ELSEVIER

European Journal of Pharmacology 314 (1996) 9–18

ejp

The ventral subiculum modulation of prepulse inhibition is not mediated via dopamine D_2 or nucleus accumbens non-NMDA glutamate receptor activity

Fang-Jung Wan [1], S. Barak Caine [2], Neal R. Swerdlow *

Departments of Neuroscience and Psychiatry, UCSD School of Medicine, La Jolla, CA 92093-0804, USA

Received 15 April 1996; revised 27 June 1996; accepted 5 July 1996

Abstract

Prepulse inhibition of the acoustic startle reflex is an operational measure of sensorimotor gating. The neural substrates of prepulse inhibition may be relevant to the pathophysiology of neuropsychiatric disorders that are characterized by sensorimotor gating deficits, including schizophrenia. Studies have demonstrated abnormalities within the hippocampal formation of schizophrenia patients, and animal studies have revealed that the hippocampus, and specifically the ventral subiculum, regulates prepulse inhibition. The ventral subiculum sends a dense glutamatergic projection to the nucleus accumbens, and the nucleus accumbens is known to potently regulate prepulse inhibition via dopaminergic and non-*N*-methyl-D-aspartate (non-NMDA) glutamatergic mechanisms. In the present study, we examined whether the hippocampal regulation of prepulse inhibition is mediated through subiculo-accumbens glutamatergic efferents. Intra-ventral subiculum infusion of NMDA dose dependently reduced prepulse inhibition, and this effect of NMDA was reversed by co-infusion of the NMDA receptor antagonist D,L-amino-5-phosphonovaleric acid (AP5). The prepulse inhibition-disruptive effect of intra-ventral subiculum NMDA infusion was not prevented by infusion of the non-NMDA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) into the nucleus accumbens core or shell subregions. Pretreatment with the D_2 receptor antagonist haloperidol also failed to block the prepulse inhibition-disruptive effects of intra-ventral subiculum NMDA infusion. Thus, the present findings suggest that while prepulse inhibition is regulated by NMDA activity in the ventral subiculum, this effect does not appear to be mediated via nucleus accumbens dopamine D_2 receptors or via nucleus accumbens non-NMDA glutamatergic substrates.

Keywords: Ventral subiculum; NMDA (*N*-methyl-D-aspartate); CNQX (6-cyano-7-nitroquinoxaline-2,3-dione); Dopamine; Prepulse inhibition; Sensorimotor gating; Schizophrenia; Startle

1. Introduction

Prepulse inhibition is the normal decrease in a startle response that occurs when the startling stimulus is preceded by a weaker stimulus or 'prepulse' (Ison and Hoffman, 1983). Prepulse inhibition is an operational measure of sensorimotor gating: greater inhibition of the reflex reflects more sensorimotor gating. In humans, evidence suggests that prepulse inhibition is deficient in patients with neuropsychiatric disorders characterized by central inhibitory deficits such as schizophrenia (Bolino et al., 1994; Braff et al., 1978, 1992; Grillon et al., 1992), Huntington's disease (Swerdlow et al., 1995b) and obsessive compulsive disorder (Swerdlow et al., 1993). For example, schizophrenia patients exhibit less prepulse inhibition of the eye blink component of the startle reflex than do normal control subjects. Theoretically, deficient sensorimotor gating mechanisms in schizophrenia may be linked to disturbances in information processing and cognition (Braff et al., 1992).

Studies of acoustic startle in rats have revealed that prepulse inhibition appears to be regulated by forebrain activity within limbic cortico-striato-pallido-pontine circuitry (Swerdlow et al., 1994), while the primary acoustic startle response in controlled predominantly by brainstem nuclei (Davis et al., 1982; Lingenhohl and Friauf, 1994).

* Corresponding author. Tel.: (1-619) 543-6270; Fax: (1-619) 543-2493, e-mail: nswerdlow@ucsd.edu

[1] Present address: P.O. Box 90048-504, Department of Pharmacology, National Defense Medical Center, Taipei, Taiwan.

[2] Present address: Alcohol and Drug Abuse Research Center, McLean Hospital, Harvard Medical School, 115 Mill Street, Belmont, MA 02178, USA.

PII S0014-2999(96)00535-3

At the level of the limbic cortex, prepulse inhibition is reduced by muscarinic cholinergic activity within the hippocampus (Caine et al., 1991, 1992), dopamine receptor blockade or 6-hydroxydopamine lesions in prefrontal cortex (Ellenbroek et al., 1995; Koch and Bubser, 1994) or excitotoxic lesions of basolateral amygdala (Wan and Swerdlow, 1996c). Excitotoxic lesions of the hippocampus in adult rats has been reported by some (Seybold et al., 1995), but not others (Swerdlow et al., 1995a) to reduce prepulse inhibition. At the level of the 'limbic striatum', prepulse inhibition is reduced by dopaminergic or glutamatergic activity in the nucleus accumbens, or by excitotoxic lesions of this area (Kodsi and Swerdlow, 1994; Reijmers et al., 1995; Wan and Swerdlow, 1993; Wan et al., 1994, 1995a). Within the ventral pallidum, prepulse inhibition is reduced by the $GABA_A$ receptor antagonist picrotoxin, and the GABA receptor agonist muscimol reverses the prepulse inhibition-disruptive effects of intra-nucleus accumbens dopamine infusion or nucleus accumbens excitotoxic lesions (Swerdlow et al., 1990; Kodsi and Swerdlow, 1994). Finally, electrical or excitotoxic lesions of pedunculopontine tegmental nucleus, or muscimol infusions into this region, reduce prepulse inhibition (Kodsi et al., 1995; Swerdlow and Geyer, 1993b). The pedunculopontine tegmental nucleus may be a final common output pathway for the forebrain structures regulating prepulse inhibition, by its cholinergic projection to the nucleus reticularis pontis caudalis in the primary acoustic startle circuit (Koch et al., 1993).

There is substantial evidence for a direct glutamatergic projection from the ventral subiculum of the hippocampus to the nucleus accumbens (Groenewegen et al., 1987; Kelley and Domesick, 1982; Totterdell and Smith, 1989), and dysfunction in this glutamatergic subiculo-accumbens projection has been implicated in the pathophysiology of schizophrenia (Bogerts et al., 1985; Luchins, 1990). Additionally, behavioral and neurochemical studies indicate that lesions of ventral hippocampus result in an increase in nucleus accumbens dopamine activity (Lipska et al., 1992; Wilkinson et al., 1993), and that hippocampal damage-induced hyperactivity can be reversed by dopamine terminal denervation in the nucleus accumbens (Emerich and Walsh, 1990). It has also been reported that intra-hippocampal infusion of carbachol or an acetylcholinesterase inhibitor increase locomotor activity (Flicker and Geyer, 1982; Zheng et al., 1983), an effect which was shown to be reversed by prior injection of a glutamate receptor antagonist into the nucleus accumbens (Mogenson and Nielson, 1984). Since both the ventral subiculum and the nucleus accumbens are critical substrates regulating prepulse inhibition in rats, it is conceivable that the hippocampal regulation of prepulse inhibition – or at least the ventral subiculum regulation of prepulse inhibition – is mediated via changes in glutamatergic activity in the subiculo-accumbens projection. Consistent with this, we have reported that prepulse inhibition is reduced by infusion of the non-NMDA receptor agonist (±)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid hydrobromide (AMPA) into the nucleus accumbens core or shell subregions (Wan et al., 1995a). In the nucleus accumbens core, this AMPA effect is mediated by dopamine-dependent mechanisms (Wan et al., 1995a), while in the nucleus accumbens shell, it is mediated by dopamine-independent mechanisms (Wan and Swerdlow, 1996b). The present study was designed to characterize the ventral subiculum regulation of prepulse inhibition in rats, and to investigate whether this behavioral role of the ventral subiculum is mediated via changes in nucleus accumbens non-NMDA neurotransmission.

