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Hyperactivity, decreased startle reactivity, and disrupted prepulse inhibition following disinhibition of the rat ventral hippocampus by the GABA_A receptor antagonist picrotoxin

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Abstract *Rationale:* Functional imaging studies have revealed overactivity of the hippocampus in schizophrenic patients. Neuropathological data indicate that hyperactivity of excitatory hippocampal afferents and decreased hippocampal GABA transmission contribute to this overactivity. In rats, excitation of the ventral hippocampus, e.g. by NMDA, results in hyperactivity and disruption of sensorimotor gating measured as prepulse inhibition (PPI) of the acoustic startle response, behavioral effects related to psychotic symptoms in humans. *Objective:* The present study examined whether disinhibition of the ventral hippocampus by the GABA_A antagonist picrotoxin would result in similar psychosis-related behavioral disturbances (hyperactivity, decreased PPI) as NMDA stimulation. *Methods and results:* Wistar rats received bilateral infusions of subconvulsive doses of picrotoxin (100 or 150 ng/0.5 µl per side) into the ventral hippocampus and were then immediately tested for open field locomotor activity or startle reactivity and PPI. Only the higher dose induced hyperactivity and decreased PPI. Both doses decreased acoustic startle reactivity to a similar extent. The decreased PPI appeared not to result from decreased startle reactivity, but was associated with a diminished potency of the prepulses to inhibit the startle reaction to the startle pulse, indicating a sensorimotor gating deficit. All effects were temporary, i.e. disappeared when the rats were tested 24 h after infusion. *Conclusions:* Decreased GABAergic inhibition in the ventral hippocampus of rats yielded psychosis-related behavioral effects, very similar to those induced by NMDA stimulation. Thus, a concurrence of decreased GABAergic inhibition and increased afferent excitation in the hippocampus of schizophrenic patients might contribute to psychotic symptoms.

Keywords GABA · Locomotor activity · Prepulse inhibition · Schizophrenia · Sensorimotor gating · Ventral hippocampus

Introduction

Animal studies concerned with hippocampal functioning receive particular interest, as aberrant hippocampal functioning in humans has been implicated in neuropsychiatric disorders such as anxiety and schizophrenia (Gray et al. 1991; Gray 1995; Benes 2000; Grace 2000). Functional imaging studies indicate that hippocampal activity is increased in schizophrenic patients and hippocampal overactivity has been associated with the experience of positive symptoms (Friston et al. 1992; Liddle et al. 1992; Silbersweig et al. 1995; Kawasaki et al. 1996; Heckers et al. 1998; Dierks et al. 1999; Frith 1999; Shergill et al. 2000).

In rats, overactivity of the ventral hippocampus, induced, for example, by infusion of NMDA to stimulate the NMDA-type receptor of the excitatory transmitter glutamate, generates behavioral effects which might be related to some positive symptoms occurring in schizophrenia. Locomotor activity in the open field is increased following NMDA stimulation of the ventral hippocampus (Yang and Mogenson 1987; Wu and Brudzynski 1995; Brudzynski and Gibson 1997; Bardgett and Henry 1999; Legault and Wise 1999; Bast et al. 2001b). Aberrant locomotor activity in the rat might be homologous to some changes in human cognitive function observed in acute schizophrenia (Gray et al. 1999). Furthermore, prepulse inhibition (PPI) of the acoustic startle response is disrupted following NMDA stimulation of the ventral hippocampus (Wan et al. 1996; Klarner et al. 1998; Koch et al. 1999; Zhang et al. 1999; Bast et al. 2001b). PPI is the reduction of the startle response to an intense acoustic pulse by an immediately preceding weaker stimulus, or prepulse. It may reflect sensorimotor gating mechanisms induced by the prepulse and preventing its processing from being inter-

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rupted (Graham 1975; Norris and Blumenthal 1996). Deficient sensorimotor gating, as reflected by disruption of PPI, has been found in several neuropsychiatric disorders, especially in schizophrenia (Braff et al. 1978; Grillon et al. 1992; Perry and Braff 1994; Karper et al. 1996; Braff et al. 1999; Perry et al. 1999; Kumari et al. 2000; Parwani et al. 2000; Weike et al. 2000). Although there is little doubt about the existence of a PPI deficit in schizophrenia, its contribution to schizophrenic symptoms is not yet clear. However, deficient PPI has been postulated to contribute to sensory overload and cognitive fragmentation, which in turn result in psychotic symptoms, and correlations between decreased PPI and the severity of psychotic symptoms, in particular positive symptoms, have been reported by some studies (Perry and Braff 1994; Karper et al. 1996; Braff et al. 1999; Perry et al. 1999; Weike et al. 2000). Disrupted PPI in rats is used to model sensorimotor gating deficits observed in schizophrenia (Swerdlow et al. 1994, 2000a).

