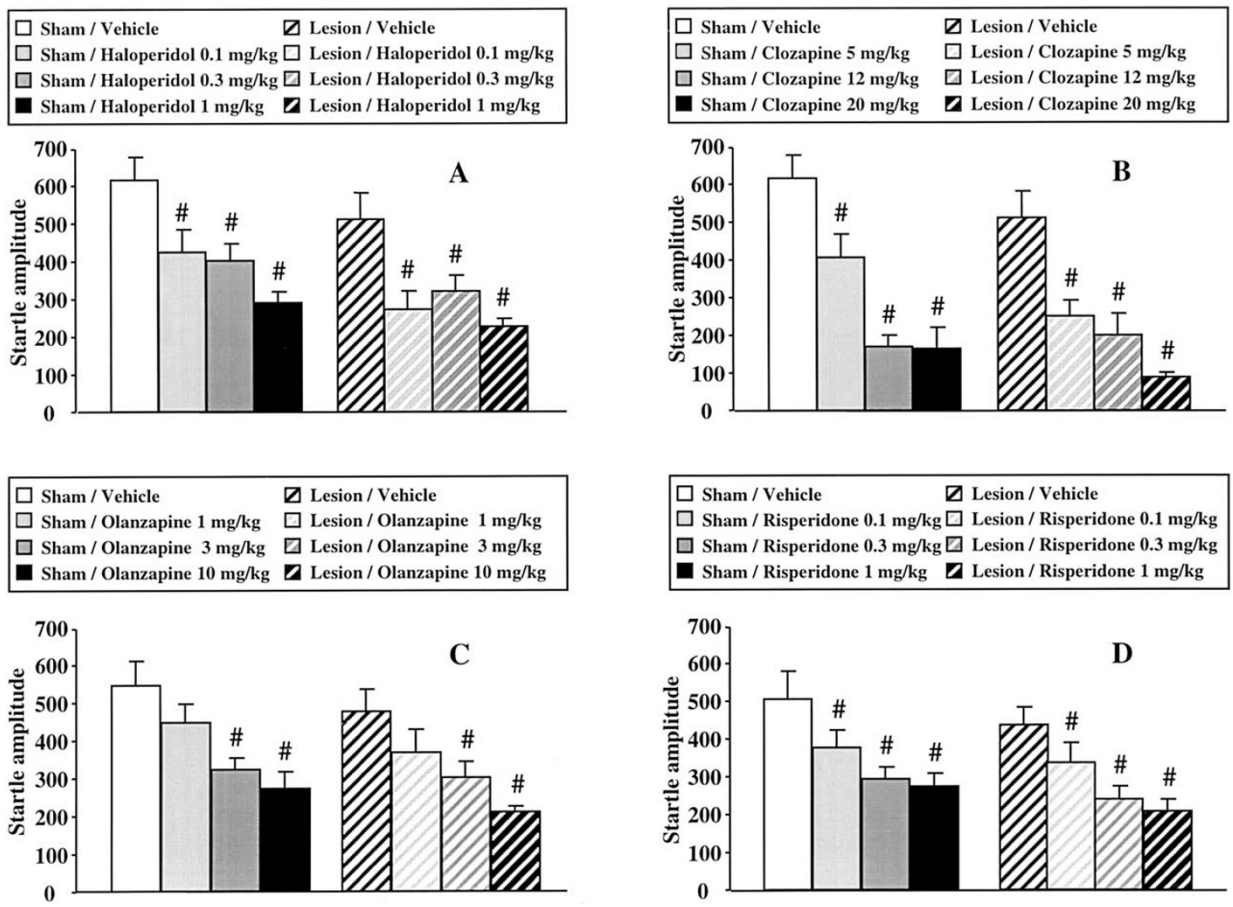

Figure 6. Effects of haloperidol (A), clozapine (B), olanzapine (C) and risperidone (D) on startle amplitude in sham-operated and neonatal ventral hippocampal lesioned rats. # $p < .05$ at least compared with respective control group.

We showed that atypical antipsychotics, but not a typical antipsychotic, haloperidol, are able to reverse PPI deficits observed in NVH-lesioned rats. This suggests that these deficits might be particularly sensitive to some critical properties linked to the "atypicality" of those antipsychotic drugs. Interestingly, intra-ventral hippocampus or subiculum infusions of NMDA induce disruptions of PPI which are antagonized by a systemic administration of clozapine but not by haloperidol (Wan et al. 1998; Zhang et al. 1999). Thus, to normalize PPI deficits, atypical antipsychotics such as clozapine, olanzapine and risperidone probably interact with brain systems affected by NVH lesions through their action on receptors other than DA receptors. In contrast to haloperidol, atypical antipsychotics also interact, among others, with 5HT2A, α2 adrenergic, muscarinic and histaminergic receptors. All of them could play an important role for the unique action of atypical antipsychotics in our experiments. Thus, for example, it would be interesting to test the capacity of M100907 and atipamezole, selective antagonists of 5-HT2A and α2 adrenergic receptors respectively, to reverse PPI deficits observed in NVH lesioned rats.

Atypical antipsychotics were also found to be more potent than typical ones to reverse behavioral changes induced by GLU receptor antagonists. Indeed, clozapine, olanzapine, or risperidone, in contrast to haloperidol, attenuated PCP-induced reduction of PPI in rats (Keith et al. 1991; Bakshi et al. 1994; Bakshi and Geyer 1995; Varty and Higgins 1995; Swerdlow et al. 1996; Yamada et al. 1999). Yamada and colleagues have shown that the ability of drugs to reverse PCP-induced PPI disruption is correlated to their affinity for 5HT2A, not D2 receptors (Yamada et al. 1999) consistent with the hypothesis that serotonin (via 5HT2A receptor) and glutamate could interact in modulating PPI (Varty et al. 1999). These results suggest that NVH-induced PPI deficits could result from a dysfunctioning of the glutamate system which could be antagonized more potently by atypical antipsychotics. This hypothesis is also supported by various data obtained in NVH-lesioned rats. Indeed, in the hippocampal formation as well as in the frontal cortex of NVH lesioned rats, a hypofunctioning of the glutamatergic system was shown by measuring ex vivo amino acid release from tissue slices (Schroeder et al. 1999). Moreover, it has been

shown that NVH-lesioned rats are hypersensitive to GLU receptor antagonists MK-801 (Lillrank et al. 1996; Al-amin et al. 2000, 2001) and to PCP (Hori et al. 2000; Kato et al. 2000).

In conclusion, the present study shows that the NVH lesion model is endowed with a fair predictive validity as, in lesioned animals like in schizophrenic patients, PPI deficits are reversed by atypical antipsychotics but not by the typical neuroleptic haloperidol.

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