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Prepulse inhibition in rats with temporary inhibition/inactivation of ventral or dorsal hippocampus

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Abstract

Prepulse inhibition (PPI) of the acoustic startle response is a measure of sensorimotor gating and is decreased in neuropsychiatric diseases, including schizophrenia. Hippocampal involvement in PPI has been the subject of several studies, in particular, as aberrant hippocampal activity has been associated with schizophrenia. In rats, chemical stimulation of the ventral hippocampus reduced PPI, while normal PPI was found following hippocampal lesions, suggesting that ventral hippocampal overactivity is detrimental for PPI, but that normal hippocampal activity does not contribute substantially to PPI. In the present study, we investigated the importance of hippocampal activity for PPI by examining PPI in Wistar rats with temporarily decreased hippocampal activity, aiming to avoid compensatory processes that may occur with permanent lesions. Bilateral ventral or dorsal hippocampal infusions of the γ-aminobutyric acid A ($GABA_A$) receptor agonist muscimol (1 μg/side) or the sodium-channel blocker tetrodotoxin (TTX, 10 ng/side) reduced PPI. This reduction is probably neuroleptic-resistant since haloperidol and clozapine did not antagonize the muscimol-induced decreases in PPI. PPI reduction by muscimol inhibition or TTX inactivation of the dorsal or ventral hippocampus indicates that hippocampal activity contributes to sensorimotor gating, suggesting intact PPI after permanent hippocampal lesions to reflect compensatory processes. The data are discussed with respect to hippocampal dysfunction in schizophrenia.

Keywords: Clozapine; Haloperidol; Muscimol; Neuroleptics; Prepulse inhibition; Schizophrenia; Sensorimotor gating; Startle; TTX; Ventral and dorsal hippocampus

1. Introduction

In rats and humans, prepulse inhibition (PPI) of the acoustic startle response, i.e. the reduction of the response by a weak prepulse preceding the startle pulse, is used to measure sensorimotor gating mechanisms protecting neural information processing (Graham, 1975; Norris and Blumenthal, 1996; Koch, 1999). Deficient sensorimotor gating, as reflected by disrupted PPI, exists in several neuropsychiatric disorders. In particular, sensorimotor gating deficits are well documented in schizophrenia and may correlate with positive symptoms, even though the relation between PPI deficits and schizophrenia remains to be clarified (Braff et al., 2001; Hamm et al., 2001). Experimentally induced disruption of PPI in rats is used to elucidate the neurological aberrations underlying deficient sensorimotor gating (Swerdlow et al., 2000a).

The hippocampal involvement in the regulation of PPI has been the subject of several studies, in particular, as aberrant hippocampal activity is widely believed to contribute to schizophrenic symptoms (Gray et al., 1991; Benes, 2000; Gothelf et al., 2000; Grace, 2000). Overactivity of the ventral hippocampus, induced, for example, by infusion of *N*-methyl-D-aspartate (NMDA; e.g., Wan et al., 1996; Klarner et al., 1998; Zhang et al., 1999; Bast et al., 2001d) or the γ-aminobutyric acid A ($GABA_A$) receptor antagonist picrotoxin (Bast et al., 2001b), clearly disrupts PPI. It is not clear, however, whether normal hippocampal activity contributes to the maintenance of PPI. Infusion of the noncompetitive NMDA antagonist MK-801 into the dorsal hippocampus (Bakshi and Geyer, 1998, 1999) or neonatal lesions of the ventral hippocampus (Lipska et al., 1995; Le Pen et al., 2000) have been reported to impair PPI,

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and rats with ventral hippocampal lesions exhibited increased sensitivity to PPI disruption induced by the dopamine agonist apomorphine (Swerdlow et al., 1995, 2000b). However, MK-801 infusion into the ventral hippocampus did not affect PPI (Bakshi and Geyer, 1998; Bast et al., 2000) and we also found intact PPI following MK-801 infusion into the dorsal hippocampus (Zhang et al., 2000b). In particular, several studies that found intact basal PPI following lesions to the ventral, dorsal, or complete hippocampus (Kemble and Ison, 1971; Pouzet et al., 1999; Swerdlow et al. 1995, 2000b) did not support the view that normal hippocampal activity contributes to PPI, even though slightly decreased PPI has very recently been reported after lesions to the ventral, but not dorsal, subiculum (Caine et al., 2001).

Permanent lesions may fail to reveal a structure's normal function since, for example, other structures may rapidly compensate for the permanent loss of one structure (Bures and Buresova, 1990; Lomber, 1999). Moreover, we recently found that temporary inhibition or inactivation of the ventral hippocampus by the $GABA_A$ receptor agonist muscimol or the sodium channel blocker tetrodotoxin (TTX), respectively, decreased locomotor activity (which is in line with the hyperactivity following stimulation of the ventral hippocampus), whereas ventral hippocampal lesions tend to increase activity (see Bast et al., 2001c). In the present study, in view of the possible problems associated with permanent lesions (see Bast et al., 2001a), we temporarily inhibited or inactivated the ventral or dorsal hippocampus of Wistar rats during PPI testing to examine whether hippocampal activity is necessary to maintain normal sensorimotor gating. In addition, the effects of the neuroleptics haloperidol and clozapine on the PPI disruption induced by hippocampal inhibition were examined. The present data have previously been published in preliminary form (Feldon et al., 2001).

2. Experimental procedures

2.1. Subjects

Seventy-six male Wistar rats (Zur:WIST[HanIbm], Research Unit Schwerzenbach, Schwerzenbach, Switzerland), weighing about 250 g at the time of surgery, were used in this study. They were housed in groups of four per cage under a reversed light–dark cycle (lights on: 19:00–07:00) in a temperature (21 ± 1 °C) and humidity (55 ± 5%) controlled room. All animals were allowed free access to food and water. Forty-eight rats received bilateral implantation of guide cannulae aiming at the dorsal hippocampus, and 28 rats received bilateral implantation of guide cannulae aiming at the ventral hippocampus. After surgery, all rats were individually caged. Starting one day before surgery and then throughout the studies, all rats were handled daily. Behavioral testing was carried out in the dark phase of the cycle. All experiments were conducted in accordance with Swiss regulations for animal testing.