2. Materials and methods

2.1. Animals and surgery

Male Sprague-Dawley rats (225–250 g) were housed in groups of 2–3 and maintained on a reversed 12 h:12 h light/dark schedule (lights off at 07:00 h) with food and water provided continuously. Behavior testing occurred between 09:00 and 15:00 h, during the dark phase, when acoustic startle is most robust and least variable (Chabot and Tayler, 1992). Rats were handled individually within 3 days of arrival. All surgery occurred between 7 and 14 days after arrival, using Equithesin anesthesia and a Kopf stereotaxic instrument. Bilateral intra-nucleus accumbens 23 gauge cannulae (10 mm) were aimed 3 mm above the following coordinates according to a stereotaxic atlas (Paxinos and Watson, 1986): the nucleus accumbens core, AP +1.1 (bregma), L ±2.2, DV −7.1 (skull); the nucleus accumbens shell, AP +1.2, L ±0.8, DV −7.2, ventral subiculum, AP −6.5, L ±5.0, DV −8.0. Cannulae were anchored to the skull with cement and screws, and filled with wire stylets.

2.2. Apparatus

Each of 4 startle chambers (SR-LAB, San Diego Instruments, San Diego, CA, USA) was housed in a sound-attenuated room with a 60 dB(A) ambient noise level, and consisted of a Plexiglas cylinder 8.2 cm in diameter resting on a 12.5 × 25.5 cm Plexiglas frame within a ventilated enclosure. Acoustic noise bursts were presented via a speaker mounted 24 cm above the animal. A piezoelectric accelerometer mounted below the Plexiglas frame detected and transduced motion within the cylinder. The delivery of acoustic stimuli was controlled by the SR-LAB microcomputer and interface assembly which also digitized (0–4095), rectified and recorded stabilimeter readings, with 100 1-ms readings collected beginning at stimulus onset. Startle amplitude was defined as the average of the 100 readings. Background noise and all acoustic stimuli were delivered through one Radio Shack Supertweeter (frequency response predominantly between 5 and 16 kHz) in each

chamber. Stimulus intensities and response sensitivities were calibrated to be nearly identical in each of the four startle chambers (maximum variability $< 1\%$ of stimulus range and $< 5\%$ of response ranges), and chambers were also balanced across all experiment groups. Sound levels were measured and calibrated with a Quest Sound Level Meter, A scale (relative to 20 $\mu N/M^2$), with the microphone placed inside the Plexiglas cylinder; response sensitivities were calibrated using an SR-LAB Startle Calibration System.

2.3. Test sessions

In order to balance the dose groups and reduce intergroup variability, rats were assigned to groups based on matched startle amplitude from a brief pretest session 7 days post-surgery. Test sessions were identical for all experiments in this study. Immediately prior to a test session, stylet wires were removed from the intracerebral cannulae and replaced by a 30 gauge needle (13 mm). Injection volume was 0.5 μl over 42 s injection time using a Hamilton microsyringe connected to the needle via polyethylene tubing. Needles were left in place for 30 s following each injection, and then were replaced with a wire stylet. Rats were then placed in the startle chambers for a 5 min acclimation period with a 70 dB(A) background noise. After the acclimation period, rats were exposed to 4 types of stimuli: a startle pulse [P-alone: a 120 dB(A) 40-ms broad band burst] and 3 types of prepulses [3 dB, 5 dB or 10 dB: a 73, 75 or 80 dB(A) 20-ms broad band burst] presented 100 ms prior to the startle pulse. Prepulse intensities were chosen to span a range of relatively weak (3 dB) and intense (10 dB) stimuli. We have previously demonstrated that inhibitory effects of prepulses in this range are most sensitive to disruption by drug treatments (Wan et al., 1994, 1995b). The session was designed with 5 trial types: P-alone, each of the 3 prepulse trials followed by a P-alone or no stimulus (NOSTIM). For each test session, 50 trials (10 P-alone, 10 NOSTIM, and 10 of each prepulse trial types) were presented in pseudorandom order. A variable inter-trial interval averaged 15 s.

2.4. Statistics and histology

After completion of behavioral testing, all animals were killed by a lethal overdose of pentobarbital and perfused with a 10% formalin-saline solution. Brains were removed and kept in 10% formalin-saline until histological assessment was performed to verify cannula placement. Data from a given animal were excluded from statistical analyses when the infusion sites fell outside target areas. Histological verifications of the sites of infusions for all experiments are diagrammed in Fig. 1.

Prepulse inhibition was defined as $100 - [\{$(startle amplitude on prepulse trials)/(startle amplitude on P-alone trials)$\} \times 100]$, and was analyzed by mixed-design analyses of variance (ANOVAs), with specific comparisons noted for each experiment. In this study, prepulse inhibition data shown in figures represent mean values of the prepulse inhibition across trials with 3, 5, 10 dB prepulse types. Using this description of prepulse inhibition, a high degree of sensorimotor gating is reflected in a high percentage prepulse inhibition value while less gating results in a

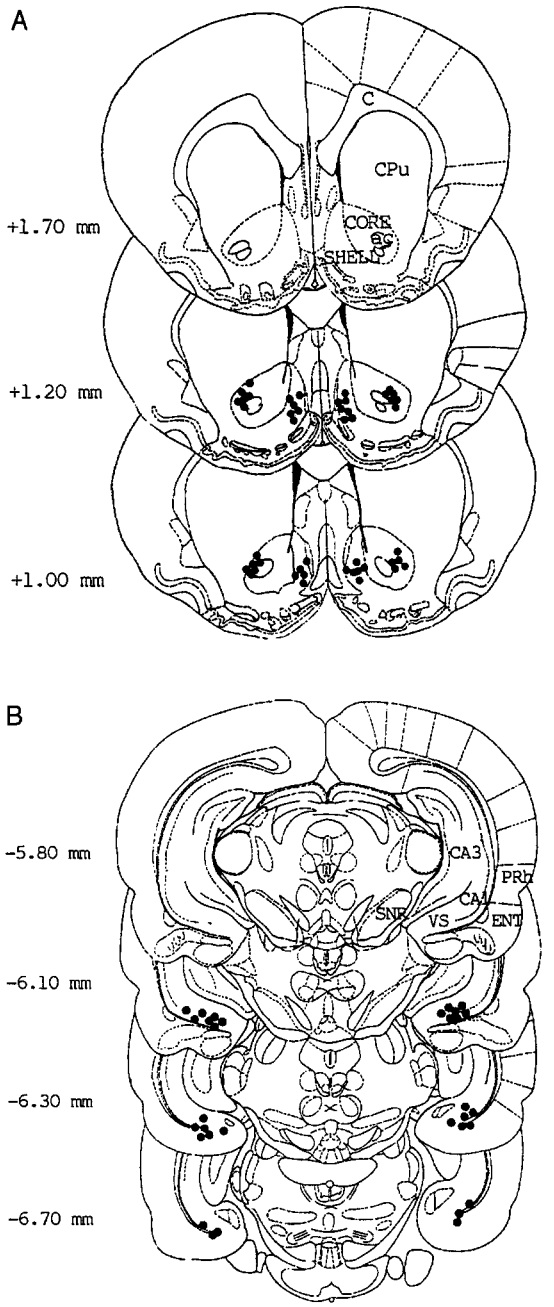

Fig. 1. Locations of representative cannulae tips in the regions of the nucleus accumbens core and shell (A), and in the ventral subiculum (B), plotted on modified coronal sections from Paxinos and Watson (1986). Values represent distance in mm from bregma. C corpus callosum, CPu caudate-putamen, AC anterior commissure, VS ventral subiculum, SNR substantia nigra pars reticulata, Ent entorhinal cortex, PRh perirhinal cortex. For coordinates see text.

small percentage prepulse inhibition value. Correlations of startle amplitude and prepulse inhibition were accomplished using a Spearman Rank Correlation. α was 0.05 for all statistical analyses.