Overactivity of a brain structure can come about by increased excitatory neurotransmission and by disinhibition, i.e. a decrease of inhibitory transmission. In the hippocampus, inhibition is mainly mediated by actions of GABA, which is released by hippocampal interneurons, at the GABA_A receptor, a ligand-operated Cl⁻-channel (Buhl et al. 1994). Neuropathological studies indicate that increased excitatory transmission via hippocampal afferents in concert with a local decrease of GABAergic inhibition (possibly due to a loss of hippocampal GABA interneurons) might yield the hippocampal overactivity revealed by functional imaging studies in schizophrenic patients (for review see: Benes 2000). Moreover, dysfunctions of GABA transmission have been implicated in the processes leading to psychosis (Keverne 1999; Lacroix et al. 2000) and psychotic symptoms in schizophrenia have been found to be correlated with reduced GABAergic inhibition in the medial temporal region (Busatto et al. 1997). Thus, decreased inhibitory GABA transmission in the hippocampus of schizophrenic patients might contribute to psychotic symptoms in schizophrenia.

In the present study, we tested in Wistar rats if the disinhibition of the ventral hippocampus by local microinfusion of the GABA_A receptor antagonist picrotoxin would yield effects on PPI and locomotor activity in the open field that are similar to those resulting from stimulation of the ventral hippocampus by NMDA (Zhang et al. 1999; Bast et al. 2001b). In a recent study, bilateral infusion of 5 or 10 ng picrotoxin/side into the ventral hippocampus of Sprague-Dawley rats did not significantly affect startle amplitude or PPI (Japha and Koch 1999). The authors reported difficulties in testing higher doses because of convulsions occurring at higher doses. In our own pilot studies, doses up to 50 ng picrotoxin/side did not reveal any considerable behavioral effect or convulsive properties. Therefore, we used doses of 100 or 150 ng picrotoxin/side in the present study.

Materials and methods

Animals

A total of 50 male adult Wistar rats (Zur:Wist[HanIbm]; Research Unit Schwerzenbach, Schwerzenbach, Switzerland), weighing about 250 g at the time of surgery, were used in this study. The animals were housed in groups of four per cage under a reversed light-dark cycle (lights on: 1900–0700 hours) in a temperature (21±1°C) and humidity (55±5%) controlled room and were allowed free access to food and water. All rats received bilateral implantation of infusion guide cannulae aiming at the ventral hippocampus. After surgery, they were individually caged. Beginning 3 days before surgery and 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 experimentation.

Implantation of guide cannulae for intracerebral infusion

Rats were anaesthetized with 1 ml of Nembutal (sodium pentobarbital, 50 mg/ml; Abbott Labs, North Chicago, Ill., USA) per kg body weight and their head was placed in a Kopf stereotaxic frame. After application of a local anaesthetic (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 diameter) was drilled on each side of the skull to reveal the dura covering the cortex overlying the ventral hippocampus. Three small stainless steel screws were screwed into the skull and two guide cannulae (9 mm, 26 gauge; stainless steel) were implanted bilaterally into the brain through boreholes in the skull. The tips of the guide cannulae were aiming above the ventral hippocampus (5.2 mm posterior and ±5 mm lateral to bregma, and 5 mm ventral to dura). Guide cannulae were fixed by dental cement for which the three screws served as anchors to the skull. 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 were allowed to recover for 5 days during which the experimenters gave the rats daily health checks and gentle handling, and replaced missing stylets.

Intracerebral microinfusion

The rats were manually restrained, the stylets were removed from the guide cannulae, and infusion cannulae (34 gauge), connected to 10- μ l Hamilton microsyringes mounted on a microinfusion pump (KD scientific or WPI sp200i), were inserted into the guide cannulae. The tips of the infusion cannulae protruded into the ventral hippocampus 1.5 mm beyond the tips of the guide cannulae, thus aiming at a final dorsoventral coordinate of 6.5 mm below the dura. The rats were bilaterally infused with 100 or 150 ng picrotoxin in 0.5 μ l vehicle or 0.5 μ l vehicle only. The infusion speed was 0.5 μ l/min. After infusion, the infusion cannulae were left in the brain for 60 s to allow for absorption of the infusion bolus by the brain tissue and then replaced by the stylets. Rats were then immediately subjected to behavioral testing.

Drug preparation

The picrotoxin solutions were prepared freshly on the day of experiment. Picrotoxin (C₃₀H₃₄O₁₃; Fluka, Switzerland) was dissolved in 0.9% saline as vehicle to obtain concentrations of 200 or 300 μ g/ml for infusion of 100 or 150 ng (0.17 or 0.25 nmol)/0.5 μ l. The final pH was 6–7.

Apparatus and procedures for behavioral testing

Open field locomotor activity

Locomotor activity was measured in four closed square arenas (76.5 cm×76.5 cm×49 cm) made of dark gray plastic and placed in a dimly illuminated (20±0.5 Lux provided by two halogen lights) room. Behavior in the arenas was recorded by a video camera suspended from the ceiling and relayed to a monitor and a video tracking, motion analysis and behavior recognition system (Etho-Vision, Noldus, Wageningen, The Netherlands).