2.2. Surgery

Rats were anesthetized with 1 ml of nembutal (sodium pentobarbital, 50 mg/ml, Abbott Labs, North Chicago, IL) per kg body weight and their head was placed in a Kopf stereotaxic frame. After application of a local anesthetic (lidocaine), the scalp was incised to expose the skull. Bregma and lambda were aligned in the same horizontal plane. A small hole (1.5 mm in diameter) was drilled on each side of the skull to reveal the dura covering the cortex overlying the hippocampus. Stainless steel guide cannulae (26 gauge, 9 or 7 mm for ventral or dorsal hippocampus, respectively) in a Perspex holder were implanted bilaterally into the brain aiming above the ventral (− 5.2 mm posterior and ± 5.0 mm lateral to bregma, and − 5.0 mm ventral to dura) or dorsal (− 3.0 mm posterior and ± 1.5 mm lateral to bregma, and − 2.5 mm ventral to dura) hippocampus. The guide cannulae were fixed to the skull with three anchoring skull screws and dental cement. Stainless steel stylets (34 gauge) extending 0.5 mm beyond the tips of the guide cannulae were placed inside the guide cannulae to prevent occlusion. After surgery, rats had at least 5 days of recovery before being subjected to any behavioral testing. Moreover, they received daily health checks, and missing stylets were replaced.

2.3. Intracerebral drug infusion

Muscimol [$C_4H_6N_2O_2$(1/2 H_2O); Tocris, Bristol, UK] was dissolved in 0.9% saline at a concentration of 2 μg/μl on the day of infusion. TTX ($C_{11}H_{17}N_3O_8$; Tocris) was stored at − 40 °C in aliquots containing 40 ng/μl in 0.9% saline. On the day of infusion, these aliquots were thawed and diluted with 0.9% saline to obtain solutions with a concentration of 20 ng/μl. For the intracerebral infusion, rats were manually restrained, the stylets removed carefully, and infusion cannulae (34 gauge, stainless steel) were inserted into the brain through the previously implanted guide cannulae. The tips of the infusion cannulae protruded 1.5 mm beyond the tip of the guide cannulae into the ventral or dorsal hippocampus. Thus, the final dorso-ventral coordinate for the ventral and dorsal hippocampus was 6.5 and 4.0 mm below the dura, respectively. The infusion cannulae were connected to 10-μl Hamilton microsyringes by flexible polyetheretherketone (PEEK) tubing. The syringes were mounted on a Kds microinfusion pump. All rats were infused bilaterally and the infusion volume was 0.5 μl/side, delivered with a speed of 0.5 μl/min. Following infusion, the infusion cannulae were kept in place for an additional 60 s to allow the injection bolus to be absorbed by the tissue and were then replaced by the stylets. As in our previous study (Bast et al., 2001c), muscimol (1 μg/0.5 μl/side) was infused immediately and TTX (10 ng/0.5 ml/side) 20 min before the

behavioral sessions. Accordingly, half of the rats infused with vehicle, i.e. 0.9% saline (0.5 μl/side), received infusion immediately before the behavioral sessions, the other half 20 min before the behavioral sessions. Rats used in the present study received at most four intracerebral infusions, each of them 1 week apart.

2.4. Systemic drug administration

Haloperidol from ampoules containing 5 mg/ml solvent (Janssen-Cilag, Baar, Switzerland) was diluted with 0.9% saline to a concentration of 0.2 mg/ml. Clozapine (Novartis, Basel, Switzerland) was dissolved in 0.9% saline, acidified by 0.1 M HCl, at a concentration of 5 or 10 mg/ml, and the solution was adjusted to pH 5–6 by addition of Na_2CO_3. Vehicle, i.e. 0.9% saline, haloperidol (0.2 mg/kg), and clozapine (5 or 10 mg/kg) were injected intraperitoneally, in a volume of 1 ml/kg, 45 min prior to the test sessions.

2.5. Apparatus and procedure for behavioral testing

Startle response and PPI were tested in four startle chambers (SR-LAB, San Diego Instruments, San Diego, CA), 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. Motion inside the tube was detected by a piezoelectric accelerometer below the frame. The amplitude of the whole body startle response to an acoustic pulse was defined as the average of one hundred 1-ms accelerometer readings collected from pulse onset. Each rat was put into the PPI chamber for a 5-min acclimatization period with a 68-dB(A) background noise level that continued throughout the session. After the acclimatization period, four startle pulses of 120 dB(A) broad band burst for 30 ms were presented. These four initial startle pulses served to achieve a relatively stable level of startle reactivity for the remainder of the test session, as most rapid habituation of the startle reflex occurs within the first few startle pulse presentations (Koch, 1999). After the four initial pulses, six blocks of 11 trials were presented to measure PPI. Each block consisted of four different trial types, presented pseudorandomly throughout the session: pulse alone (two trials), prepulse alone (one trial for each prepulse intensity), prepulse followed by pulse (one trial for each prepulse intensity), or no stimulus (one trial). The four different prepulses had an intensity of either 72, 76, 80, or 84 dB(A) and a duration of 20 ms. The time interval between the prepulse offset and the pulse onset was 80 ms. The different trial types were presented pseudorandomly with an intertrial interval of 10–20 s (average 15 s). Altogether, a complete test session lasted about 23 min. The percentage of PPI (%PPI) induced by each prepulse intensity was calculated as: [100 − (100 × startle amplitude on prepulse trial)/(startle amplitude on pulse-alone trial)].

2.6. Experimental design and groups

2.6.1. General

The experiments were conducted on three successive days. Rats were tested in squads of four. The different testing boxes and the order of testing was counterbalanced among the experimental groups as far as possible. On Day 1, all experimental groups were subjected to a startle and PPI testing without infusion to verify that they had similar baseline values of startle and PPI. If necessary, the experimental groups were rearranged for further testing so that they were matched for their baseline values as far as possible. On Day 2 (day of infusion), rats were tested for startle response and PPI following the different intracerebral infusions and systemic injections. By comparing startle amplitude and PPI of the different groups on Day 2, acute effects of the treatments were assessed (between-subjects design). On Day 3, all rats were subjected to a further testing of startle response and PPI without a preceding treatment as on Day 1 to test for possible long-term effects of the drug treatments on Day 2.

Before being subjected to the experiments of the present study, most animals had been used in one or two previous experiments. Unless otherwise mentioned, animals were allocated to the experimental groups counterbalanced according to their previous experimental history (see below). Startle and PPI data on Day 1 of the present study's experiments were virtually identical to that measured in our Wistar rats in previous studies (Bast et al., 2000, 2001a,b,d; Zhang et al., 1999, 2000b, 2002), demonstrating that the preceding experiments to which the rats used in the present study had been subjected did not affect baseline startle and PPI values. Moreover, in the data analysis (see below), the experimental history of the animals was considered in order to exclude interactions between the treatments in the present and the preceding experiments.