2.5. Drugs

The following drugs were obtained from Research Biochemicals International (RBI): *N*-methyl-D-aspartic acid (NMDA), (±)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid hydrobromide (AMPA), 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX). Haloperidol was purchased from Solopark Laboratory. NMDA and AMPA were dissolved in 0.9% saline. CNQX was dissolved first in 0.1 M NaOH and adjusted by 0.1 M HCl to pH range from 5 to 7. Haloperidol was diluted with saline from a stock 5 mg/ml water/lactic acid solution to an injection volume of 1 ml/kg; injections were made via subcutaneous route 10 min prior to intracerebral drug treatment. For experiments involving drug infusion into two brain regions (3.3, 3.4), infusions into the nucleus accumbens were followed 10 min later by infusions into the ventral subiculum. For co-infusion studies (3.2, 3.5), drugs were administered simultaneously. Doses in this study were chosen based on behavioral observations in other studies that used the startle reflex as a dependent variable (Wan et al., 1995b). CNQX was infused immediately prior to intra-ventral subiculum NMDA infusions, and haloperidol was given 10 min before NMDA infusions.

3. Results

3.1. Effects of intra-ventral subiculum NMDA infusion on prepulse inhibition

Previous studies in our laboratory have shown that prepulse inhibition can be reduced after infusion of carbachol into several areas within the hippocampal formation, including the dentate gyrus, the CA1 area and the ventral subiculum (Caine et al., 1992). Cells in the ventral subiculum receive excitatory glutamatergic inputs from several brain regions, and these ventral subiculum cells also form the major hippocampal projection to the nucleus accumbens (Groenewegen et al., 1987). In the present study, we examined prepulse inhibition after glutamatergic activation of the ventral subiculum.

The effects of NMDA (0, 0.4, 0.8 μg) infusion into the ventral subiculum on prepulse inhibition are seen in Fig. 2. Prepulse inhibition was reduced in a dose-dependent manner after NMDA infusion into the ventral subiculum. A two-way ANOVA using dose of NMDA as the between-subject factor with repeated measures on prepulse type revealed a significant effect of dose [$F(2,20) = 4.31$, $P = 0.028$]. There was no significant effect of prepulse type [$F(2,40) = 1.31$, NS], and no significant dose × prepulse

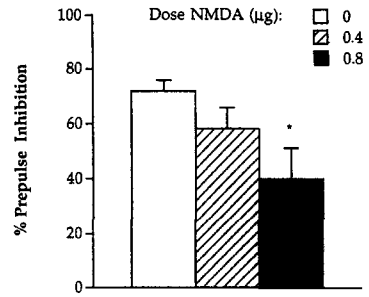

Fig. 2. Effects of intra-ventral subiculum NMDA infusion on the prepulse inhibition of acoustic startle. Prepulse inhibition was dose-dependently reduced by intra-ventral subiculum NMDA infusion. * $P < 0.05$, by Tukey comparison after significant main effect by overall ANOVA. $n = 7$, 7 and 8 for NMDA doses 0, 0.4 and 0.8, respectively. Data represent mean percent prepulse inhibition across all prepulse conditions.

type interaction [$F(4,40) < 1$; NS]. Post-hoc Tukey comparison revealed that, compared to saline-infused rats, prepulse inhibition was significantly reduced in rats after intra-ventral subiculum infusion of 0.8 μg NMDA [$F(1,13) = 5.01$, $P < 0.05$]. Analysis of startle amplitude revealed no significant effect of NMDA on P-alone amplitude [$F(2,20) < 1$, NS] (startle amplitude (means ± S.E.M.) for 0, 0.4 and 0.8 μg doses, respectively, 489.57 ± 96.72, 551.49 ± 85.42 and 493.99 ± 101.98). These results extend previous findings, and confirm that glutamatergic activation of the ventral subiculum reduces prepulse inhibition.

3.2. Effects of AP5 on the intra-ventral subiculum NMDA-induced disruption of prepulse inhibition

To verify that the prepulse inhibition-disruptive effects of intra-ventral subiculum NMDA infusion are mediated by activation of NMDA receptors, we examined the effects intra-ventral subiculum co-infusion of NMDA and the NMDA receptor antagonist AP5. Consistent with the above results, intra-ventral subiculum NMDA (0.8 μg) caused a significant reduction in prepulse inhibition; this effect was reversed dose dependently by co-infusion with AP5 (Fig. 3). ANOVA using dose of AP5 (0, 0.75, 1.5 μg) as the between subject factor, with NMDA (0, 0.8 μg) and prepulse type as the within subject factors, revealed a significant effect of NMDA [$F(1,14) = 13.99$, $P < 0.01$], no significant effect of AP5 dose [$F(2,14) < 1$, NS], and a significant AP5 × NMDA interaction [$F(2,14) = 11.56$, $P < 0.01$]. There was a significant effect of prepulse type [$F(2,28) = 4.96$, $P = 0.01$], but no other two- or three-ways interactions ($P > 0.05$, all comparisons). Post-hoc independent ANOVAs revealed a significant effect of NMDA in rats co-infused with 0 μg AP5 [$F(1,5) = 5.71$, $P < 0.05$], but not in rats co-infused with 0.75 or 1.5 μg AP5 [both $F < 1$, NS]. Analysis of startle amplitude revealed that NMDA significantly reduced P-alone amplitude [$F(1,14) = 9.34$, $P < 0.01$]; there was no significant effect of AP5 [$F(2,14) = 1.56$, NS], but there was a near-signifi-

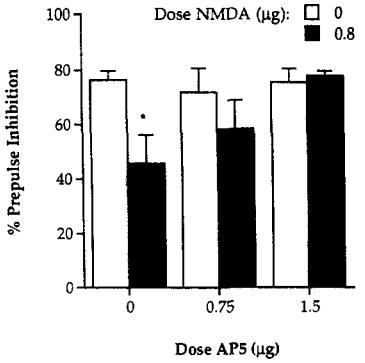

Fig. 3. Effects of AP5 on the intra-ventral subiculum NMDA-induced disruption of prepulse inhibition. The NMDA-disruption of prepulse inhibition was blocked by co-infusion of AP5 into the ventral subiculum. Independent ANOVAs revealed a significant effect of NMDA in rats co-infused with saline (* $P < 0.05$), but not in rats co-infused with 0.75 and 1.5 μg AP5, after a significant effect of NMDA on prepulse inhibition and a significant AP5 × NMDA interaction by overall ANOVA. $n = 6$, 4, 7 for AP5 doses 0, 0.75 and 1.5, respectively. Data represent mean percent prepulse inhibition across all prepulse conditions.