Startle and prepulse inhibition

The testing was conducted in four ventilated startle chambers (SR-LAB, San Diego Instruments, San Diego, Calif., USA), containing a transparent Plexiglas tube (diameter 8.2 cm, length 20 cm) mounted on a Plexiglas frame. 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 to an acoustic pulse was defined as the average of 100 1-ms accelerometer readings collected from pulse onset. A background noise level of 68 dB(A) was maintained throughout the test sessions. A test session started with 5 min of acclimatization, after which four startle pulses [30 ms, 120 dB(A)] 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 startle pulses, six blocks of 11 trials were presented to measure PPI. The 11 trials of each block included: two pulse alone trials, one prepulse followed by pulse as well as one prepulse alone trial for each of four prepulse intensities, and one no stimulus trial. The prepulses were broad band bursts of 20 ms duration and an intensity of 72, 76, 80, or 84 dB(A). The time span between prepulse offset and pulse onset was 80 ms. The different trial types were presented pseudorandomly with an inter-trial interval of 10–20 s (average 15 s). Altogether, a complete test session lasted about 23 min.

Experimental design

The experimental groups comprised three infusion groups to receive bilateral infusion of vehicle (VEH), 100 ng picrotoxin/side (PTX100) or 150 ng picrotoxin/side (PTX150) into the ventral hippocampus. The effects of picrotoxin infusion into the ventral hippocampus were tested on (1) open field locomotor activity or (2) startle response and PPI. All 50 animals used in the present study had received one vehicle infusion or infusion of 50 ng picrotoxin/0.5 µl per side throughout previous pilot experiments. In addition, 27 rats were used in the PPI experiment before being subjected to the open field experiment of this study. Those which received vehicle infusion during the PPI experiment received picrotoxin (150 ng/side) infusion during the open field experiment, and vice versa. Between the different infusions and experiments there was always a time span of at least seven days. Since both the PPI and the open field experiment included one day of testing before the day of infusion it could be verified that the rats with a different “experimental and infusion history” did not differ in the measurements relevant to the present study. In addition, both the PPI and the open field experiment included 1 test day following the day of infusion to check for possible long-term effects of the picrotoxin infusion.

Open field experiment

The open field experiment was run on 3 successive days and included two groups: VEH ($n=17$) and PTX150 ($n=14$). The picrotoxin dose was based on pilot studies yielding no hint of a loco-

motor effect of infusions of 10–50 ng picrotoxin/side into the ventral hippocampus. A PTX100 group was not included because open field testing of the first few animals of the PTX150 group suggested that even the locomotor effects of the higher picrotoxin dose were moderate. On day 1, each rat was placed in the center of one arena and its locomotor activity was recorded for 30 min. On day 2 (day of infusion), each rat was placed in the center of one of the arenas and its locomotor activity in the open field was monitored for 30 min. Then, the rats were returned to their home cages and moved to an infusion room to receive their infusions. After the infusion, all rats were replaced into the arena for an additional 60 min to check for the acute effect of picrotoxin infusion into the ventral hippocampus on locomotor activity (between-subjects design). On day 3 (day after infusion), each rat was placed in the center of one of the arenas and its locomotor activity was monitored for 30 min.

Prepulse inhibition experiment

The PPI experiment was conducted on 3 successive days and included three groups: VEH ($n=16$), PTX100 ($n=7$), and PTX150 ($n=18$). On day 1, basal startle and PPI were tested without infusion for all rats. On day 2 (day of infusion), startle and PPI were measured immediately following infusion to compare the acute effect of picrotoxin and vehicle infusion (between-subjects design). On day 3 (day after infusion), all rats were tested for startle and PPI without an infusion.

Histology

After completion of the behavioral experiments, rats were deeply anesthetized with 2.5 ml/kg Nembutal (sodium pentobarbital, 50 mg/ml, IP) and transcardially perfused with 0.9% saline solution to rinse out the blood, followed by 250 ml of 4% formalin (4°C) to fix the brain tissue. The brains were extracted from the skull, post-fixed in 4% formalin solution, and subsequently cut into 40-µm coronal sections on a freezing microtome. For the verification of the infusion sites, every fifth section through the ventral hippocampus was mounted on gelatine-treated slides and stained with cresyl violet. After staining, the sections were dehydrated and coverslipped. Subsequently, they were examined by light microscopy to verify that the tips of the infusion cannulae were placed in the ventral hippocampus and to draw their approximate locations onto plates taken from the atlas of Paxinos and Watson (1998).