2.6.2. Effects of TTX or muscimol infusion into the dorsal or ventral hippocampus on the startle response and its PPI

In the first two experiments, the effects of dorsal or ventral hippocampal muscimol and TTX infusion on startle response and PPI were examined. The rats were allocated to three different experimental groups to receive either vehicle (VEH), muscimol (MUS), or TTX infusion before testing on Day 2. Forty-two rats with cannulae aiming at the dorsal hippocampus were used to test the effects of dorsal hippocampal TTX and muscimol infusion (VEH, $n = 16$; MUS and TTX, $n = 13$). These rats had received the same infusion as in the present study in an open field experiment 1 week before, and another bilateral infusion (0.5 μl saline/side, or 0.5 μg NMDA or 6.25 μg MK-801 in 0.5 μl saline/side) in a fear conditioning experiment (with a tone being used as conditioned stimulus and freezing being used as measure of conditioned fear) 2 weeks before. Twenty-eight rats with cannulae aiming at the ventral hippocampus were used to test the effects of ventral hippocampal TTX and muscimol

infusion (VEH, $n=12$; MUS and TTX, $n=8$). Fourteen of them were naive, the other 14 had received one bilateral infusion (0.5 μl saline/side or 6.25 μg MK-801 in 0.5 μl saline/side) in a fear conditioning experiment 1 week before. Rats allocated to the MUS or TTX group were either naive or received saline infusion in the previous fear conditioning experiment. Given that some of the rats used in the present study had previously received an infusion of NMDA or MK-801, i.e. substances with neurotoxic potential (Hajos et al., 1986; Olney et al., 1989), it is important to note that our histological examinations using cresyl violet staining and visualization of the neuronal marker protein NeuN by means of immunostaining demonstrated that single NMDA or MK-801 infusions at the relevant doses into the dorsal hippocampus do not induce considerable additional neuronal damage in comparison to vehicle infusion (Bast et al., in press).

2.6.3. Effects of neuroleptic pretreatment on PPI disruption induced by muscimol infusion into the ventral or dorsal hippocampus

In the first two experiments, TTX inactivation as well as muscimol inhibition of both the ventral and dorsal hippocampus resulted in decreased PPI. Increased dopamine transmission, in particular in the nucleus accumbens, is widely held to be one important cause of decreased PPI, and some forms of experimentally induced PPI disruption are antagonized by neuroleptics (Koch, 1999; Zhang et al., 2000a; Geyer et al., 2001; Swerdlow et al., 2001a). Thus, even though there is evidence for stimulation rather than deactivation of (ventral) hippocampal activity to increase accumbal dopamine transmission (e.g., Brudzynski and Gibson, 1997; Mitchell et al., 2000; Taepavarapruk et al., 2000; Legault and Wise, 2001), we conducted two further experiments to examine the effects of pretreatment with the typical neuroleptic haloperidol and the atypical neuroleptic clozapine on PPI disruption induced by muscimol infusion into the dorsal or ventral hippocampus. We chose muscimol infusions since the first two experiments yielded that the decrease in PPI was stronger after hippocampal muscimol infusions than after TTX infusions. Moreover, this decrease was not accompanied by significant alterations in startle reactivity and clearly reflected a genuine impairment of sensorimotor gating (see Results). The experimental groups received the following treatments on Day 2: systemic injection of saline followed by infusion of vehicle (Sal-VEH) or systemic injection of saline, 0.2 mg/kg haloperdiol, or 5 mg/kg clozapine followed by infusion of muscimol (Sal-MUS, Hal-MUS, Clo5-MUS). In the experiment testing neuroleptics' effects on PPI disruption by dorsal hippocampal muscimol infusion, we also included a group receiving 10 mg/kg clozapine before infusion of muscimol (Clo10-MUS). Thus, the experiment to test the effects of neuroleptic pretreatment on PPI disruption induced by dorsal hippocampal muscimol infusion included five groups (Sal-VEH, $n=9$; Sal-MUS, $n=10$; Hal-MUS, $n=9$; Clo5-MUS and Clo10-MUS, $n=10$), and the experiment to test neuroleptics' effects on PPI disruption by ventral hippocampal muscimol infusion included four groups (Sal-VEH, Sal-MUS, Hal-MUS, and Clo5-MUS, $n=7$). In the experiments involving neuroleptic pretreatment and muscimol infusion, the rats that had been used in the first two PPI experiments 1 week before, as well as six additional rats with cannulae aiming at the dorsal hippocampus, were used. The six additional rats had previously been subjected to the same fear conditioning and open field experiments as the other 42 rats with cannulae aiming at the dorsal hippocampus but had then, 1 week before the present experiment, been used in a pilot experiment involving dorsal hippocampal TTX infusion (10 ng/side) and PPI testing immediately (instead of 20 min as in the present study) thereafter.

2.6.4. Histology

After completion of the behavioral experiments, rats were deeply anesthetized with an overdose of 2.5 ml/kg nembutal (sodium pentobarbital, 50 mg/ml, ip) and transcardially perfused with 0.9% NaCl solution, followed by 120 ml of 4% formalin (4 °C) to fix the brain tissue. Brains were extracted from the skull, postfixed in 4% formalin solution, and subsequently cut into 40-μm coronal sections on a freezing microtome. To verify the injection sites, every fifth section through the ventral or dorsal hippocampus was mounted on gelatin-treated slides and stained with cresyl violet. After staining, the sections were dehydrated through an alcohol series, cleared with xylene, and coverslipped with Eukitt (Kindler, Freiburg, Germany). Subsequently, the sections were examined with a light microscope to verify the appropriate location of the tips of the infusion cannulae and draw it onto plates taken from the atlas of Paxinos and Watson (1998).

2.6.5. Data analysis

Statistical analyses were performed with the StatView and SuperANOVA software system (Abacus Concepts, Berkeley, CA, 1992). Data were first subjected to ANOVA. Groups were used as between-subjects factor. For the %PPI data, the four different prepulse intensities were used as repeated-measures factor. For the startle data, repeated-measures factors were the 16 repeated pulse-alone trials as well as the pulse-alone and prepulse followed by pulse trials throughout the six blocks to measure PPI. Post hoc comparisons were conducted using Fisher's protected least significant difference test. Significant differences were accepted at $P<.05$. All values are presented as means. In the text and in bar plots, variance is indicated by the standard error of the mean (S.E.M.). In line plots, for the sake of clarity, variance is indicated by the standard error (S.E.) derived from the appropriate mean square of the ANOVA. Since the data of the rats infused with vehicle did not differ significantly whether the infusions were given immediately or 20 min prior to PPI testing, they were collapsed for the analysis presented in the Results section. Finally, data were subjected to statistical analyses using the different experimental his-

tories of the animals as between-subjects factor. This analysis yielded that the experimental history of the animals was not a significant factor in the present study.