cant interaction of APV × NMDA [$F(2,14) = 2.88$, $P < 0.09$]. This interaction reflected the fact that NMDA reduced startle amplitude in rats treated with 0 μg AP5 (means ± S.E.M.: 0 μg NMDA, 518.73 ± 138.02; 0.8 μg NMDA, 229.45 ± 43.97), but not in rats treated with 0.75 μg AP5 (means ± S.E.M.: 0 μg NMDA, 629.45 ± 55.46; 0.8 μg NMDA, 623.08 ± 159.57) or 1.5 μg AP5 (means ± S.E.M.: 0 μg NMDA, 587.14 ± 98.20; 0.8 μg NMDA, 456.41 ± 86.86). No significant correlation between prepulse inhibition and P-alone amplitude was found in rats with intra-ventral subiculum NMDA infusion at any prepulse type ($0 \leq R \leq 0.4$, NS all comparisons). These results support the possibility that NMDA receptor activation in the ventral subiculum regulates prepulse inhibition.

3.3. Effects of intra-nucleus accumbens shell CNQX on the intra-ventral subiculum NMDA-induced disruption of prepulse inhibition

Subiculo-accumbens glutamatergic fibers terminate largely in the nucleus accumbens shell (Groenewegen et al., 1987; Kelley and Domesick, 1982). Since intra-shell infusion of AMPA results in a dose-dependent reduction in prepulse inhibition (Wan and Swerdlow, 1996b), it is possible that the prepulse inhibition-disruptive effects of intra-ventral subiculum NMDA are mediated via excitation of the subiculo-accumbens shell glutamate projection, and the consequent activation of shell AMPA receptors. We examined this possibility in the present study.

The effects of intra-nucleus accumbens shell infusion of the AMPA receptor antagonist CNQX (0 or 2.5 μg) on the prepulse inhibition-disruptive effects of intra-ventral subiculum NMDA (0.8 μg) are seen in Fig. 4. A two-way ANOVA of prepulse inhibition, using dose of CNQX as the between-subject factor, and dose of NMDA and prepulse type as the within-subject factors, revealed a significant effect of NMDA [$F(1,14) = 8.73$, $P = 0.01$], no significant effect of CNQX [$F(1,14) = 1.85$, NS], and no significant CNQX × NMDA interaction [$F(1,14) < 1$, NS]. There was no significant effect of prepulse type [$F(2,28) < 1$, NS] or other significant interactions. Post-hoc independent ANOVAs revealed a significant effect of NMDA in rats with intra-nucleus accumbens shell 0 μg CNQX infusion [$F(1,7) = 6.21$, $P < 0.01$], and in rats with intra-nucleus accumbens shell 2.5 μg CNQX infusion [$F(1,14) = 8.05$, $P < 0.01$]. Inspection of the data indicated that intra-nucleus accumbens shell CNQX infusion has a tendency to reduce prepulse inhibition, consistent with our previous finding (Wan et al., 1995a) that prepulse inhibition was significantly reduced by a higher concentration of CNQX. Analysis of startle amplitude revealed no significant effect of NMDA or CNQX on P-alone amplitude [both $F < 1$, NS]. In rats pretreated with 0 μg CNQX, NMDA did non-significantly reduce startle amplitude from (means ± S.E.M.) 521.73 ± 43.50 to 401.01 ± 46.27 startle units. These findings suggest that non-NMDA receptors in the shell of the nucleus accumbens do not mediate the prepulse inhibition-disruptive effect of intra-ventral subiculum NMDA infusion.

3.4. Effects of intra-nucleus accumbens core CNQX on the intra-ventral subiculum NMDA-induced disruption of prepulse inhibition

The nucleus accumbens core and shell subregions are characterized by distinct anatomical (Heimer et al., 1991; Voorn et al., 1989; Zahm and Brog, 1992), neurochemical (Deutch and Cameron, 1992; Zahm, 1991) and functional properties (Maldonado-Irizarry and Kelley, 1994; Pulvirenti et al., 1994). While the subiculo-accumbens projection terminates primarily within the nucleus accumbens

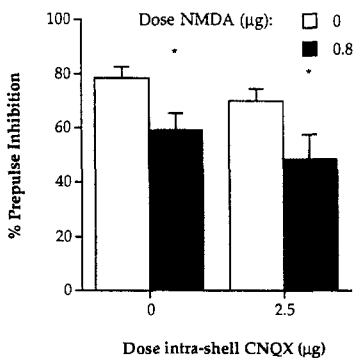

Fig. 4. Effects of intra-nucleus accumbens shell CNQX on the intra-ventral subiculum NMDA-induced disruption of prepulse inhibition. Intra-nucleus accumbens shell infusion of the non-NMDA receptor antagonist CNQX (2.5 μg) did not oppose the prepulse inhibition-disruptive effect of intra-ventral subiculum NMDA (0.8 μg). * $P < 0.05$, by independent ANOVA after significant main effect of NMDA by overall ANOVA. $n = 8$ and 8 for CNQX doses 0 and 2.5, respectively. Data represent mean percent prepulse inhibition across all prepulse conditions.

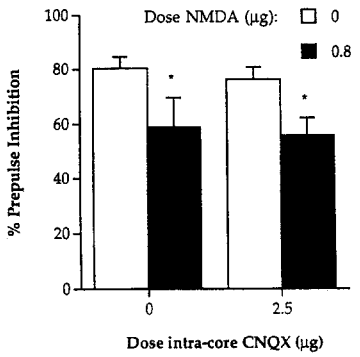

Fig. 5. Effects of intra-nucleus accumbens core CNQX on the intra-ventral subiculum NMDA-induced disruption of prepulse inhibition. Intra-nucleus accumbens core infusion of the non-NMDA receptor antagonist CNQX (2.5 μg) did not oppose the prepulse inhibition-disruptive effect of intra-ventral subiculum NMDA (0.8 μg). * $P < 0.05$, by independent ANOVA after significant main effect of NMDA by overall ANOVA. $n = 8$ and 8 for CNQX doses 0 and 2.5, respectively. Data represent mean percent prepulse inhibition across all prepulse conditions.

shell, nucleus accumbens core and shell subregions differ in their neurochemical regulation of prepulse inhibition (Wan and Swerdlow, 1996b), and thus it is conceivable that the smaller innervation of the nucleus accumbens core subregion might be responsible for a subiculo-accumbens AMPA regulation of prepulse inhibition. In this experiment, we examined the effects of intra-ventral subiculum NMDA infusion on prepulse inhibition after blockade of non-NMDA receptors in the nucleus accumbens core subregion.