Data analysis

All statistical analyses were performed with the StatView software system (Abacus Concepts, Inc., Berkeley, Calif., USA, 1992) using analysis of variance (ANOVA). Data are presented as means. In the text and in bar plots, the variability is indicated by the standard error of the mean (SEM). In line plots, for the sake of clarity, twice the standard error (SE) derived from the appropriate mean square yielded by the ANOVA was used to indicate variability. Fisher's protected least significant difference test was used for post hoc comparisons following a significant main effect revealed by ANOVA. In order to interpret significant interactions indicated by ANOVA, significant differences between the mean values of interest were estimated by using 2 SE derived from the appropriate mean square of the ANOVA (see Winer 1971, p. 199), since the StatView software only conducts post hoc comparisons relevant to main effects. Significant differences were accepted at $P<0.05$.

Open field experiment

The total distance the rat moved in cm throughout the complete arena was calculated for each 10-min block of testing. Groups

were taken as between-subjects factor and the 10-min blocks as repeated measures.

Prepulse inhibition experiment

The percentage PPI (%PPI) induced by each prepulse intensity was calculated as: $[100 - (100 \times \text{startle amplitude on prepulse followed by pulse trial}) / (\text{startle amplitude on pulse alone trial})]$ from the data taken during the six test blocks to measure PPI. For statistical analysis of the startle and %PPI data, groups were used as between-subjects factor and the 16 pulse alone trials (startle data) or four prepulse intensities (%PPI data) were taken as repeated measures. On the day of infusion, decreased %PPI occurred with a concomitant decrease of the average startle amplitude in the 16 pulse alone trials. As recently discussed extensively by Swerdlow et al. (2000a), decreased %PPI with concomitant changes of startle amplitude in pulse alone trials cannot unequivocally be ascribed to deficient induction of sensorimotor gating processes by the prepulses. In order to assess if the prepulses' potency to reduce the startle response was affected, PPI was also assessed by comparing the startle magnitude in the pulse alone and the prepulse followed by pulse trials of the six test blocks. For this purpose, startle data of the pulse alone trials and the four different prepulse followed by pulse (one for each prepulse intensity) trials were subjected to ANOVA using the five trial types as repeated measures.

Results

Location of infusion sites

In all 50 cannulated rats, the tips of the infusion cannulae were located within or around the border of the ventral hippocampus (Fig. 1). Damage resulting from the implantation of the guide cannulae was restricted to the area immediately surrounding the tracks of guide and infusion cannulae.

Picrotoxin infusions into the ventral hippocampus did not induce convulsions

Picrotoxin infusions (100 and 150 ng/side) into the ventral hippocampus did not induce convulsions. Also, tremor, sniffing, or whisker shaking, which sometimes occur following NMDA infusions (Bast et al. 2001b), were not observed. Some rats which received 150 ng picrotoxin/side exhibited shaking of their hind body during a period of some minutes beginning briefly after infusion.

Picrotoxin infusion into the ventral hippocampus increased locomotor activity

On day 1 of the open field experiment (day before infusion), PTX150 and VEH groups did not differ in the distance moved in the open field [$F(1,29)=0.1$, $P>0.7$; data not shown]. ANOVA revealed only a highly significant effect of 10-min block [$F(2,58)=133.8$, $P<0.0001$], reflecting habituation to the open field. On day 2 (day of infusion), both groups did not differ throughout the 30 min preceding the infusion [$F(1,29)=2.8$, $P>0.1$;