3. Results

3.1. Histology

In all 76 cannulated rats, the centers of the infusion sites, i.e. the tips of the infusion cannulae, were located in the targeted areas within or around the border of the ventral or dorsal hippocampus, respectively (Fig. 1). Visible tissue damage was restricted to the area immediately surrounding the guide and infusion cannulae.

3.2. Effects of TTX and muscimol infusion into the dorsal or ventral hippocampus on the startle response and its PPI

3.2.1. Startle

Startle amplitudes throughout the 16 pulse-alone trials were differently affected by the muscimol and TTX infusions into the dorsal and ventral hippocampus (Fig. 2A). Infused into the dorsal hippocampus, TTX but not muscimol tended to increase the startle response in the 16 pulse-alone trials, even though neither drug induced significant alterations as compared to the VEH group (Fig. 2A, left). Separate ANOVA of the startle data of each day yielded a significant main effect of pulse-alone trials for each of the 3 days [$F(15,585)=6.47$, $F(15,585)=3.32$, and $F(15,585)=3.70$, all $P<.0001$], reflecting short-term habituation of the startle response (Koch, 1999). In addition, there was a significant main effect of groups on the day of infusion [Day 2; $F(2,39)=6.25$, $P<.005$] but not on the day preceding [Day 1; $F(2,39)=0.87$, $P>.9$] or following [Day 3; $F(2,39)=0.78$, $P>.45$] infusion. Post hoc comparisons indicated that on the day of infusion, the mean startle response over the 16 pulse-alone trials was increased in the TTX group (1413 ± 61) as compared to the MUS (1065 ± 77, $P<.002$). Compared to the VEH group (1232 ± 63), the startle amplitude tended to be increased in the TTX ($P=.06$) and decreased in the MUS ($P<.09$) group. Infused into the ventral hippocampus, TTX decreased the startle response in the 16 pulse-alone trials while muscimol had no significant effect (Fig. 2A, right).

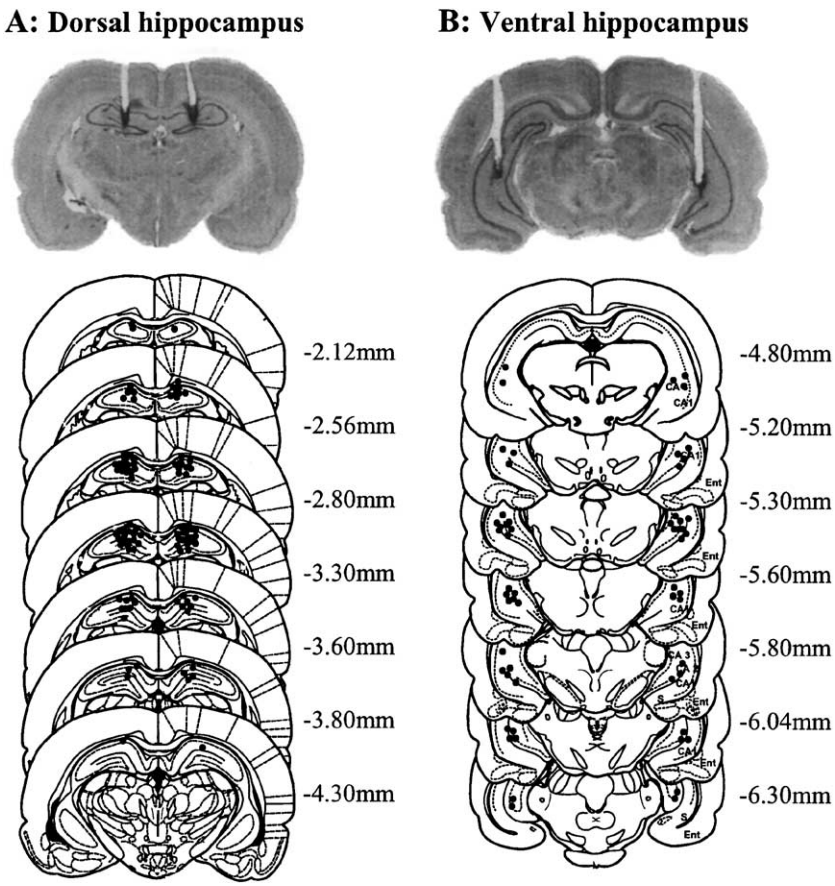

Fig. 1. Infusion sites in the dorsal ($n=48$, left) and ventral ($n=28$, right) hippocampus: photomicrograph of a coronal brain section with the tracks of the guide cannulae and beneath them the infusion sites visible in both hemispheres (top) and approximate location of the tips of the infusion cannulae depicted on plates of coronal sections through the rat brain (Paxinos and Watson, 1998) (bottom). Values represent distance from bregma. CA1, CA2, and CA3: CA1, CA2, and CA3 field of the hippocampus; DG: dentate gyrus; Ent: entorhinal cortex; S: subiculum.