The effects of intra-nucleus accumbens core infusion of CNQX (0 or 2.5 μg) on the prepulse inhibition-disruptive effects of intra-ventral subiculum infusion of NMDA (0.8 μg) are seen in Fig. 5. A two-way ANOVA using dose of CNQX as the between-subject factor, and dose of NMDA and prepulse type as the within-subject factors, revealed a significant effect of NMDA [$F(1,14) = 13.09$, $P < 0.01$], no significant effect of CNQX [$F(1,14) = 1.03$, NS], and no significant CNQX × NMDA interaction [$F(1,14) < 1$, NS]. There was a significant effect of prepulse type [$F(2,28) = 5.06$, $P = 0.01$], but no other significant interactions. Post-hoc independent ANOVAs revealed a significant effect of NMDA in rats with intra-nucleus accumbens core 0 μg CNQX infusion [$F(1,7) = 5.90$, $P < 0.01$], and in rats with intra-nucleus accumbens core 2.5 μg CNQX infusion [$F(1,14) = 7.65$, $P < 0.01$]. Analysis of startle amplitude revealed no significant effect of NMDA or CNQX on P-alone amplitude [both $F < 1$, NS]. In rats pretreated with 0 μg CNQX, NMDA non-significantly reduced startle amplitude from (means ± S.E.M.) 554.09 ± 150.86 to 476.45 ± 108.09 startle units. These findings suggest that non-NMDA receptors in the core of the nucleus accumbens do not mediate the prepulse inhibition-disruptive effects of intra-ventral subiculum infusion of NMDA, and together with results of nucleus accumbens shell infusions of CNQX, support the notion that non-NMDA receptors in the nucleus accumbens do not mediate the prepulse inhibition-disruptive effects of glutamatergic stimulation of the ventral subiculum.

3.5. Effects of intra-nucleus accumbens core CNQX and AMPA co-infusion on prepulse inhibition

To verify that the dose of CNQX (2.5 μg) used in above experiments is adequate to prevent the prepulse inhibition-disruptive effects of nucleus accumbens non-NMDA receptor activation, we examined the effects of 2.5 μg CNQX on the reduction in prepulse inhibition after intra-nucleus accumbens core infusion of the non-NMDA receptor agonist AMPA.

The effects of intra-nucleus accumbens core co-infusion of CNQX (0 or 2.5 μg) and AMPA (0 or 0.5 μg) on prepulse inhibition are seen in Fig. 6. A two-way ANOVA using group of treatment (4 groups: vehicle/saline, vehicle/AMPA, CNQX/saline, CNQX/AMPA; $n = 8$ for each group) as the between-subject factor with repeated measures on prepulse type revealed a significant effect of group [$F(3,28) = 3.65$, $P < 0.02$], a significant effect of prepulse type [$F(2,56) = 4.76$, $P = 0.01$], and no significant group × prepulse type interaction [$F(6,56) < 1$, NS]. Post-hoc Tukey Compromise test revealed a significant difference in prepulse inhibition between vehicle/saline and vehicle/AMPA groups ($P < 0.05$), but there was no significant difference between CNQX/saline and CNQX/AMPA groups, nor were there other significant group differences. Analysis of startle amplitude revealed no significant effect of group on P-alone amplitude [$F(3,28) = 1.14$, NS]. These results suggest that the intra-nucleus accumbens core AMPA-induced disruption of prepulse inhibition can be prevented after blockade of non-

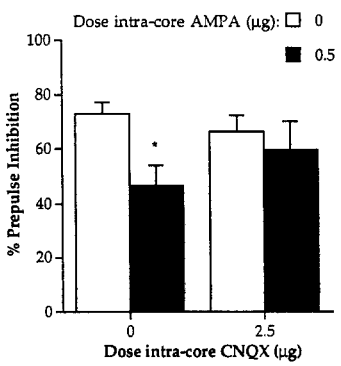

Fig. 6. Effects of intra-nucleus accumbens core CNQX and AMPA co-infusion on prepulse inhibition. Intra-nucleus accumbens core infusion of the non-NMDA agonist AMPA (0.5 μg) caused a significant reduction of prepulse inhibition. * $P < 0.05$, by Tukey comparison after significant main effect of treatment by overall ANOVA. In contrast, there was no significant effect of AMPA (0.5 μg) in rats co-infusion with the non-NMDA receptor antagonist CNQX (2.5 μg). $n = 8$, 8, 8 and 8 for the four treatment groups. Data represent mean percent prepulse inhibition across all prepulse conditions.

NMDA receptors by co-infusion of 2.5 μg CNQX. Since this dose of CNQX infused into either the nucleus accumbens core or shell subregions fails to abolish intra-ventral subiculum NMDA-induced disruption of prepulse inhibition, the prepulse inhibition-disruptive effects of intra-ventral subiculum NMDA do not appear to be mediated through activation of an accumbens non-NMDA glutamate substrate.

3.6. Effects of systemic injection of haloperidol on the intra-ventral subiculum NMDA-induced disruption of prepulse inhibition

Dopaminergic substrates figure prominently in the nucleus accumbens regulation of prepulse inhibition. Intra-nucleus accumbens infusion of dopamine or dopamine D_2 receptor agonists reduce or eliminate prepulse inhibition (Swerdlow et al., 1986; Wan and Swerdlow, 1993; Wan et al., 1994), and these effects are reversed by dopamine receptor blockade with haloperidol (Wan and Swerdlow, 1993). If the prepulse inhibition-disruptive effects of intra-ventral subiculum infusion of NMDA reflect some changes in subiculo-accumbens efferent activity, it is possible that such effects on prepulse inhibition are ultimately regulated by changes in nucleus accumbens dopamine transmission. For example, the prepulse inhibition-disruptive effects of intra-nucleus accumbens AMPA infusion are blocked by systemic administration of the dopamine D_2 receptor antagonist haloperidol, and by nucleus accumbens dopamine depletion with 6-hydroxydopamine (Wan et al., 1995a), suggesting that this non-NMDA regulation of prepulse inhibition is dependent on intact nucleus accumbens dopamine activity. To determine whether the prepulse inhibition-disruptive effects of intra-ventral subiculum NMDA infusion are mediated via central dopamine activation, we examined the effects of intra-ventral subiculum NMDA infusion on prepulse inhibition after antagonism of dopamine D_2 receptors with haloperidol.

A two-way ANOVA using haloperidol (0 or 0.1 mg/kg) as the between-subject factor, and dose of NMDA (0 or 0.8 μg) and prepulse type as the within-subject factors revealed a significant effect of NMDA [$F(1,12) = 12.90$, $P < 0.01$], no significant effect of haloperidol [$F(1,12) < 1$, NS], and no significant haloperidol × NMDA interaction [$F(1,12) < 1$; NS] (Fig. 7). There was a significant effect of prepulse type [$F(2,24) = 10.87$, $P < 0.01$], but no other significant interactions. Post-hoc independent ANOVAs revealed a significant effect of NMDA on prepulse inhibition in rats pretreated with saline [$F(1,6) = 6.29$, $P < 0.01$], and in rats pretreated with 0.1 mg/kg haloperidol [$F(1,12) = 7.82$, $P < 0.01$]. This dose of haloperidol reverses the prepulse inhibition-disruptive effects of intra-nucleus accumbens infusion of either dopamine (Swerdlow et al., 1994) or the dopamine D_2 receptor agonist quinpirole (Wan and Swerdlow, 1993). Analysis of startle amplitude

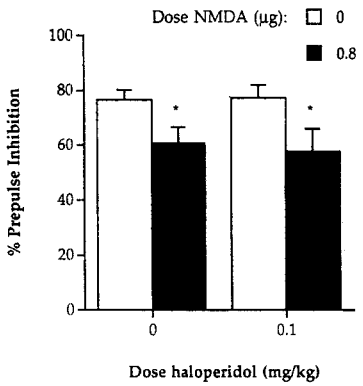

Fig. 7. Effects of systemic injection of haloperidol on the intra-ventral subiculum NMDA-induced disruption of prepulse inhibition. The NMDA-disruption of prepulse inhibition was not blocked by systemic injection of haloperidol. * $P < 0.05$, by independent ANOVA after significant main effect of NMDA by overall ANOVA. $n = 7$ and 7 for haloperidol doses 0 and 0.1, respectively. Data represent mean percent prepulse inhibition across all prepulse conditions.

revealed no significant effect of NMDA or haloperidol on P-alone amplitude [$F < 1$, $F = 3.14$, respectively; NS]. In rats pretreated with 0 mg/kg haloperidol, NMDA did not reduce startle amplitude ((means ± S.E.M.): 0 μg NMDA, 571.14 ± 120.82; 0.8 μg NMDA, 575.26 ± 121.53). Thus, the present findings do not support a role for brain dopamine overactivity in the reduction of prepulse inhibition that follows glutamatergic activation of the ventral subiculum.