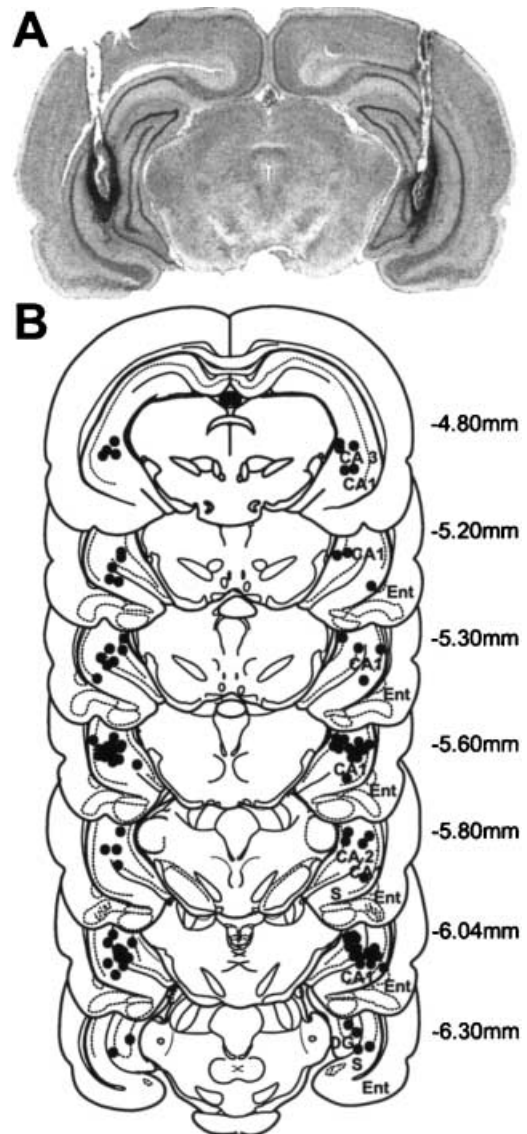


Fig. 1A, B Infusion sites in the ventral hippocampus. **A** Photomicrograph of a coronal brain section with the tracks of the guide cannulae and beneath them the infusion sites visible in both hemispheres. **B** Approximate location of the tips of the infusion cannulae depicted on plates of coronal sections through the rat brain (Paxinos and Watson 1998). Values on the right 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, left]. For these 30 min, ANOVA yielded only a highly significant effect of 10-min block [$F(2,58)=79.0$, $P<0.0001$], reflecting habituation. Following infusion, the PTX150 group exhibited increased activity as compared to the VEH group (Fig. 2, middle). ANOVA of the total distance moved yielded a significant effect of group [$F(1,29)=4.5$, $P<0.05$], a highly significant effect of 10-min block [$F(5,145)=40.2$, $P<0.0001$], as well as a highly significant group \times 10-min block interaction [$F(5,145)=6.9$, $P<0.0001$]. The latter reflected that the locomotor activity in the PTX150 group was significant-

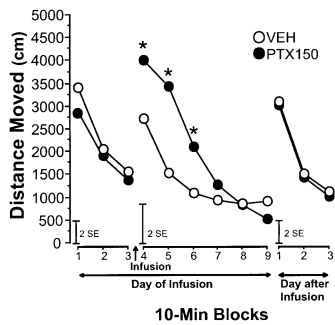


Fig. 2 Locomotor activity in the open field after picrotoxin infusion into the ventral hippocampus. On the day of infusion, the rats' locomotor activity in the open field was recorded for 30 min before infusion of vehicle (VEH; $n=17$) or 150 ng picrotoxin/side (PTX150; $n=14$) into the ventral hippocampus (left). Following infusion, activity was further recorded for 60 min (middle). The day after infusion (right), the rats' locomotor activity was recorded for 30 min. Locomotor activity is represented as the distance moved (mean in cm) during consecutive 10-min blocks. The bar represents 2 SE derived from the ANOVA. Asterisks denote a difference of more than 2 SE between the two groups

ly increased relative to the VEH group only during the first three 10-min blocks following infusion, whereas both groups exhibited similar locomotor activity throughout the rest of the session (based on comparisons using the SE derived from ANOVA). Thus, locomotor activity in the PTX150 group was normalized at about 40 min after infusion. On day 3 (day after infusion), both groups exhibited similar activity levels [$F(1,29)=0.2$, $P>0.6$] and ANOVA revealed only a highly significant effect of 10-min block [$F(2,58)=118.4$, $P<0.0001$], reflecting habituation (Fig. 2, right).

Picrotoxin infusion into the ventral hippocampus decreased the startle amplitude and caused a dose-dependent disruption of prepulse inhibition

The startle reactivity measured in the pulse alone trials was decreased by infusion of both 100 and 150 ng picrotoxin/side into the ventral hippocampus (Fig. 3A). ANOVA yielded a significant effect of group on the average startle amplitude during the 16 pulse alone trials on the day of infusion [day 2; $F(2,38)=8.4$, $P<0.002$], but not on the day before infusion [day 1; $F(2,38)=0.8$, $P>0.4$] or the day after infusion [day 3; $F(2,38)=1.1$, $P>0.3$]. Post hoc comparisons revealed that on the day of infusion the average startle amplitude (mean \pm SEM) was decreased in the PTX100 (660 ± 128 ; $P=0.053$) and PTX150 (460 ± 72 ; $P<0.0002$) groups, which did not differ ($P>0.25$), as compared to the VEH group (1020 ± 130). Short-term habituation of the startle response (Koch 1999) was not affected by picrotoxin infusion into the ventral hippocampus. This was reflected by a highly significant effect of pulse alone trial (all $P<0.0001$) occurring without a group \times pulse alone trial interaction (all $P>0.1$) on each of the 3 days.