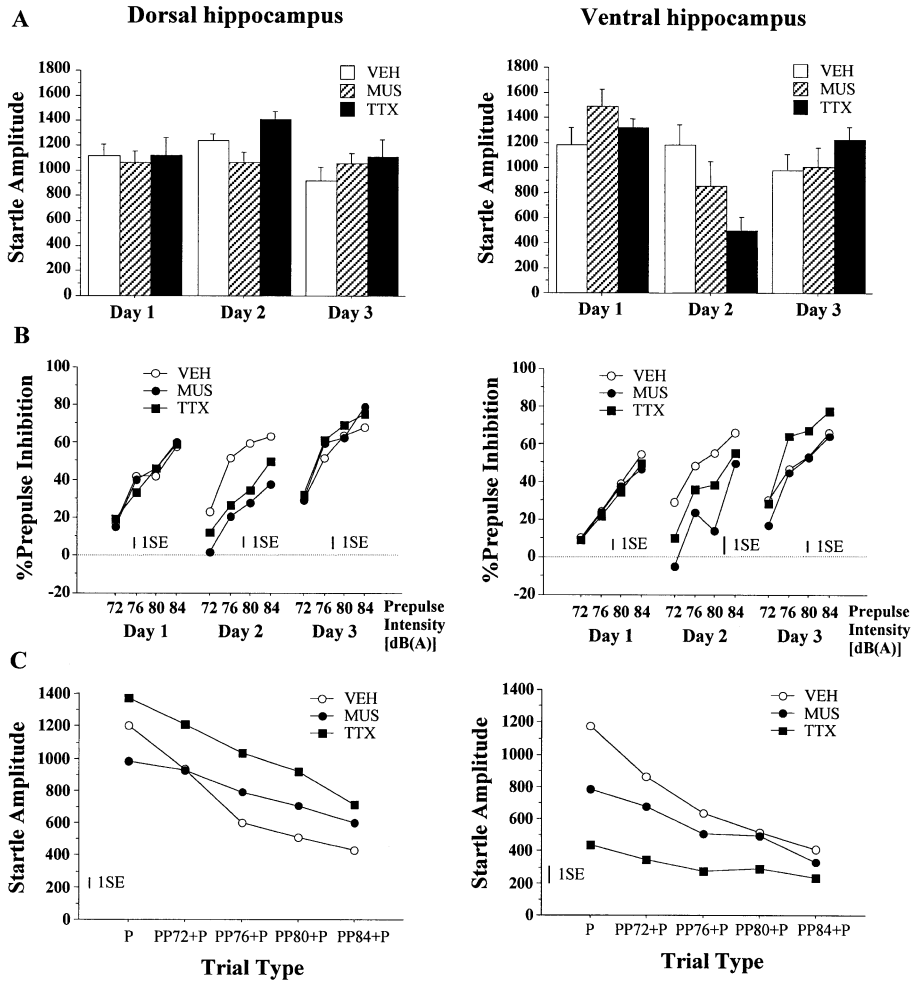

Fig. 2. Effects of tetrodotoxin or muscimol infusion into the dorsal (left) and ventral (right) hippocampus on startle magnitude during the 16 pulse-alone trials (A), %PPI induced by the four prepulse intensities (B), and startle amplitude throughout the pulse alone (P) and prepulse followed by pulse (PP + P) trials (C). Rats were bilaterally infused with vehicle (VEH), muscimol (MUS), or tetrodotoxin (TTX) immediately before test sessions on Day 2. All groups were tested for PPI without infusion 1 day before (Day 1) and 1 day after (Day 3) the infusion day. Values are presented as mean ± S.E.M. Bars represent 1 S.E. derived from ANOVA. Group sizes: see Experimental procedures, Experimental design and groups.

Separate ANOVA of the startle data of each day yielded a significant main effect of pulse-alone trials for the day of infusion [Day 2; $F(15,375) = 3.28$, $P < .0001$] and the following day [Day 3; $F(15,375) = 3.38$, $P < .0001$]. For the day preceding infusion (Day 1), the effect of pulse-alone trials did not reach statistical significance [$F(15,375) = 1.31$, $P > .19$], possibly due to a comparatively high variance in startle responses since the rats were not familiar with the testing procedure. In addition, a significant main effect of groups was revealed for the day of infusion [Day 2; $F(2,25) = 4.54$, $P < .03$] but not for the day preceding [Day 1; $F(2,25) = 1.46$, $P > .25$] or following [Day 3; $F(2,25) = 1.06$, $P > .35$] infusion. This reflected that on the day of infusion, the mean startle amplitude over the 16 pulse-alone trials was decreased in the TTX (504 ± 109; $P < .006$) as compared to the VEH (1186 ± 158) group. Startle amplitude in the MUS group (851 ± 199) fell between that of the TTX ($P > .15$) and the VEH ($P > .17$) group.

3.2.2. Prepulse inhibition

Both TTX and muscimol infusion into the dorsal (Fig. 2B, left) as well as ventral (Fig. 2B, right) hippocampus decreased the %PPI. One day after infusion, PPI was completely restored. Separate ANOVA of the PPI data of each day yielded a significant main effect of prepulse intensities on the %PPI for each of the 3 days [dorsal infusions: $F(3,117) = 59.9$, $F(3,117) = 57.7$, and $F(3,117) = 68.9$; all $P < .0001$; ventral infusions: $F(3,75) = 48.21$, $F(3,75) = 24.81$, and $F(3,75) = 54.31$, all $P < .0001$], reflecting a gradual increase in PPI as a function of the intensity of the prepulse (Koch, 1999). In addition, a significant main effect of groups was found for the day of infusion [Day 2; dorsal infusions: $F(2,39) = 10.97$, $P < .0002$; ventral infusions: $F(2,25) = 4.30$, $P < .03$], but not for the day preceding [Day 1; dorsal infusions: $F(2,39) = 0.008$, $P > .99$; ventral infusions: $F(2,25) = 0.044$, $P > .95$] and following [Day 3; dorsal infusions: $F(2,39) = 0.87$, $P > .4$; ventral infusions: $F(2,25) = 1.28$, $P > .29$]

infusion. On the day of infusion, the %PPI averaged over all prepulse intensities was significantly decreased in the MUS (dorsal infusions: 22.0 ± 3.6, $P < .0001$; ventral infusions: 20.6 ± 11.8; $P < .008$) groups as compared to the VEH groups (dorsal infusions: 49.1 ± 4.4; ventral infusions: 49.7 ± 4.3). The decrease of PPI in the TTX group only reached statistical significance for the dorsal infusions (dorsal infusions: 30.7 ± 4.6, $P < .005$; ventral infusions: 34.9 ± 5.4, $P = .15$) although, for ventral ($P > .2$) as well as for dorsal ($P > .17$) hippocampal infusions, TTX and MUS groups did not differ significantly.