4. Discussion

We report here that NMDA infusion into the ventral subiculum disrupts sensorimotor gating of acoustic startle. The prepulse inhibition-disruptive effects of NMDA are dose-dependent, and are reversed by co-infusion of the selective NMDA receptor antagonist AP5. The effects of intra-ventral subiculum NMDA infusion on prepulse inhibition are not opposed by non-NMDA receptor blockade in the nucleus accumbens core or shell subregions, and are not blocked by dopamine D_2 receptor blockade. The present findings extend our previous reports that prepulse inhibition can be reduced by pharmacologic stimulation of the hippocampus (Caine et al., 1991, 1992). Koch (1995) recently reported that pharmacologic stimulation of the septo-hippocampal pathway reduced prepulse inhibition, and that this effect was blocked by systemic or intra-hippocampal injection of the acetylcholine receptor antagonist scopolamine. These findings, as well as reports of reduced prepulse inhibition after neonatal lesions of the ventral hippocampus (Lipska et al., 1995), suggest that the hippocampus is a critical substrate in the regulation of sensorimotor gating. While caution must be used in interpreting the anatomical specificity of the present effects of intracerebral infusion of NMDA, clear regional differences in

the NMDA regulation of prepulse inhibition are evident from the finding that prepulse inhibition is significantly reduced after infusion of the *NMDA receptor antagonist AP5* into the basolateral amygdala (Wan and Swerdlow, 1996c).

We have previously reported that prepulse inhibition can be reduced after manipulations that increase either dopamine or glutamate activity in the nucleus accumbens (Wan and Swerdlow, 1993, 1996b; Wan et al., 1994, 1995a). Specifically, prepulse inhibition is reduced by intra-nucleus accumbens infusion of either the indirect dopamine receptor agonist amphetamine or the non-NMDA receptor agonist AMPA (Wan et al., 1995a, Wan and Swerdlow, 1996b). While prepulse inhibition can be affected by manipulations of the hippocampus and nucleus accumbens independently, the present study does not provide evidence that changes in prepulse inhibition after hippocampal manipulations result from effects 'downstream', at non-NMDA receptor targets of the subiculo-accumbens projection. The present studies do not address the possible role of nucleus accumbens NMDA or metabotropic glutamate receptors in the prepulse inhibition-disruptive effects of intra-ventral subiculum NMDA infusion. Published findings suggest that intra-nucleus accumbens infusions of NMDA reduce prepulse inhibition (Reijmers et al., 1995).

The observation that the prepulse inhibition-disruptive effects of intra-ventral subiculum NMDA infusion are apparently not mediated via increased brain dopamine activity, suggests a dopamine-independent substrate for the hippocampal regulation of prepulse inhibition, and is consistent with our earlier observations that: (1) the prepulse inhibition-disruptive effects of intra-hippocampal carbachol infusion are not reversed by pretreatment with the dopamine D_2 receptor antagonist spiperone (Caine et al., 1991); and (2) the reduction in prepulse inhibition after AMPA infusion into the nucleus accumbens shell is mediated by dopamine-independent mechanisms (Wan and Swerdlow, 1996b). While these data suggest that any regulation of prepulse inhibition by the ventral subiculum-nucleus accumbens shell projection is likely to be independent of dopaminergic substrates, a similar mechanism cannot be assumed for the regulation of prepulse inhibition by hippocampal projections to the nucleus accumbens core region. For example, Groenewegen et al. (1987) demonstrated that the subicular projection to the nucleus accumbens core originates primarily in the dorsal subiculum, while the subicular projection to the nucleus accumbens shell originates primarily in the ventral subiculum. Furthermore, lesions restricted to different subicular subregions have differential effects on dopamine activity in the nucleus accumbens (Burns et al., 1993). Thus, the present findings do not exclude the possibility that prepulse inhibition might be regulated in a dopamine-dependent manner via a glutamatergic projection from the dorsal subiculum to the nucleus accumbens core. Indeed, the regulation of prepulse inhibition by AMPA activity in the nucleus accumbens core is clearly dopamine-dependent (Wan et al., 1995a).

Other findings suggest that changes in nucleus accumbens dopamine activity after ventral hippocampal manipulations may result in reduced prepulse inhibition. Thus, excitotoxic lesions of the ventral hippocampus in neonatal rats results in a post-pubertal reduction in prepulse inhibition and an increased sensitivity to the prepulse inhibition-disruptive effects of the direct dopamine D_1/D_2 receptor agonist apomorphine (Lipska et al., 1995); the latter effect (increased apomorphine sensitivity) was also noted in rats after adult lesions of the ventral hippocampus (Swerdlow et al., 1995a). While it is not known which substrates mediate these changes in dopamine sensitivity after lesions of the ventral hippocampus, there is no evidence from the present studies that related substrates are involved in the reduction of prepulse inhibition after intra-ventral subiculum infusion of NMDA.

We have previously reported that carbachol infusion into the hippocampus reduces startle amplitude (Caine et al., 1991, 1992). In the present study, intra-ventral subiculum infusion of NMDA tended to reduce startle amplitude in most, but not all experiments, and this effect only reached statistical significance on one occasion (Experiment 3.2). Importantly, we have reported that changes in prepulse inhibition are not dependent on changes in startle amplitude, that prepulse inhibition can be reduced by manipulations that either increase (Kodsi and Swerdlow, 1994; Swerdlow and Geyer, 1993b), decrease (Swerdlow et al., 1990), or do not change startle amplitude (Swerdlow and Geyer, 1993a; Swerdlow et al., 1994; Wan and Swerdlow, 1996a), and that prepulse inhibition can actually be increased by drugs that decrease startle amplitude (Swerdlow et al., 1993). In the present study, the fact that intra-ventral subiculum NMDA only significantly reduced startle amplitude in one experiment, but significantly reduced prepulse inhibition in all experiments, adds support to the notion that prepulse inhibition and startle amplitude are regulated by at least partially independent mechanisms.