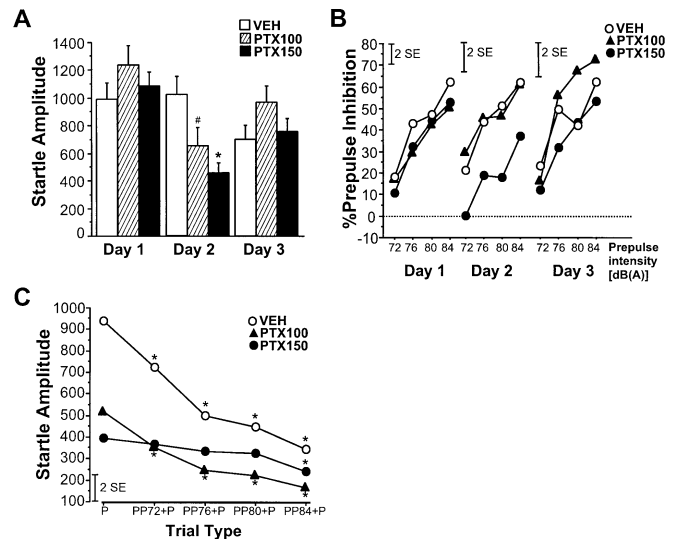


Fig. 3A–C Startle reactivity and prepulse inhibition after picrotoxin infusion into the ventral hippocampus. Rats were bilaterally infused with vehicle (VEH; $n=16$), 100 ng picrotoxin/side (PTX100; $n=7$) or 150 ng picrotoxin/side (PTX150; $n=18$) into the ventral hippocampus on day 2. All groups were tested for PPI without infusion 1 day before (day 1) and one day after (day 3) the infusion day (day 2). **A** Average startle magnitude (mean \pm SEM) during the 16 pulse alone trials for all 3 days. Differences to the VEH group indicated by post hoc comparisons are denoted (* $P<0.0002$; # $P=0.053$). **B** Mean percentage of prepulse inhibition averaged across all prepulse intensities for all three days. The bars represent 2 SE derived from ANOVA. **C** Mean startle amplitude throughout the pulse alone (P) and the prepulse followed by pulse (PP+P) trials of the six test blocks to measure PPI on the day of infusion. The different prepulse intensities in dB(A) are indicated. The bar represents 2 SE derived from ANOVA. Startle amplitudes in the prepulse followed by pulse trials (PP+P) which differed by more than 2 SE from that during the pulse alone trials (P) of the same group are denoted by asterisks

Infusion of 150, but not 100 ng picrotoxin/side decreased the %PPI (Fig. 3B). ANOVA yielded a significant effect of group on the %PPI on the day of infusion [day 2; $F(2,38)=7.0$, $P<0.005$], but not on the day before infusion [day 1; $F(2,38)=0.6$, $P>0.5$] or the day after infusion [day 3; $F(2,38)=1.4$, $P>0.25$]. Post hoc comparisons revealed that on the day of infusion the average %PPI (mean \pm SEM) over all four prepulse intensities was decreased in the PTX150 (18.2 ± 4.7) as compared to both the PTX100 (45.4 ± 10.4 ; $P<0.01$) and the VEH group (44.1 ± 5.8 ; $P<0.002$), which did not differ ($P>0.9$). A gradual increase of the %PPI with an increase in prepulse intensity (Koch 1999) was evident in all groups on each of the three days. This was reflected by a highly significant effect of prepulse intensity (all $P<0.0001$) occurring without a group \times prepulse intensity interaction (all $P>0.1$) on each day.

A comparison of the startle amplitude throughout the pulse alone trials and the prepulse followed by pulse trials of the six blocks to measure PPI revealed that the prepulse potency to decrease the startle amplitude to the pulse was markedly diminished in the PTX150 group, whereas it was intact for all prepulse intensities in the

PTX 100 and VEH groups (Fig. 3C). ANOVA of the startle data measured throughout the six blocks to test PPI on the day of infusion yielded a significant effect of group [$F(2,38)=3.8$, $P<0.05$], reflecting the decreased startle reactivity in the PTX100 and PTX150 as compared to the VEH group, a highly significant effect of trial type [$F(4,152)=31.5$, $P<0.0001$], and a highly significant group \times trial type interaction [$F(8,152)=6.7$, $P<0.0001$]. The interaction reflected that the PTX100 and the VEH group exhibited a similar gradual decrease in startle reaction to the pulse when the pulse was preceded by increasing prepulses, whereas this effect of the prepulses was markedly decreased in the PTX150 group. In the VEH and the PTX100 group, the startle amplitude was significantly decreased in all prepulse followed by pulse trials as compared to the pulse alone trials, whereas in the PTX150 group only the highest, but not the three lower prepulse intensities had the potency to significantly reduce the startle reaction to the pulse (based on comparisons using the SE derived from the ANOVA). Moreover, in the pulse alone trials, startle amplitude (mean \pm SEM) appeared to be higher in the PTX100 (520 \pm 130) than in the PTX150 (400 \pm 71) group. This relation seemed to be reversed in the prepulse followed by pulse trials. When the pulses were preceded by prepulses of 76, 80, and 84 dB(A), the startle amplitude to the pulses appeared to be higher in the PTX150 (330 \pm 69, 330 \pm 63, 240 \pm 42) than in the PTX100 (250 \pm 48, 220 \pm 48, 170 \pm 33) group. Thus, the decreased %PPI in the PTX150 group was not just due to a decreased startle reactivity in the pulse alone trials but associated with a diminished potency of the prepulses to reduce the startle amplitude in the prepulse followed by pulse trials.