Reduced %PPI accompanied by alterations in startle amplitude may not completely reflect a genuine deficit in sensorimotor gating, but may be partly due to altered startle reactivity (Swerdlow et al., 2000a). Although only the ventral hippocampal TTX infusions induced a statistically significant alteration in startle amplitude throughout the 16 pulse-alone trials, we addressed the issue of whether alterations in startle amplitude may have contributed to the reduced %PPI. For that purpose, similar to a previous study (Bast et al., 2001b), we scrutinized the average startle amplitudes in the pulse alone and the prepulse followed by pulse trials of the six test blocks to measure PPI on the day of infusion (Fig. 2C). With respect to TTX and muscimol infusion into the dorsal hippocampus (Fig. 2C, left), this analysis indicated a genuine impairment of sensorimotor gating. ANOVA yielded a significant effect of group [$F(2,39) = 4.9$, $P < .02$], reflecting the increased startle reactivity in the TTX group. Moreover, ANOVA indicated a significant effect of trial type [$F(4,156) = 95.7$, $P < .0001$], and a highly significant Group × Trial type interaction [$F(8,156) = 5.0$, $P < .0001$]. This reflected that the prepulse-induced inhibition of the startle response to the pulse and the gradual increase in inhibition with increasing prepulse intensity was stronger in the VEH than in the MUS and TTX group. Thus, the startle amplitude in the MUS group was slightly lower than that of the VEH group during the pulse-alone trials, whereas this relation was reversed throughout the trials with the three higher prepulses. Furthermore, the increase in startle magnitude in the TTX group as compared to the VEH group was much more pronounced in the prepulse followed by pulse trials than in the pulse-alone trials. With respect to the infusions of muscimol and TTX into the ventral hippocampus, analysis of the startle amplitudes in the pulse alone and the prepulse followed by pulse trials of the six test blocks to measure PPI on the day of infusion yielded a slightly different picture (Fig. 2C, right). ANOVA indicated a nearly significant effect of group [$F(2,25) = 3.1$, $P < .066$], mainly reflecting the decreased startle reactivity in the TTX group, a significant effect of trial type [$F(4,100) = 23.09$, $P < .0001$], and a significant Group × Trial type interaction [$F(8,100) = 3.41$, $P < .002$]. However, in contrast to the situation for the dorsal infusions, in no trial type were startle amplitudes higher in the TTX and MUS groups than in the VEH group. Therefore, in particular for the TTX group, the decreased potency of the prepulses to inhibit the startle amplitude may have been related to a floor effect, i.e. the lower basal startle response of the TTX (440 ± 119) group in the pulse-alone trials was more resistant to reduction than the higher startle response of the VEH group (1180 ± 165). However, in a recent study (Bast et al., 2001b), we observed intact PPI in spite of markedly reduced startle amplitudes in pulse-alone trials (520 ± 130) in our Wistar rats following ventral hippocampal infusion of 100 ng picrotoxin/side. In these rats, the highest prepulse intensity lowered the startle amplitude to the pulse to 170 ± 33. Altogether, it can be stated that muscimol infusions into the dorsal or ventral hippocampus unequivocally induced a genuine impairment in sensorimotor gating. Although less clear, this appears to apply also to the TTX infusions. In the following experiments to test the effects of neuroleptics on PPI impairments that result from decreased hippocampal activity, we used hippocampal muscimol infusions so that decreased %PPI can unequivocally be attributed to impaired sensorimotor gating.

3.3. Effects of neuroleptic pretreatment on PPI disruption induced by muscimol infusion into the ventral or dorsal hippocampus

3.3.1. Startle

Consistent with the results from the first two experiments, the startle response in the 16 pulse-alone trials was not significantly affected by any treatment combination in the two experiments involving neuroleptic pretreatment and dorsal (Fig. 3A, left) or ventral (Fig. 3A, right) hippocampal muscimol infusions. Separate ANOVA of the startle data of each day yielded only a significant main effect of pulse-alone trials for each of the 3 days [dorsal infusions: $F(15,645) = 5.94$, $F(15,645) = 13.58$, and $F(15,645) = 5.90$, all $P < .0001$; ventral infusions: $F(15,360) = 3.92$, $F(15, 360) = 11.76$, and $F(15,360) = 5.86$, all $P < .0001$], but no main effect of groups [dorsal infusions: $F(4,43) = 0.73$, $P > .5$; $F(4,43) = 1.67$, $P > .17$; $F(4,43) = 1.39$, $P > .25$; ventral infusions: $F(3,24) = 0.22$, $P > .8$; $F(3,24) = 0.62$, $P > .6$; $F(3,24) = 1.11$, $P > .36$].

3.3.2. Prepulse inhibition

PPI disruption induced by dorsal (Fig. 3B, left) or ventral (Fig. 3B, right) hippocampal muscimol inhibition was not antagonized by a preceding injection of haloperidol or clozapine. Separate ANOVA of the PPI data of each day yielded a significant main effect of prepulse intensities on the %PPI for each of the 3 days [dorsal infusions: $F(3,129) = 137.6$, $F(3,129) = 36.7$, and $F(3,129) = 103.6$; all $P < .0001$; ventral infusions: $F(3,72) = 70.5$, $F(3,72) = 16.0$, and $F(3,72) = 37.9$; all $P < .0001$]. Although inspection of the data (Fig. 3B) indicated that muscimol infusions into the dorsal or ventral hippocampus on Day 2 decreased %PPI, the effect of groups on the %PPI over all four prepulse intensities did not reach statistical significance for any of the 3 days [dorsal infusions: Day 1, $F(4,43) = 0.033$, $P > .99$; Day 2,

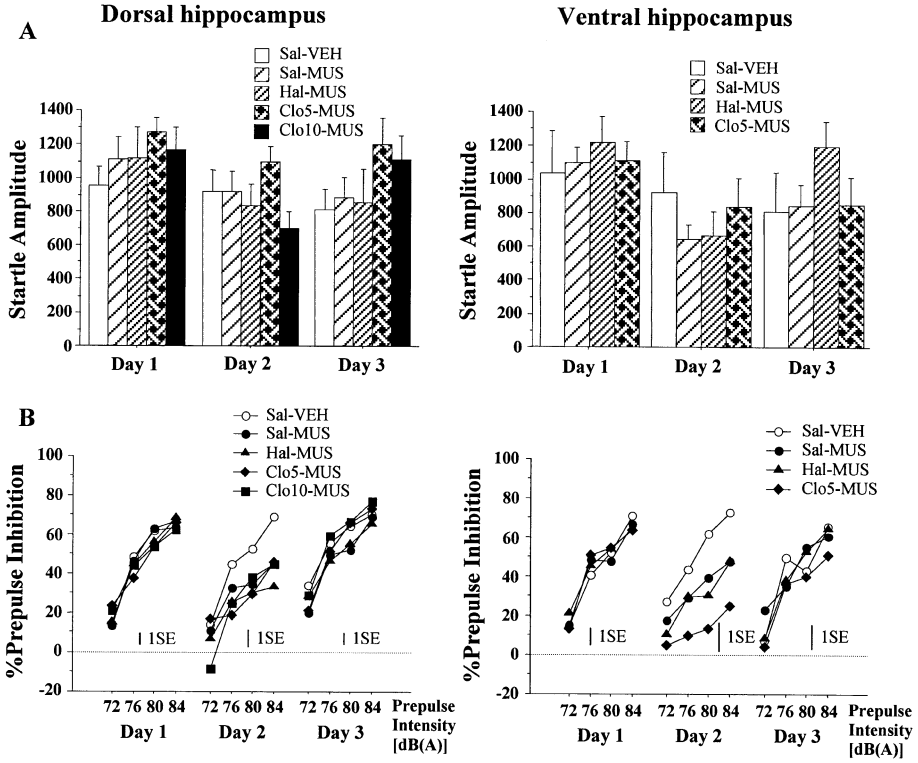

Fig. 3. Effects of haloperidol and clozapine pretreatment on disruption of PPI by muscimol infusion into the dorsal (left) and ventral (right) hippocampus: startle magnitude during the 16 pulse-alone trials (A), %PPI induced by the four prepulse intensities (B). Rats received pretreatment with saline (Sal), 0.2 mg/kg haloperidol (Hal), 5 or 10 mg/kg clozapine (Clo5, Clo10), 45 min, and bilateral infusion of vehicle (VEH) or muscimol (MUS), immediately, before testing on Day 2. All groups were tested for PPI without injection and infusion 1 day before (Day 1) and 1 day after (Day 3) the infusion day. Values are presented as mean ± S.E.M. Bars represent 1 S.E. derived from ANOVA. Group sizes: see Experimental procedures, Experimental design and groups.