A number of clinical studies have documented abnormalities within the hippocampal formation of schizophrenia patients, including reduced volume and cell densities (Bogerts et al., 1985; Suddath et al., 1989), disorganized cytoarchitecture (Altshuler et al., 1987; Arnold et al., 1991; Conrad et al., 1991), and abnormal metabolic activity (Wu et al., 1990). The present observation that pharmacologic stimulation of the ventral subiculum of the hippocampus disrupts prepulse inhibition in rats is consistent with the notion that hippocampal pathology may contribute to deficient sensorimotor gating in schizophrenia. However, other studies in schizophrenia patients have also identified structural or metabolic abnormalities at every level of the limbic cortico-striato-pallido-pontine circuitry that is known to regulate prepulse inhibition in rats, as well as in thalamic structures that should theoretically interact

with cortico-striato-pallido-pontine activity (Pakkenberg, 1990). Thus, the present findings do not specifically suggest a causal relationship between hippocampal pathology and reduced prepulse inhibition in schizophrenia patients. Future studies will examine whether the regulation of prepulse inhibition by NMDA receptor activity in the ventral subiculum is mediated via NMDA or metabotropic glutamate receptors in the nucleus accumbens. According to our present findings, even if such substrates are found to regulate the prepulse inhibition-disruptive effects of subiculum NMDA receptor activation, we would predict that this regulation would be independent of accumbens dopamine D_2 receptor mechanisms.

Acknowledgements

These studies were supported by NIMH Awards MH-48381 and MH-42228 and by funding from Sandoz Pharmaceuticals. F.-J.W. was supported by the National Defense Medical Center, Taipei, Taiwan. Excellent technical assistance was provided by Ms. Pamela Auerbach and Mr. Navid Taaid.

References

Altshuler, L.L., A. Conrad, J.A. Kovelman and A. Scheibel, 1987, Hippocampal pyramidal cell orientation in schizophrenia, Arch. Gen. Psychiatry 44, 1094.

Arnold, S.E., B.T. Hyman, G.W. Van Hoesen and A.R. Damasio, 1991, Some cytoarchitectural abnormalities of the entorhinal cortex in schizophrenia, Arch. Gen. Psychiatry 48, 625.

Bogerts, B., E. Meertz and R. Schonfeld-Bausch, 1985, Basal ganglia and limbic system pathology in schizophrenia, Arch. Gen. Psychiatry 42, 784.

Bolino, F., V. DiMichele, L. DiCicco, V. Manna, E. Daneluzzo and M. Cassachia, 1994, Sensorimotor gating and habituation evoked by electro-cutaneous stimulation in schizophrenia, Biol. Psychiatry 36, 670.

Braff, D.L., C. Stone, E. Callaway, M. Geyer, I. Glick and L. Bali, 1978, Prestimulus effects on human startle reflex in normals and schizophrenics, Psychophysiology 15, 339.

Braff, D.L., C. Grillon and M.A. Geyer, 1992, Gating and habituation of the startle reflex in schizophrenic patients, Arch. Gen. Psychiatry 49, 206.

Burns, L., T.W. Robbins and B.J. Everitt, 1993, Differential effects of excitotoxic lesions of the basolateral amygdala, ventral subiculum and medial prefrontal cortex on responding with conditioned reinforcement and locomotor activity potentiated by intra-accumbens infusions of D-amphetamine, Behav. Brain Res. 55, 167.

Caine, S.B., M.A. Geyer and N.R. Swerdlow, 1991, Carbachol infusion into the dentate gyrus disrupts sensorimotor gating of startle in the rat, Psychopharmacology 105, 347.

Caine, S.B., M.A. Geyer and N.R. Swerdlow, 1992, Hippocampal modulation of acoustic startle and prepulse inhibition in the rat, Pharmacol. Biochem. Behav. 43, 1201.

Chabot, C.C. and D.H. Tayler, 1992, Circadian modulation of the rat acoustic startle response, Behav. Neurosci. 106, 846.

Conrad, A.J., T. Abebe, R. Austin, S. Forsythe and A.B. Scheibel, 1991, Hippocampal pyramidal cell disarray in schizophrenia as a bilateral phenomenon, Arch. Gen. Psychiatry 48, 413.

Davis, M., D. Gendelamn, M. Tischler and P. Gendelman, 1982, A primary acoustic startle circuit: lesion and stimulation studies, J. Neurosci. 2, 791.

Deutch, A.Y. and D.S. Cameron, 1992, Pharmacological characterization of dopamine systems in the nucleus accumbens core and shell, Neuroscience 46, 49.

Ellenbroek, B.A., S. Budde and A.R. Cools, 1995, The role of dopamine D_1 and D_2 receptors in the medial prefrontal cortex in prepulse inhibition, Abstr. Soc. Neurosci. 21, 297.17

Emerich, D.F. and T.J. Walsh, 1990, Hyperactivity following intradentate injection of colchicine: a role for dopamine systems in the nucleus accumbens, Pharmacol. Biochem. Behav. 37, 149.

Flicker, C. and M.A. Geyer, 1982, Behavior during hippocampal microinfusions: II. Muscarinic locomotor activation, Brain Res. Rev. 4, 105.

Grillon, C., R. Ameli, D.S. Charney, J. Kristal and D.L. Braff, 1992, Startle gating deficits occur across prepulse intensities in schizphrenic patients, Biol. Psychiatry 32, 939.

Groenewegen, H.J., E. Vermeulen-Van der Zee, A. Te Kortschot and M.P. Witter, 1987, Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of *Phaseolus vulgaris* leucoagglutinin, Neuroscience 23, 103.

Heimer, L., D.S. Zahm, L. Churchill, P.W. Kalivas and C. Wohltmann, 1991, Specificity in the projection patterns of accumbal core and shell, Neuroscience 41, 89.

Ison, J.R. and H.S. Hoffman, 1983, Reflex modifications in the domain of startle: II. The anomalous history of a robust and ubiquitous phenomenon, Psychopharmacol. Bull. 94, 3.

Kelley, A.E. and V.B. Domesick, 1982, The distribution of the projection from the hippocampal formation to the nucleus accumbens in the rat: an antegrade- and retrograde-horseradish peroxidase study, Neuroscience 7, 2321.

Koch, M., 1995, The septohippocampal system is involved in prepulse inhibition of the acoustic startle response in rats, Abstr. Soc. Neurosci. 21, 637.1.

Koch, M. and M. Bubser, 1994, Deficient sensorimotor gating after 6-hydroxydopamine lesion of the rat medial prefrontal cortex is reversed by haloperidol, Eur. J. Neurosci. 6, 1837.

Koch, M., M. Kungel and H. Herbert, 1993, Cholinergic neurons in the pedunculopontine tegmental nucleus are involved in the mediation of prepulse inhibition of the acoustic startle response in the rat, Exp. Brain Res. 97, 71.

Kodsi, M.H. and N.R. Swerdlow, 1994, Quinolinic acid lesions of the ventral striatum reduce sensorimotor gating of acoustic startle in rats, Brain Res. 643, 59.

Kodsi, M.H., N. Taaid, H.J. Hartston, D. Zisook, F.J. Wan and N.R. Swerdlow, 1995, Regulation of prepulse inhibition in the rat by ventral pallidal projections, Abstr. Soc. Neurosci. 21, 652.4.

Lingenhohl, K. and E. Friauf, 1994, Giant neurons in the rat reticular formation: a sensorimotor interface in the elementary acoustic startle circuit?, J. Neurosci. 14, 1176.

Lipska, B.K., G.E. Jaskiw, S. Chrapusta, F. Karoum and D.R. Weinberger, 1992, Ibotenic acid lesion of the ventral hippocampus differentially affects dopamine and its metabolites in the nucleus accumbens and prefrontal cortex in the rat, Brain Res. 585, 1.