Discussion

Disinhibition of the ventral hippocampus by local microinfusion of the GABA_A antagonist picrotoxin induced hyperactivity in the open field, decreased startle reactivity, and disrupted PPI. All effects were evident only throughout the test sessions immediately following infusion but not 24 h later, indicating that they were due to temporary alterations of neuronal activity in the ventral hippocampus. Infusions of 100 or 150 ng picrotoxin/side into the ventral hippocampus of our Wistar rats did not induce convulsions. In contrast, Japha and Koch (1999) reported doses above 10 ng picrotoxin/side to be convulsive when infused into the ventral hippocampus of Sprague-Dawley rats. The different observations might be related to strain differences. In agreement with our observation, however, doses higher than 300 ng/side had to be applied to the amygdala to induce the slightest seizure grade in Wistar rats in an animal model of temporal lobe epilepsy (Turski et al. 1985).

Hyperactivity following picrotoxin infusion into the ventral hippocampus

The hyperactivity in the open field following disinhibition of the ventral hippocampus by picrotoxin adds to the evidence that activity of the ventral hippocampus drives locomotor activity. Thus, infusions of stimulatory neuroactive substances into the ventral hippocampus stimulate locomotor activity (Yang and Mogenson 1987; Wu and Brudzynski 1995; Brudzynski and Gibson 1997; Brenner and Bardgett 1998; Bardgett and Henry 1999; Legault and Wise 1999; Bast et al. 2001b), whereas increased inhibition of the ventral hippocampus by the GABA_A receptor agonist muscimol or complete inactivation by the sodium channel blocker tetrodotoxin result in hypoactivity in the open field (Bast et al. 2001a). In view of the data from infusion studies, hyperactivity observed under certain circumstances after ventral hippocampal lesions (Nadel 1968; Lipska et al. 1992; Richmond et al. 1999) does not appear to reflect a suppressive influence of the ventral hippocampus on locomotor activity. This hyperactivity might rather be related to lesion-induced damage in extra-hippocampal areas involved in the regulation of locomotor activity, like midbrain dopamine nuclei and their forebrain projection fields (Halim and Swerdlow 2000). The effects of ventral hippocampal infusions might be mediated by the meso-accumbens dopamine system, which can be influenced by the ventral hippocampus via direct projections to the nucleus accumbens (Groenewegen et al. 1987) or via a loop including projections from the ventral hippocampus to the prefrontal cortex (Verwer et al. 1997; see Legault et al. 2000). For example, the hyperactivity induced by NMDA stimulation of the ventral hippocampus seems to be due to increased dopamine transmission in the nucleus accumbens (Wu and Brudzynski 1995; Brudzynski and Gibson 1997; Bardgett and Henry 1999; Legault and Wise 1999; Bast et al. 2001b).

Decreased startle reactivity and disruption of prepulse inhibition following picrotoxin infusion into the ventral hippocampus

While infusion of both 100 and 150 ng picrotoxin/side into the ventral hippocampus decreased the startle reactivity to a similar extent, only the higher dose decreased PPI. This is in line with several findings demonstrating that the startle reflex and PPI can be modulated independently and, specifically, that alterations of the startle amplitude do not necessarily result in changes of PPI (e.g. Caine et al. 1992; Wan et al. 1996; Bast et al. 2000; Zhang et al. 2000). Nevertheless, changes in startle reactivity may in some instances result in decreased PPI. Consequently, decreased PPI cannot unequivocally be ascribed to impaired sensorimotor gating when it is paralleled by changes of the startle amplitude throughout the pulse alone trials (for a detailed discussion see

Swerdlow et al. 2000a). In the present study, %PPI was reduced only by the higher dose of picrotoxin, whereas both doses led to a similar decrease in startle reactivity, indicating that this decrease cannot account for the PPI deficit. Moreover, the comparison of the startle amplitude in the different trial types demonstrated that the higher dose of picrotoxin specifically impaired the prepulses' potency to reduce the startle amplitude in prepulse followed by pulse trials. Thus, the decreased PPI following infusion of 150 ng picrotoxin/side into the ventral hippocampus appears to reflect a genuine impairment of sensorimotor gating.

Decreased startle reactivity and disruption of PPI following disinhibition of the ventral hippocampus by picrotoxin resemble the effects of ventral hippocampal stimulation by infusion of excitatory substances, like NMDA (Wan et al. 1996; Klarner et al. 1998; Koch et al. 1999; Zhang et al. 1999; Bast et al. 2001b) and the acetylcholine agonist carbachol (Caine et al. 1992). Thus, overactivity of the ventral hippocampus might be a critical factor to induce these effects. In contrast, ventral hippocampal lesions did not alter basal PPI (Pouzet et al. 1999), but enhanced sensitivity to PPI disruption by the dopamine agonist apomorphine (Swerdlow et al. 1995, 2000b), and one study reported increased startle reactivity following ventral hippocampal lesions (Swerdlow et al. 1995). Moreover, though the non-competitive NMDA antagonist MK-801 disrupts PPI very potently when administered systemically, ventral hippocampal MK-801 infusions did not affect PPI (Bakshi and Geyer 1998; Bast et al. 2001b). However, in view of our own results indicating decreased startle reactivity and disrupted PPI following tetrodotoxin or muscimol infusion into the ventral hippocampus (T. Bast, W.-N. Zhang, J. Feldon, unpublished observations), one has to consider that not only overactivity but also other alterations of activity of the ventral hippocampus may affect startle reactivity and PPI.