$F(4,43) = 1.63$, $P = .18$; Day 3, $F(4,43) = 0.61$, $P = .66$; ventral infusions: Day 1, $F(3,24) = 0.011$, $P > .99$; Day 2, $F(3,24) = 2.49$, $P = .08$; Day 3, $F(3,24) = 0.43$, $P > .73$]. However, excluding the data for the trials with the lowest prepulse intensity, the effect of groups on the %PPI very closely approached statistical significance for the day of infusion [Day 2; dorsal infusions: $F(4,43) = 2.53$, $P = .054$; ventral infusions: $F(3,24) = 2.79$, $P = .062$], but not for the day preceding [Day 1; dorsal infusions: $F(4,43) = 0.32$, $P > .86$; ventral infusions: $F(3,24) = 0.011$, $P > .99$] and following [Day 3; dorsal infusions: $F(4,43) = 0.84$, $P > .5$; ventral infusions: $F(3,24) = 0.35$, $P > .79$] infusion. For the experiment involving dorsal hippocampal infusions, post hoc comparisons revealed that on the day of infusion, the %PPI averaged over the three higher prepulse intensities was significantly decreased in the Sal-MUS (37.3 ± 4.7, $P < .05$), Hal-MUS (29.8 ± 6.3, $P < .008$), Clo5-MUS (31.4 ± 6.2, $P = .01$), and Clo10-MUS (35.9 ± 8.6, $P < .05$) groups as compared to the Sal-VEH group (55.4 ± 3.9). For the experiment involving ventral hippocampal infusions, the %PPI averaged over the three higher prepulse intensities appeared to be decreased in the Sal-MUS (38.7 ± 6.0, $P = .18$), Hal-MUS (36.1 ± 12.2, $P = .14$), and Clo5-MUS (15.8 ± 13.6, $P < .008$) groups as compared to the Sal-VEH group (59.5 ± 9.6), even though this decrease was only significant in the case of the Clo5-MUS group. Finally, in view of the results of the first two experiments, one-tailed t tests based on the S.E. derived from the ANOVA were conducted to confirm that PPI was decreased in the groups that received ventral hippocampal muscimol infusions (since our statistics software does not conduct these comparisons, they were calculated according to Winer, 1971, p. 199). The t tests indicated that %PPI in the groups that received muscimol infusions was significantly (all $P < .05$) decreased as compared to the VEH group at each of the three highest (Sal-MUS, Hal-MUS) or even at all four prepulses (Clo-MUS). In the experiments involving hippocampal muscimol infusion and neuroleptic pretreatment, statistical power to reveal differences between groups was decreased as compared to the first two experiments without the neuroleptic pretreatment (four to five groups with $n = 7–10$ as compared to three groups with $n = 8–16$). Considering this, the results of the experiments involving neuroleptic pretreatment and muscimol infusions confirmed that dorsal and ventral hippocampal inhibition by muscimol decreases PPI, even though some of the relevant effects only approached significance. Moreover, they clearly indicated that pretreatment with haloperidol or clozapine does not antagonize this decrease of PPI. If anything, clozapine pretreatment slightly intensified the decrease in PPI following ventral hippocampal MUS infusion.

4. Discussion

In the present study, temporary inactivation by TTX (10 ng/side) or inhibition by muscimol (1 μg/side) of the dorsal or ventral hippocampus impaired PPI. Muscimol inhibits local neuronal activity by acting on the $GABA_A$ receptor while TTX is also inactivating signal conduction by fibers of passage. Given that both compounds similarly decreased PPI, one can conclude that neuronal activity within the dorsal as well as ventral hippocampus is necessary for normal PPI. Effects on startle amplitude were less clear-cut. TTX significantly increased startle reactivity when infused into the dorsal hippocampus, but tended to decrease it when infused into the ventral hippocampus. Muscimol had no significant effects on startle reactivity, but tended to decrease it when infused into the ventral hippocampus. Effects on startle reactivity have been observed after different manipulations of the ventral or dorsal hippocampus (e.g. Caine et al., 1991, 1992; Wan et al., 1996; Bakshi and Geyer, 1998, 1999; Zhang et al., 1999, 2000b, 2002; Bast et al., 2001b; Swerdlow et al., 2000b) and may be mediated by hippocampal projections to the amygdala or the bed nucleus of the stria terminalis, which have access to the brain stem startle circuit (Koch, 1999). Similar to the hippocampal manipulations in the present study, ventral hippocampal NMDA infusions, for example, affected startle reactivity less markedly and less reliably than PPI (Wan et al., 1996; Zhang et al., 1999, 2002; Bast et al., 2001d). Importantly, in the present study, in-depth analysis of the startle data yielded that the alterations in startle reactivity are unlikely to account for the observed reductions of PPI. This indicates that the PPI impairment following TTX inactivation and muscimol inhibition of the dorsal or ventral hippocampus reflects a genuine impairment of sensorimotor gating. Moreover, this PPI impairment is probably neuroleptic-resistant and, thus, not caused by excess dopamine transmission (as a result of the hippocampal manipulation) since both clozapine (5 and 10 mg/kg or 5 mg/kg, respectively) and haloperidol (0.2 mg/kg) did not antagonize the PPI impairment induced by dorsal or ventral hippocampal inhibition by muscimol.

4.1. Permanent lesions versus temporary deactivation

Previous studies using permanent lesions (Kemble and Ison, 1971; Pouzet et al., 1999; Swerdlow et al., 1995, 2000b), in contrast to the present study, did not indicate that activity of the ventral, as well as dorsal, hippocampus is important for the maintenance of PPI, even though a very recent study reported slight impairments of PPI after ventral, but not dorsal, subiculum lesions (Caine et al., 2001). Based on previous studies and our infusion parameters, considerable effects of TTX and muscimol during testing in the present study should have been restricted to a spherical region of less than 1 mm radius surrounding the injection sites within the dorsal or ventral hippocampus (Martin, 1991; Zhuravin and Bures, 1991). Thus, our results are unlikely to reflect drug diffusion to extrahippocampal sites. Permanent lesions of the hippocampus or its subparts may result in changes in other brain areas during the period between surgery and testing (Stein, 1979; Halim and Swerdlow, 2000). Thus, the effects of permanent hippocampal lesions may actually reflect massive neuronal reorganization throughout the brain rather than only the loss of hippocampal function. In particular, compensatory changes are likely to occur and possible recovery of function is considered a problem for the interpretation of studies using permanent lesions (Bures and Buresova, 1990; Lomber, 1999). Given that lesion-induced changes and compensatory mechanisms are likely to need some time after surgery to occur (e.g. Halim and Swerdlow, 2000), PPI may be found to be decreased when measured during the first few days following hippocampal lesions. In any case, the present results, as well as our recent study (Bast et al., 2001c), where we observed locomotor effects of ventral hippocampal inhibition or inactivation that markedly differed from those reported after lesions, indicate that the application of temporary deactivation techniques may lead to concepts of a brain structure's normal function that substantially differ from those based on studies using permanent lesions. Thus, some issues that have previously only been examined by means of permanent lesions may deserve re-examination by means of acute manipulations (see also Bast et al., 2001a).