Lipska, B.K., N.R. Swerdlow, M.A. Geyer, G.E. Jaskiw, D.L. Braff and D.R. Weinberger, 1995, Neonatal excitotoxic hippocampal damage in rats causes post-pubertal changes in prepulse inhibition of startle and its disruption by apomorphine, Psychopharmacology 122, 35.

Luchins, D.J., 1990, A possible role of hippocampal dysfunction in schizophrenic symptomatology, Biol. Psychiatry 28, 87.

Maldonado-Irizarry, C.S. and A.E. Kelley, 1994, Differential behavioral effects following microinjection of an NMDA antagonist into nucleus accumbens subregions, Psychopharmacology 116, 65.

Mogenson, G.J. and M. Nielson, 1984, A study of the contribution of hippocampal-accumbens-subpallidal projections to locomotor activity, Behav. Neural. Biol. 42, 38.

Pakkenberg, B., 1990, Pronounced reduction of total neuron number in mediodorsal thalamic nucleus and nucleus accumbens in schizophrenics, Arch. Gen. Psychiatry 47, 1023.

Paxinos, G. and C. Watson, 1986, The Rat Brain in Stereotaxic Coordinates, 2nd edn. (Academic Press, Australia).

Pulvirenti, L., R. Berrier, M. Kreifeldt and G.F. Koob, 1994, Modulation of locomotor activity by NMDA receptors in the nucleus accumbens core and shell regions of the rat, Brain Res. 664, 231.

Reijmers, L.G.J.E., P.M.L. Vanderheyden and B.W.M.M. Peeters, 1995, Changes in prepulse inhibition after local administration of NMDA receptor ligands in the core region of the rat nucleus accumbens, Eur. J. Pharmacol. 272, 131.

Seybold, K.S., K. Smith, J. Wrigley and R.L. Port, 1995, Diminished prepulse inhibition following kainic acid-induced hippocampal damage to model some schizophrenia neuropathology, Abstr. Soc. Neurosci. 21, 297.11.

Suddath, R.L., M.F. Casanova, T.E. Goldberg, D.G. Daniel, J.R. Kelsoe, Jr. and D.R. Weinberger, 1989, Temporal lobe pathology in schizophrenia: a quantitative magnetic resonance imaging study, Am. J. Psychiatry 146, 464.

Swerdlow, N.R. and M.A. Geyer, 1993a, Clozapine and haloperidol in an animal model of sensorimotor gating deficits in schizophrenia, Pharmacol. Biochem. Behav. 44, 741.

Swerdlow, N.R. and M.A. Geyer, 1993b, Prepulse inhibition of acoustic startle in rats after lesions of the pedunculopontine nucleus, Behav. Neurosci. 107, 104.

Swerdlow, N.R., M.A. Geyer, D.L. Braff and G.F. Koob, 1986, Central dopamine hyperactivity in rats mimics abnormal acoustic startle in schizophrenics, Biol. Psychiatry 21, 23.

Swerdlow, N.R., D.L. Braff and M.A. Geyer, 1990, GABAergic projection from nucleus accumbens to ventral pallidum mediates dopamine-induced sensorimotor gating deficits of acoustic startle in rats, Brain Res. 532, 146.

Swerdlow, N.R., C.H. Benbow, S. Zisook, M.A. Geyer and D.L. Braff, 1993, A preliminary assessment of sensorimotor gating in patients with obsessive compulsive disorder, Biol. Psychiatry 33, 298.

Swerdlow, N.R., D.L. Braff, N. Taaid and M.A. Geyer, 1994, Assessing the validity of an animal model of sensorimotor gating deficits in schizophrenic patients, Arch. Gen. Psychiatry 51, 139.

Swerdlow, N.R., B.K. Lipska, D.R. Weinberger, D.L. Braff, G.E. Jaskiw and M.A. Geyer, 1995a, Increased sensitivity to the sensorimotor gating-disruptive effects of apomorphine after lesions of medial prefrontal cortex or ventral hippocampus in adult rats, Psychopharmacology 122, 27.

Swerdlow, N.R., J. Paulsen, D.L. Braff, N. Butters, M.A. Geyer and M.R. Swenson, 1995b, Impaired prepulse inhibition of acoustic and tactile startle in patients with Huntington's Disease, J. Neurol. Neurosurg. Psychiatry 58, 192.

Totterdell, S. and A.D. Smith, 1989, Convergence of hippocampal and dopaminergic input onto identified neurons in the nucleus accumbens of the rat, J. Chem. Neuroanat. 2,285.

Voorn, P., C.R. Gerfen and H.J. Groenewegen, 1989, Compartmental organization of the ventral striatum of the rat: immunohistochemical distribution of enkephalin, substance P, dopamine, and calcium-binding protein, J. Comp. Neurol. 289, 189.

Wan, F.J. and N.R. Swerdlow, 1993, Intra-accumbens infusion of quinpirole impairs sensorimotor gating of acoustic startle in rats, Psychopharmacology 113, 103.

Wan, F.J. and N.R. Swerdlow, 1996a, Do D_1/D_2 interactions regulate prepulse inhibition in rats?, Neuropsychopharmacology 14, 265.

Wan, F.J. and N.R. Swerdlow, 1996b, Sensorimotor gating in rats is regulated by different dopamine-glutamate interactions in the nucleus accumbens core and shell subregions, Brain Res. 722, 168.

Wan, F.J. and N.R. Swerdlow, 1996c, The basolateral amygdala regulates sensorimotor gating of acoustic startle in the rat, Neuroscience (in press).

Wan, F.J., M.A. Geyer and N.R. Swerdlow, 1994, Accumbens D_2 modulation of sensorimotor gating in rats: assessing anatomical localization, Pharmacol. Biochem. Behav. 49, 155.

Wan, F.J., M.A. Geyer and N.R. Swerdlow, 1995a, Presynaptic dopamine-glutamate interactions in the nucleus accumbens regulate sensorimotor gating, Psychopharmacology 120, 433.

Wan, F.J., M.H. Kodsi, S.B. Caine and N.R. Swerdlow, 1995b, Corticostriatal substrates of prepulse inhibition of acoustic startle in the rat, Abstr. Soc. Neurosci. 21, 1659.

Wilkinson, L.S., G. Mittleman, E. Torres, T. Humby, F.S. Hall and T.W. Robbins, 1993, Enhancement of amphetamine-induced locomotor activity and dopamine release in nucleus accumbens following excitotoxic lesions of the hippocampus, Behav. Brain Res. 55, 143.

Wu, J.C., B.V. Segal, R.J. Haier and M.S. Buchsbaum, 1990, Testing the Swerdlow/Koob model of schizophrenia pathophysiology using positron emission tomography, Behav. Brain Sci. 13, 169.

Zahm, D.S., 1991, Compartment in rat dorsal and ventral striatum revealed following injection of 6-hydroxydopamine into the ventral mesencephalon, Brain Res. 552, 164.

Zahm, D.S. and J.S. Brog, 1992, On the significance of subterritories in the "accumbens" part of the rat ventral striatum, Neuroscience 50, 751.

Zheng, S., H.A. Berman and M.A. Geyer, 1983, Behavior during hippocampal microinfusions: anticholinesterase-induced locomotor activation, Behav. Brain Res. 9, 295.