The PPI disruption following NMDA stimulation of the ventral hippocampus seems to be dopamine-independent (Wan et al. 1996; Zhang et al. 1999; Bast et al. 2001b) and might be mediated by non-dopaminergic processes in the prefrontal cortex, the nucleus accumbens, or in the amygdala, all of which receive projections from the ventral hippocampus (Groenewegen et al. 1987; Verwer et al. 1997; Pitkänen et al. 2000; see Bast et al. 2001b). The same might hold for the PPI disruption following disinhibition of the ventral hippocampus by picrotoxin. However, Japha and Koch (1999), based on the fact that haloperidol seemed to antagonize a non-significant PPI impairment after infusion of 10 ng picrotoxin/side into the ventral hippocampus of Sprague-Dawley rats, proposed the opposite. Testing the effects of haloperidol pretreatment on the PPI disruption induced by infusion of 150 ng picrotoxin/side into the ventral hippocampus of our Wistar rats could clarify this issue. The circuits mediating the decrease of startle reactivity following stimulation or disinhibition of the ventral hippocampus might involve projections from the ventral hip-

pocampus to the amygdala or the bed nucleus of the stria terminalis (Swanson and Cowan 1977; Pitkänen et al. 2000), which have access to the brain stem startle circuit (Koch 1999).

Only the higher dose of picrotoxin disrupted PPI, whereas both doses decreased the startle reactivity markedly and to a similar extent. In contrast, infusions of NMDA doses which potently disrupted PPI were not always found to decrease startle reactivity (Wan et al. 1996; Klarner et al. 1998; Koch et al. 1999; Zhang et al. 1999; Bast et al. 2001b; W.-N. Zhang, T. Bast, J. Feldon, unpublished observations). Thus, disinhibition of the ventral hippocampus by picrotoxin has a stronger impact on the startle reactivity, whereas NMDA stimulation more strongly affects PPI. This indicates slight differences in the neuronal processes induced by these two forms of ventral hippocampal activation.

As a protective reaction to an aversive stimulus, the startle response is enhanced by aversive states, such as anxiety and fear, in rats as well as humans, and enhanced startle reactivity is a diagnostic criterion of human anxiety disorders (Lang 1995; Rodgers 1997; Filion et al. 1998; Koch 1999). Anxiety-related states, i.e. enhanced behavioral reactivity to aversive stimuli, have been associated with activity in the septo-hippocampal system (Gray 1995) and particularly with decreased GABA_A receptor-mediated inhibition in the hippocampus (see Crestani et al. 1999; Löw et al. 2000). The markedly decreased startle reactivity following infusion of the GABA_A antagonist picrotoxin into the ventral hippocampus does not support these concepts.

Previous work has indicated that motor activity may decrease startle reactivity and also PPI (Wecker and Ison 1986; Plappert et al. 1993). Whereas in particular grooming had a strong effect, gross postural changes, such as turning, did not affect startle and PPI (Wecker and Ison 1986). Picrotoxin infusion into the ventral hippocampus induced increased locomotor activity, which results from gross postural changes, while there was no evidence of increased grooming. Thus, the hyperactivity induced by the picrotoxin infusion into the ventral hippocampus cannot account for the decreased startle reactivity and PPI observed in the present study.

Conclusion

Blockade of GABA_A receptors in the ventral hippocampus induced hyperactivity in the open field and an impairment of sensorimotor gating. These effects are similar to those induced by direct excitation of the ventral hippocampus and related to psychotic symptoms. A concurrence of increased afferent excitation and decreased GABAergic inhibition might contribute to the hippocampal overactivity in schizophrenic patients (Benes 2000). In order to clarify the relevance of these aberrations with respect to schizophrenic symptoms, it is of interest to examine whether excitation or disinhibition of the ventral hippocampus in rats elicits further psychosis-related be-

havioral disturbances, such as disruption of latent inhibition and other attentional processes (Gray et al. 1991; Feldon and Weiner 1992). Interestingly, unpublished observations (B. Pouzet, W.-N. Zhang, and J. Feldon) indicate that NMDA stimulation, in contrast to cytotoxic lesions, of the ventral hippocampus disrupts latent inhibition. Moreover, the effects of picrotoxin in the dorsal hippocampus remain to be explored. Recent experiments, however, demonstrating NMDA stimulation of the dorsal hippocampus to hardly affect PPI and locomotor activity (W.-N. Zhang, T. Bast, J. Feldon, unpublished observations), indicate that these processes might be much less affected by dorsal than by ventral hippocampal disinhibition.

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