4.2. Hippocampal modulation of PPI

While hippocampal lesions (Kemble and Ison, 1971; Pouzet et al., 1999; Swerdlow et al., 1995, 2000b; but see Caine et al., 2001) and ventral hippocampal infusions of the psychotomimetic MK-801 (Bakshi and Geyer, 1998; Bast et al., 2000) did not result in decreased basal PPI, chemical stimulation of the ventral hippocampus has consistently been found to disrupt PPI (e.g., Caine et al., 1992; Wan et al., 1996; Klarner et al., 1998; Zhang et al., 1999; Bast et al., 2001b,d). As to the dorsal hippocampus, the picture is less clear. Stimulation of the ventral and dorsal hippocampus by the acetylcholine agonist carbachol was reported to yield similar reductions of PPI (Caine et al., 1991, 1992). In contrast, dorsal hippocampal NMDA infusion virtually did not affect PPI (Swerdlow et al., 2001b; Zhang et al., 2002). Slight PPI disruption was reported following dorsal hippocampal MK-801 infusion in Sprague–Dawley rats (Bakshi and Geyer, 1998, 1999), but was not confirmed in Wistar rats (Zhang et al., 2000b).

Altered hippocampal activity may decrease PPI by changing neuronal activity in the amygdala, the prefrontal cortex, or the nucleus accumbens. These forebrain areas receive strong hippocampal projections (Amaral and Witter, 1995) and have—directly (Sesack et al., 1989) or via the ventral pallidum—access to the brainstem circuits thought to mediate PPI. Experimental manipulations of these fore-

brain regions have been reported to disrupt PPI (Koch, 1999; Swerdlow et al., 2001a). The different neurophysiological and neurochemical changes in these target areas that result from different alterations of dorsal and ventral hippocampal activity largely remain to be examined, but it is likely that different manipulations of the ventral and dorsal hippocampus induce PPI reduction by different pathways and different mechanisms. Thus, according to the topography of hippocampal projections, ventral hippocampal manipulations may directly alter neural transmission mainly in the accumbens shell, the prefrontal cortex, and the amygdala, whereas alterations of dorsal hippocampal activity may directly affect mainly processes in the accumbens core (Swanson and Cowan, 1977; Kelley and Domesick, 1982; Groenewegen et al., 1987; Amaral and Witter, 1995; Verwer et al., 1997; Pitkänen et al., 2000). Moreover, at least some of the hippocampal manipulations decreasing PPI differ in their effects on other behavioral processes, indicating different neurochemical and neurophysiological changes in hippocampal target areas. For example, ventral hippocampal stimulation induces marked hyperactivity (e.g. Brudzynski and Gibson, 1997; Bast et al., 2001b,d) while decreasing ventral hippocampal activity by TTX and muscimol resulted in hypoactivity (Bast et al., 2001c). Increased dopamine transmission, one prominent mechanism of PPI disruption (Koch, 1999; Zhang et al., 2000a; Swerdlow et al., 2001a), can virtually be ruled out to account for the reductions in PPI following acute hippocampal manipulations since dopamine receptor antagonists did not antagonize these reductions (Caine et al., 1991; Wan et al., 1996; Zhang et al., 1999; Bast et al., 2001d; present study). Among the reductions in PPI induced by manipulations in hippocampal projection areas, only that following lesions of the amygdala has also been demonstrated to be resistant against systemic dopamine receptor antagonists (Wan and Swerdlow, 1997). Given that increased dopamine transmission is thought to disrupt PPI largely by alterations of shell or core activity (Koch, 1999; Swerdlow et al., 2001a), manipulations directly inducing such alterations may also disrupt PPI independent of increased dopamine transmission. Dorsal hippocampal manipulations may directly modulate core activity, whereas alterations of ventral hippocampal activity may modulate shell activity, and, via feedforward processing (Zham, 2000), also activity in the core (see also Bast et al., 2001d). Interestingly, decreased dopamine transmission in the prefrontal cortex has been suggested to impair PPI (Ellenbroek et al., 1996; Zavitsanou et al., 1999) and, since electrical stimulation of the ventral hippocampus has been indicated to increase extracellular dopamine in the prefrontal cortex (Gurden et al., 2000), ventral hippocampal deactivation may decrease prefrontal dopamine transmission. However, findings from our laboratory do not support the view that PPI is impaired by decreased prefrontal dopamine transmission (Lacroix et al., 2000; Pezze et al., 2001). Thus, at present, we know several specific alterations of hippocampal activity disrupting PPI, but the underlying mechanisms and pathways remain to be clarified.

4.3. Relevance with respect to schizophrenia

Pathological changes of the hippocampus have received a lot of attention with respect to the etiology of schizophrenia. Although more recent functional imaging studies have quite consistently indicated that hippocampal activity is increased in schizophrenia and that hippocampal overactivity is associated with the experience of positive symptoms (reviewed by Heckers, 2001), there is also evidence that the hippocampus in schizophrenic patients may be hypofunctional in some respects (Harrison, 1999; Harrison and Eastwood, 2001; Weinberger, 1999; Gothelf et al., 2000). In this context, it has to be considered that different etiologies might underlie the clinical syndrome recognized as schizophrenia (Lewis and Lieberman, 2000). The present and previous results from animal experiments (see above) indicate that hippocampal pathology of different kinds may contribute to PPI deficits observed in schizophrenia. Regardless of whether deficient sensorimotor gating, as reflected by decreased PPI, may contribute to positive symptoms or just reflect pathologically altered brain function in schizophrenia, the underlying mechanisms are of interest concerning a treatment of schizophrenia. Since PPI deficits induced by alterations of hippocampal activity in the rat appear to be resistant against treatment with conventional neuroleptics, their understanding might help to guide the development of new strategies to cure treatment-resistant schizophrenia (see also Bast et al., 2001d).

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